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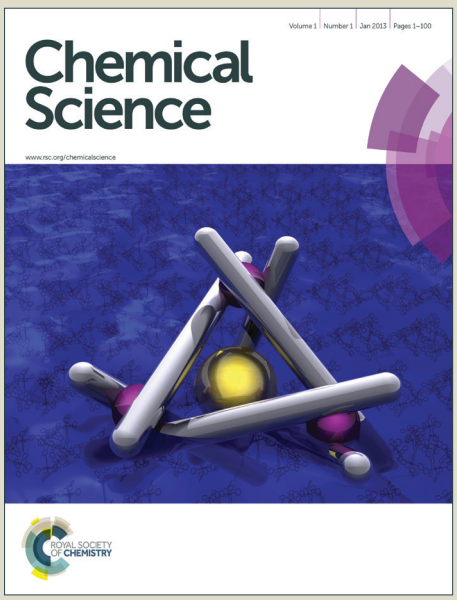

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ARTICLE TYPE

Breaking Conjugation: Unusual Regioselectivity with 2-Substituted Allylic Substrates in the Tsuji-Trost Reaction

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η^3-Allyl palladium complexes are key intermediates in Tsuji-Trost allylic substitution reactions. It is well known that (η^3-1-aryl-3-alkyl substituted allyl)Pd intermediates result in nucleophilic attack at the alkyl substituted terminus. In contrast, the chemistry of (η^3-1,2,3-trisubstituted allyl)Pd intermediates is relatively unexplored. Herein we probe the regioselectivity with 1,2,3-trisubstituted allylic substrates in Tsuji-Trost allylic substitution reactions. DFT investigation of cationic (η^3-1-Ph-2-B(pin)-3-alkyl-allyl)Pd(PPh_3)$_2$ intermediates predict that nucleophilic attack should occur preferentially on *anti*-allyls rather than the *syn*-isomers to generate benzylic substitution products under Curtin-Hammett conditions. Experimentally, systematic studies with 1,2,3-trisubstituted allylic substrates revealed that a Linear Free Energy Relationship (LFER) is observed when Charton steric parameters of the C-2 substituents are plotted against log of the ratio of regioisomers. Bulkier C-2 substituents in 1,2,3-trisubstituted η^3-allyl palladium intermediates provide stronger preference for nucleophilic attack at *anti*-oriented benzylic termini. Additionally, the geometry of 1,4-elimination products supports the presence of *anti*-allyl palladium intermediates.

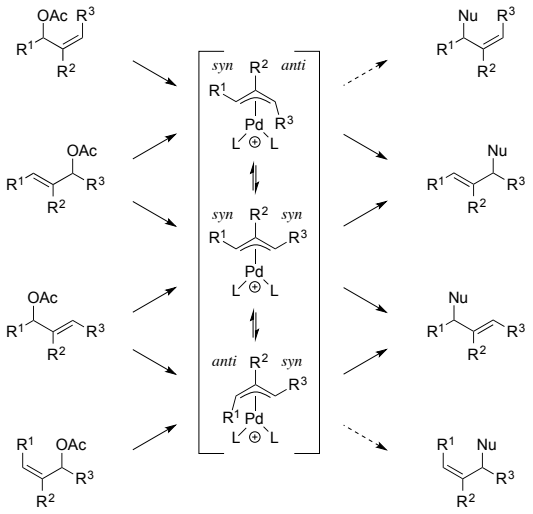
1. Introduction

Transition metal catalyzed allylic substitution reactions are among the most powerful synthetic methods in organic chemistry.[1,2] In particular, the palladium catalyzed Tsuji-Trost reaction has become an efficient method to construct carbon–carbon and carbon–heteroatom bonds.[1b,1c,2b,3] One of the most interesting and challenging aspects of allylic substitutions is the control of regioselectivity.[1a,1b,4] The regioselectivity of the palladium catalyzed allylic substitution reaction depends on several parameters[1a,4b,4c] including: the nature of ligand, solvent, counter anion, leaving group, nucleophile, base, allyl fragment, and additives.[2f,3a,5]

The mechanism of the Pd-catalyzed allylic substitution has been well investigated. Initial coordination of the allylic substrate at the double bond is followed by attack of palladium(0) on the C–O σ*-orbital of the leaving group, generating a cationic (η^3-allyl)PdL_n intermediate. Stabilized anionic nucleophiles directly attack the η^3-allyl terminus.[6] The overall process occurs with a net retention of configuration (via a double inversion pathway).[1b,1c,7] For unsymmetrical (η^3-allyl)Pd intermediates, attack can occur at either of the termini, giving rise to regioselectivity issues. Another complicating factor of η^3-allyls bearing terminal substituents is the possibility of *syn-anti* isomerization, as shown in the center of Scheme 1.[8] This isomerization can be fast, with all of the isomeric substrates feeding into the (η^3-allyl)Pd manifold and giving rise to the same product distribution (Scheme 1).[9]

However, if the isomerization is slow relative to nucleophilic attack,[10] or in the presence of chiral[11] or electronically differentiated[12] ligands, the reaction can show strong memory effects. Under conditions of slow isomerization, nucleophilic attack has a strong preference for reaction at *anti*-oriented termini.[13] In the absence of memory effects, the regioselectivity is largely dependent on the steric and electronic nature of the terminal η^3-allyl substituents.[4b,4c] In general, nucleophilic attack will occur at the allylic terminus with the highest partial positive charge.[14] Conjugated products are frequently preferred, in

Scheme 1. The Dynamic Manifold of Intermediates in Pd-Assisted Allylic Alkylation



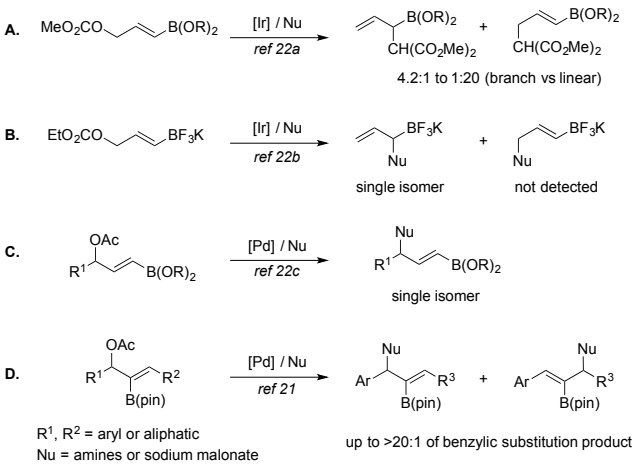
particular with strongly electron withdrawing groups.[1b,3a,15] It is possible to influence the regioselectivity to some extent by controlling the steric bulk of the ligands.[13,16] In these cases, the preferred regio- and stereo-selectivity can be understood in terms of distortion of the (η^3-allyl)Pd intermediate.[16-17]

Previous mechanistic investigations have mostly focused on substrates giving rise to mono- or 1,3-disubstituted (η^3-allyl)Pd intermediates.[1b,18] In general, 1-aryl-3-alkyl-substituted (η^3-allyl)Pd complexes have a strong preference for nucleophilic attack at the alkyl-substituted terminus, yielding conjugated products.[16-17,19] This preference can be further increased by utilization of ligands to force the alkyl substituent into the more reactive *anti*-configuration (Scheme 1).[13,16-17]

Our interest in trisubstituted (η^3-allyl)Pd intermediates grew out of methods we developed for the synthesis of 2-B(pin)-substituted allylic acetates and related compounds.[20,21] At the outset of our studies, we demonstrated the ability of 2-B(pin)-substituted allylic acetates to successfully undergo the Tsuji-Trost allylic substitution reaction.[21] In the meantime, a few methods with boron-substituted allyls have been reported in allylic substitution reactions (Scheme 2).[21,22] Before our preliminary results (Scheme 2D),[21] however, no prior examples of allylic acetates containing a boron at the 2-position were employed in transition metal-catalyzed allylic substitution reactions, although some examples of 3-boron substituted analogs had been generated or proposed as intermediates.[22]

As inferred by Scheme 2D,[21] 2-B(pin) substituted allylic acetates are expected to generate (η^3-1-aryl-2-boryl-3-alkyl-allyl) palladium intermediates. Contrary to aliphatic substitutions,[16] however, nucleophilic attack occurred at the benzylic position with very high selectivity (Scheme 2D). In general, products derived from benzylic attack of (η^3-1-aryl-3-alkyl-allyl)palladium intermediates are the minor isomer.[16-17,19a-d] Herein, we have undertaken an experimental and computational investigation of cationic (η^3-1-phenyl-2-B(pin)-3-alkyl-allyl)Pd(PPh_3)$_2$ and related intermediates. We present a systematic substrate-selectivity study to elucidate the origin of the unusual selectivity in allylic substitutions with cationic (η^3-1,2,3-trisubstituted allyl) palladium intermediates.

Scheme 2. Metal Catalyzed Allylic Substitution of Borylated Allylic Acetates and Carbonates

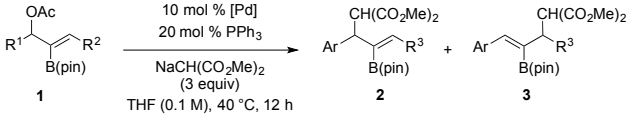


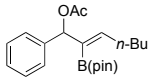
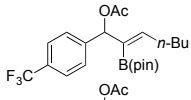
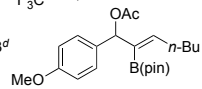
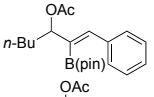
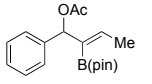
2. Results and discussion

A fundamental unanswered question in the Tsuji-Trost allylic substitution reaction with 1,2,3-trisubstituted allylic acetates is: What is the impact of the 2-substituent on the regioselectivity of nucleophilic attack? This question emerged as we explored palladium-catalyzed allylic substitution of 2-B(pin)-substituted allylic acetates, and inspired us to investigate this topic.

2.1. Reactions of 2-B(pin)-Substituted Allylic Acetates with Palladium Catalysts. We recently communicated[21] the palladium-catalyzed allylic substitution reaction employing 2-B(pin)-substituted allylic acetates (**1**, Table 1). In our initial study, we were surprised to find that the 2-B(pin) group plays a decisive role in determining the regioselectivity of nucleophilic attack. For example, 2-B(pin)-substituted allylic acetate **1a** underwent substitution with sodium dimethylmalonate to furnish 2-B(pin)-substituted allylic alkylation product **2a** with excellent regioselectivity (>90:10) in 79% yield (Table 1, entry 1). Analogous reactions with electron withdrawing or donating substituents on the aryl groups (**1b** and **1c**) provided the benzylic substitution products (**2b** and **2c**) with excellent regioselectivity (>95:5) in 92 and 80% yield, respectively (entries 2 and 3). It is noteworthy that isomeric 2-B(pin)-substituted allylic acetates **1a** and **1d** underwent substitution to afford the same product, **2a**, with nearly identical regioselectivities (entries 1 vs. 4). This result clearly demonstrates the absence of regiochemical memory effects.[10] Allylic acetate **1d**, however, afforded diminished yield of the substitution product (51%, entry 4) relative to **1a** (79% yield). Primary and secondary amines also participated in allylic

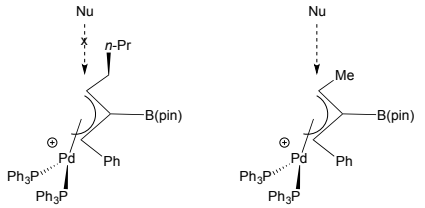
Table 1. Palladium-catalyzed Allylic Substitution Reaction with 2-B(pin)-Substituted Allylic Acetates[a]



entry	acetate		[Pd]	yield[b] (%)	ratio[c] of **2**:**3**	product
1[d]		**1a**	$[Pd(allyl)Cl]_2$	79	>90:10	**2a**
2[d]		**1b**	$Pd(OAc)_2$	92[e]	>95:5	**2b**
3[d]		**1c**	$Pd(OAc)_2$	80[e]	>95:5	**2c**
4[d]		**1d**	$[Pd(allyl)Cl]_2$	51	>90:10	**2a**
5		**1e**	$[Pd(allyl)Cl]_2$	70	>95:5	**2e**

[a] See the Supporting Information for experimental details. [b] Yield of purified and isolated products. [c] Ratios were determined by ^{1}H NMR spectroscopy of unpurified reaction mixtures. [d] Reference 21. [e] Bis(trimethylsilyl)acetamide, $CH_2(CO_2Me)_2$ and catalytic KOAc were used instead of $NaCH(CO_2Me)_2$.

Figure 1. Interference between alkyl group and incoming nucleophile.



substitution reaction to give similar regioselectivities (>90:10) by nucleophilic attack at the benzylic position.[21] We were concerned that the 3-*n*-butyl substituent might adopt a conformation 180° opposite the palladium center and hinder nucleophilic attack at the 3-position (Figure 1). To remove any potential conformational issues caused by the 3-*n*-butyl substituent, 2-B(pin)-substituted allylic acetate **1e**, with a smaller 3-methyl substituent in place of the *n*-butyl group of **1a**, was prepared (see Supporting Information for details). Interestingly, **1e** also provided benzylic substitution, affording **2e** with excellent regioselectivity (>95:5) in 70% yield (entry 5). As outlined in Table 1, the 1-aryl-2-B(pin)-3-alkyl η^3-allyls showed a strong preference for nucleophilic attack at the *benzylic site*, in contrast to the observed regioselectivity in Tsuji-Trost allylic substitution reactions with 1-aryl-substituted η^3-allyl intermediates.[19a-c,19e] The unique regioselectivity of 2-B(pin)-substituted allylic acetates makes them potentially valuable in synthesis. The factors that control the regioselectivity with 2-B(pin)-substituted allylic acetates, however, are unclear. This is the subject of the following section.

2.2. Computational Analysis. Many different computational methods have been used to investigate the reactivity of (η^3-allyl)Pd complexes.[23] In these calculations it is found that the transition state is unusually sensitive to the nature of the solvent employed.[24] To minimize such solvent related issues, we employ a neutral model nucleophile (ammonia) reacting with a cationic (η^3-allyl)Pd(PPh_3)$_2$ complex to yield a cationic allyl ammonium product coordinated to a neutral $Pd^0(PPh_3)_2$ moiety. This procedure maintains the overall charge, minimizing computational artifacts arising from imperfect solvation of complexes with different charges.[12] All calculations were performed in Jaguar[25] with B3LYP-D3, which uses the dispersion-correction of Grimme and co-workers[26] together with the classical B3LYP functional.[27] We utilized the LACVP* basis set[28] and PBF solvation[29] with default parameters for THF.

We located the approximate "transition states" by scanning the forming C–N bond distance while relaxing all other coordinates in the presence of the continuum solvent. This technique has been successful for very similar systems,[30] and is expected to yield final transitions state energies within a few kJ mol^{-1} of the expected fully converged values.[31] The final structures were also subjected to traditional transition state searching, but numerical component in solvated Jaguar calculations makes the energy surface discontinuous with small bumps that tend to negatively impact the transition search algorithm. The energy profile is also unusually flat, with changes of only a few kJ mol^{-1} over a 0.2–0.3 Å span in reaction coordinate (here taken as the forming C–N bond distance). Thus, the transition state search results differed depending on the starting point, by up to 4 kJ mol^{-1}. Furthermore, the final frequency calculation always yielded 2–3 additional imaginary frequencies, with wavenumbers up to 31 cm^{-1}. However, the reaction coordinate was always well defined, with imaginary frequencies in the range 106–207 cm^{-1}, and on visualization, this vector always corresponded well with the expected attack of the nucleophile on an allyl terminus. Qualitatively, the results from the full TS searches and the scans were the same, and numerically, the final energies were within a few kJ mol^{-1} from each other. Due to the uncertainty in the former, the energies reported herein come from the scan approach.

All transition states were fully validated by QRC calculations.[32] For the scans, the QRC was implemented by minimizing the end points on the scan and verifying that they corresponded to pre-reactive complex and an allyl ammonium complex, respectively. For the results from the TS searches, the starting points for the minimizations were constructed by distortion along the Cartesian eigenvector corresponding to the reaction coordinate, scaled by 0.3.

It has been previously demonstrated that the regioselectivity in Pd-catalyzed allylic substitution can be rationalized by considering the geometry of the intermediate η^3-allyl palladium complex,[16] and in particular the steric constraints along the path of the incoming nucleophile.[17] This rational has been successfully applied to both mono- and 1,3-disubstituted η^3-allyl complexes, the latter including a highly relevant cationic (η^3-1-phenyl-3-methyl-allyl)PdL_2 intermediate.[17] Steric interactions between the ligand and allyl moieties caused a rotation of the allyl towards a product-like conformation. Such a rotation could selectively elongate one Pd–C bond, thereby increasing its reactivity. Both of these factors are known to influence the regioselectivity of the nucleophilic attack.[17] We are unaware, however, of previously considered cases in which the regioselective benzylic attack dominates. We therefore calculated the structures of intermediates for a few model systems to rationalize the observed behavior. To avoid extensive conformational searching, we performed the computational study on the smallest relevant system, cationic (η^3-1-Ph-2-B(pin)-3-Me-allyl)Pd(PPh_3)$_2$.

We first considered three possible intermediates (Figures 2 and 3). In the absence of ligand-allyl interactions, the dominant structure-determining factor in (η^3-allyl)Pd complexes is the repulsion between the substituent and Pd. Due to the tilt of η^3-allyl moiety, an *anti*-substituent is much closer to Pd than a *syn*-substituent, as can be seen in representative X-ray structures with both *syn* and *anti* aryl moieties.[33] Measuring the distances from Pd to the aryl substituent ipso-carbons, the *anti*-aryls are closer to Pd by ca. 0.3 Å, and are clearly within the repulsive region. For this reason, unencumbered complexes almost exclusively prefer the less encumbered *syn* configuration. However, the preference can be shifted by ligands that protrude into the η^3-allyl coordination plane. For example, 2,9-dicyano-1,10-phenanthroline, which selectively interferes with *syn*-methyl groups in crotyl complexes, shifts the preference to *anti*.[13] The last important interaction is the repulsion between a 2-substituent and a *syn*-substituent. There are X-ray structures showing the

anti preference of alkyl groups in such complexes.[13] For aryl groups, the preference for *syn* isomer is stronger; the *syn*-aryl is much more in the allyl plane, and therefore better conjugated to the η^3-allyl. Phenyl groups in *anti* position also suffer from a severe 1,3-allylic strain with the hydrogen in the opposing position, causing the aryl to rotate and further reduce conjugation. Thus, *anti*-allyl groups are virtually only observed in (η^3-1,1-diphenyl allyls), where one of the phenyls must be *anti*. It is from such structures we can see the interactions in X-ray (mostly 1,1,3-triphenyl).[34] Togni has suggested that a phenyl that can adopt the *syn* or *anti* position, prefers *anti* when a very hindered ligand is employed.[34] Moreover, Faller and co-workers generalized that steric factors of substitutions on allyl moieties can change the ratio of *syn* and *anti* isomers in cationic (η^3-1,2-disubstituted allyl)Pd and (η^3-1,2,3-trisubstituted allyl)Pd intermediates.[35] Their studies demonstrate that bulky substitution on C-2 can force generation of the *anti*-allyl palladium intermediate. Additionally, the *anti* geometry of the (η^3-1-B(pin)-2-Ph-allyl) palladium complex was isolated by Yoshida and co-workers.[36] Therefore, 1-*syn*-3-*anti* **INT-3** (Figure 2) is considered the most stable intermediate, whereas 1-*anti*-3-*syn* **INT-2** is less stable than 1-*syn*-3-*syn* **INT-1**.

Next, we performed the calculation of transition states. The initial results using the 1-*syn*-3-*syn* **INT-1** indicated attack distal to the C-1-aryl group to be favored through **TS-2** by 4 kJ mol^{-1} over attack at the benzylic position through **TS-1** (Figures 2 and 3). We, therefore, broadened our calculation to include attack on 1-*anti*-3-*syn* **INT-2** and 1-*syn*-3-*anti* **INT-3** via **TS-3** and **TS-4**, respectively. A Curtin-Hammett scenario should be considered in this reaction. It is known that (η^3-allyl)Pd intermediates can rapidly equilibrate before the addition of nucleophile.[9] This is important in most enantioselective allylic substitution reactions.[5,37] If the rate of isomerization among **INT-1**, **INT-2**, and **INT-3** is fast, the more reactive **INT-2** will predominantly lead to **TS-3** instead of **TS-4** to afford the benzylic substitution product **2**. Surprisingly, despite the higher energy of 1-*anti*-3-*syn* **INT-2**, attack at the *anti*-position of 1-*anti*-3-*syn* **INT-2** was found to be favored, with a free energy of activation of only 47 kJ mol^{-1} relative to 1-*syn*-3-*anti* **INT-3** and leading to the observed major product. The next lowest path was attack at the *anti*-configured position of 1-*syn*-3-*anti* **INT-3** through **TS-4**, leading to the minor product. This pathway is only 6 kJ mol^{-1} higher in energy than **TS-3**. It is well established that *anti*-complexes are more reactive than *syn*-complexes toward nucleophilic attack.[10d,13] One reason for this is that, in general, the *syn*-substituent is pushed away from the metal, into the path of the nucleophile. This ground state affect is more severe in the presence of a 2-substituent and raises the energy of attack at the *syn*-substituted carbon, as reflected in Figure 3.

In transition states **TS-1** and **TS-3** (Figures 2 and 3), the distances between the ammonia nucleophile and C-1 is 2.72 Å in **TS-1** vs. 2.87 Å in **TS-3**. For the small NH_3 nucleophile, there is little repulsive interaction, however, larger nucleophiles will encounter more severe steric interactions in the TS. A more important effect arises upon elongation of the Pd–C bond in the TS. This elongation alleviates the repulsion between Pd and an *anti*-substituent. In contrast, the rehybridization on nucleophilic attack pushes the *syn* substituent down into the ligand, resulting in destabilization. Furthermore, the conjugation penalty that was found for 1-*anti*-3-*syn* **INT-2** is much less severe in **TS-3**, because most of the penalty has already been paid in formation of the *anti*-isomer (the aryl ring is rotated away from the plane of the allyl to avoid clashing with the *anti*-hydrogen at C-3). These combined effects lead to a drastic lowering of barriers to attack at *anti*-positions (**TS-3** and **4**) compared to *syn*-positions (**TS-1** and **2**), such that the energy for the *anti*-addition **TS** is lower despite the preceding intermediate being high in energy (Curtin-Hammett principle). The calculated 6 kJ mol^{-1} difference is similar to the observed >20:1 regioselectivity, which would correspond to ca. 8 kJ mol^{-1} difference in allylic alkylation reaction (Table 1) with a malonate nucleophile. It is in even better agreement with the ~10:1 regioselectivity that corresponds to ca. 6 kJ mol^{-1} in allylic amination reaction (Scheme 3).

It is also important that *allylic substitution products with the (Z)-olefin geometry* have not been detected in any of experiments outlined here. This clearly shows that any *anti*,*syn*-complexes are attacked exclusively at the *anti*- position, and also that *anti*,*anti*-complexes do not play a role in this chemistry, in good agreement with earlier studies.[10d,13,16-17]

Scheme 3. Palladium-catalyzed Allylic Amination Reaction with 2-B(pin)-Substituted Allylic Acetates[21]

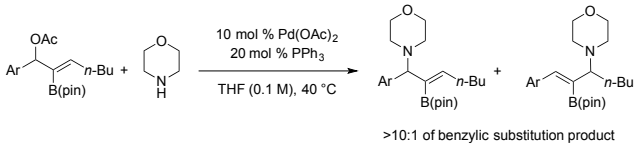


Figure 2. Four possible reaction paths for nucleophilic addition of ammonia to 1-phenyl-2-B(pin)-3-alkyl substituted η^3-allyls.

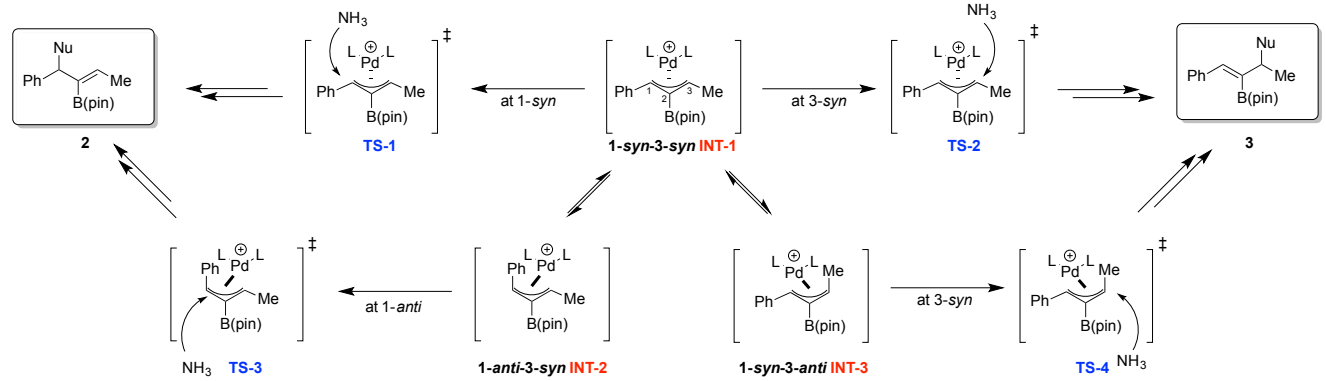
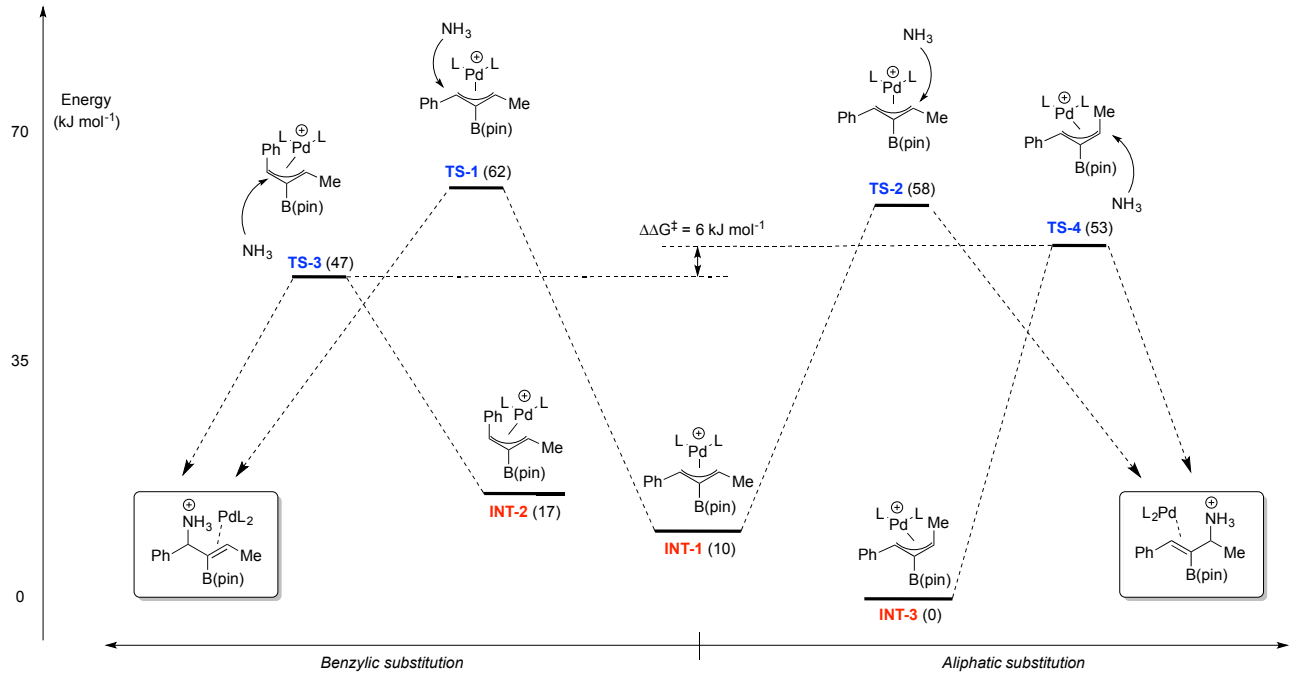


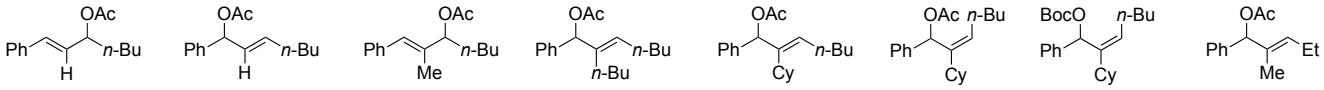
Figure 3. Calculated energy diagram for allylic substitution leading to benzylic and aliphatic substitution products. Values in parentheses are the energies relative to 1-*syn*, 3-*anti* **INT-3**.



2.3. Factors Controlling Regioselectivity with 2-alkyl substituted allylic acetates and carbonates. To determine the generality of the conclusions drawn from the unusual regioselectivity with 2-B(pin)-substituted allylic acetates, we prepared a series of 1,3-di- and 1,2,3-trisubstituted allylic acetates and carbonates. The stereodefined di- or trisubstituted allylic acetates and carbonates synthesized for this study include the parent derivatives, bearing a 2-hydrogen (**1f** and **1g**), and the 2-methyl (**1h** and **1m**), 2-*n*-butyl (**1i**), and 2-cyclohexyl (**1j–l**) derivatives (Chart 1). The synthesis of these compounds is described in the Supporting Information.

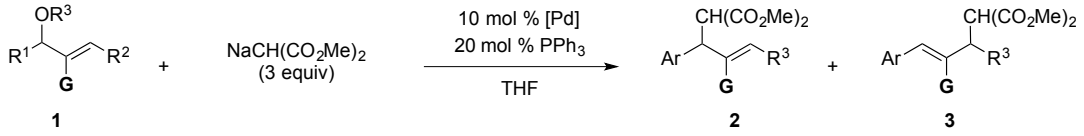
We conducted the allylic substitution reactions with the substrates in Chart 1 under the condition in Table 1. The results of this study are presented in Table 2. When subjected to catalyst generated from 10 mol % $Pd(OAc)_2$/20 mol % PPh_3 with 3 equiv of $NaCH(CO_2Me)_2$ at 40 °C the parent allylic acetate **1f (G** = H) cleanly underwent allylic substitution with nucleophilic attack distal to the aryl group with high regioselectivity (10:90) in 85% yield (Table 2, entry 1). As a control experiment, we employed the isomeric allylic acetate **1g**, which resulted in formation of the same allylic substitution product **3f** with very similar regioselectivity (9:91) in 95% yield (entry 2), confirming the absence of memory effects in this system. These results can be contrasted with the 2-B(pin)-substituted allylic acetates **1a–e**, which underwent attack at the benzylic position with high regioselectivity (>90:10, Table 1). Additionally, a catalyst precursor from $[Pd(allyl)Cl]_2$/$4PPh_3$ resulted in formation of the same allylic substitution product **3f** with slightly diminished regioselectivity (17:83) in 87% yield (entry 3). The same reaction at 25 °C provided similar regioselectivity 16:84 in 87% yield (entry 4). Unfortunately, no reaction occurred with sodium dimethylmalonate and 2-methyl-substituted allylic acetate **1h** under the identical condition using $Pd(OAc)_2$ as a catalyst precursor, highlighting the impact on reactivity of an alkyl at the 2-position (Table 2, entry 5). In the presence of catalytic $[Pd(allyl)Cl]_2$/$4PPh_3$ and 3 equiv of $NaCH(CO_2Me)_2$ in THF at 40 °C, however, the 2-methyl substrate **1h** provided the allylic substitution product with regioselectivity of 63:37 favoring benzylic attack and forming predominantly regioisomer **2h** (entry 6). While the Pd-catalyzed allylic substitution with stabilized carbon nucleophiles is usually irreversible and under kinetic control, dialkyl malonates can act as leaving groups at higher temperature and longer reaction times and product formation can be under thermodynamic control.[38] To investigate this possibility, reaction of **1h** at 40 and 70 °C with longer reaction times did not result in significant changes in the regioselectivities (entries 7 and 8). Furthermore, control experiments showed that the reaction of the mixture of **2h** and **3h** (63:37) in the presence of catalytic $[Pd(allyl)Cl]_2$/$4PPh_3$ and 3 equiv of $NaCH(CO_2Bn)_2$ in THF at 40 °C or 70 °C led to recover the same ratio of **2h** and **3h** without any detectable amount of corresponding substitution products from $NaCH(CO_2Bn)_2$.[39] The larger 2-*n*-butyl substituted allylic acetate **1i** resulted in increased benzylic attack with regioselectivity of 81:19 of **2i**:**3i** (entries 9 and 10). After observing a switch in regioselectivity upon changing the size of substituent at the 2-position, we employed the larger 2-cyclohexyl group to further explore this trend. Substrate **1j** underwent reaction with $NaCH(CO_2Me)_2$ and catalyst generated from $[Pd(allyl)Cl]_2$ or $Pd(OAc)_2$ to afford predominantly product **2j** via benzylic attack with regioselectivities of 84:16 and 86:14, respectively (entries 11–13). It is noteworthy that benzylic acetate **1j** is more reactive

Chart 1. Substrates for probing the impact of the 2-substituent on the allylic substitution

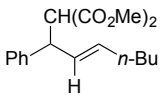
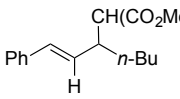
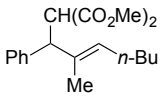
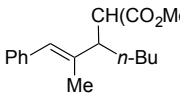
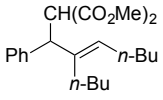
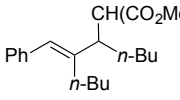
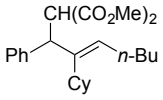
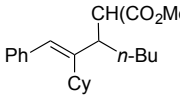
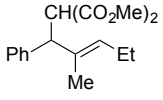
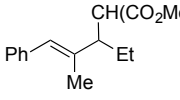


1f **1g** **1h** **1i** **1j** **1k** **1l** **1m**

Table 2. Probing Regioselectivity with 2-Alkyl Substituted Allylic Acetates[a]



1 **2** **3**

entry	acetate	[Pd]	temp (°C)	time (h)	yield[b] (%)	ratio[c] of **2**:**3**	**2**	**3**
1[d]	**1f**	$Pd(OAc)_2$	40	12	85[e]	10 : 90		
2	**1g**	$Pd(OAc)_2$	40	12	95[e]	9 : 91		
3	**1g**	$[Pd(allyl)Cl]_2$	40	0.5	87	17 : 83		
4	**1g**	$[Pd(allyl)Cl]_2$	25	0.5	83	16 : 84		
5	**1h**	$Pd(OAc)_2$	40	3	nr[e,f]	– : –		
6	**1h**	$[Pd(allyl)Cl]_2$	40	3	88	63 : 37		
7	**1h**	$[Pd(allyl)Cl]_2$	40	24	79	63 : 37		
8	**1h**	$[Pd(allyl)Cl]_2$	70	24	65	64 : 36		
9	**1i**	$[Pd(allyl)Cl]_2$	40	8	75	81 : 19		
10	**1i**	$[Pd(allyl)Cl]_2$	70	8	20	81 : 19		
11	**1j**	$Pd(OAc)_2$	40	24	68	86 : 14		
12	**1j**	$[Pd(allyl)Cl]_2$	40	24	61	84 : 16		
13	**1j**	$[Pd(allyl)Cl]_2$	70	24	15	84 : 16		
14	**1k**	$[Pd(allyl)Cl]_2$	40	24	nr[f]	– : –		
15	**1l**	$[Pd(allyl)Cl]_2$	40	24	5	83 : 17		
16	**1m**	$Pd(OAc)_2$	40	4	90	53 : 47		
17	**1m**	$[Pd(allyl)Cl]_2$	40	24	56	53 : 47		

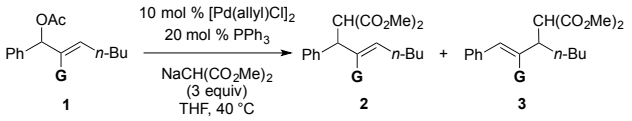
[a] See the Supporting Information for experimental details. [b] Yield of purified and isolated products. [c] Ratios determined by ^1H NMR spectroscopy of unpurified reaction mixtures. [d] Reference 21. [e] 5 mol % [Pd]. [f] No reaction.

with the $Pd(OAc)_2$-based catalyst than aliphatic acetate **1h**, which did not react with this catalyst (as noted earlier). To investigate the impact of allylic acetate geometry on product distribution we inverted the geometry of the allylic acetate substrate from the (*E*)-alkene to the (*Z*)-alkene. Unfortunately, (*Z*)-trisubstituted allylic acetate **1k** exhibited no reaction under the same condition (entry 14). Apparently, the sterically more hindered (*Z*)-alkene does not allow the formation of allyl palladium intermediate. It is known that allylic carbonates are more reactive than their acetate counterparts by about 2 orders of magnitude.[40] Using more reactive allylic carbonate **1l** led to only 5% isolated yield of the allylic substitution product **2j** with 83:17 regioselectivity (entry 15). Thus, regardless of (*E*)- or (*Z*)-geometry of the starting materials, the benzylic substitution products with (*E*)-configuration were observed (entries 12 and 15). The close regiochemical agreement from both (*E*)- and (*Z*)-substrates

strongly supported a rapid isomerization of sterically hindered 1,2,3-trisubstitued allyl palladium intermediates before the nucleophilic addition step. It is noteworthy that the smaller 3-ethyl substituted allylic acetate **1m** provided allylic substitution products with 53:47 ratio (entries 16 and 17). The investigation of the impact of size at the C-2 position revealed a tendency for the benzylic substitution product with increasing size of the C-2 substituent.

Steric effects in organic chemistry can be quantified by a range of methods, from simple A-values of substituents to explicit modeling. For the Tsuji-Trost reaction, steric influences on the activation barrier have been modeled using explicit probes.[17] More recently, Sigman and co-workers[41] demonstrated that selectivities in the Tsuji-Trost reaction can be reproduced using a linear correlation with Charton steric parameters.[42] We therefore attempted a correlation between the Charton value of the 2-substituents and the logarithm of the observed regioselectivity, as shown in Table 3. Consideration of this steric parameter quantitatively revealed its strong linear free energy relationship in Figure 4 (slope Ψ = 1.70 and R^2 = 0.97), supporting our contention that the effect we observed is due to steric effect. Our modeling studies indicate that the repulsion with the 2-substituents has a strong influence on the relative importance of *anti*- and *syn*-configured (η^3-allyl)palladium intermediates, and thus on the regioselectivity.

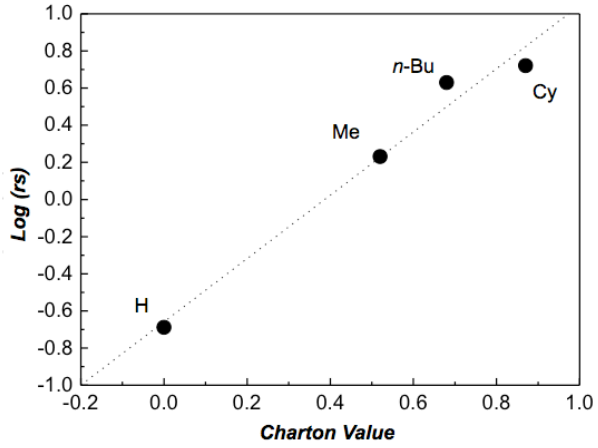
Table 3. Quantitative Analysis of Regioselectivity versus Charton Parameter of C-2 Substituent



entry	G	Charton Value of G	ratio of **2**:**3**	log (*rs*)[a]
1	H	0	17:83	–0.689
2[b]	Me	0.52	63:37	0.230
3	*n*-Bu	0.68	81:19	0.629
4	Cy	0.87	84:16	0.754

[a] logarithm of ([**2**]/[**3**]). [b] **1h** was used, instead of the regioisomer shown here.

Figure 4. Plot of logarithm of ratio of regioisomers versus Charton steric parameters of the C-2 substituents in the Pd-catalyzed allylic substitution reactions.



2.4. Palladium-Catalyzed 1,4-Elimination Reaction of 1,2,3-Trisubstituted Allylic Acetates. The palladium-catalyzed elimination reaction of allylic acetates is a useful method to form 1,3-dienes.[43] Palladium(0) mediated ionization of allylic acetates **1** forms η^3-allyl palladium(II) intermediates **5** (Scheme 3). Allyl palladium(II) regenerates palladium(0) via *anti*- or *syn*-elimination to furnish 1,3-dienes **4**.[44] Consistent with this proposed reaction pathway, we observed varying amounts of elimination byproducts (^{1}H NMR) in unpurified reaction mixtures with 2-*n*-butyl allylic acetate **1i** and 2-cyclohexyl allylic acetates **1j** (Table 2, entries 9–13). Under the same condition, the smaller 2-methyl allylic acetate **1h** did not produce elimination byproducts (^{1}H NMR).

Scheme 3. Plausible Mechanism of Allylic Acetates to Form 1,3-Dienes

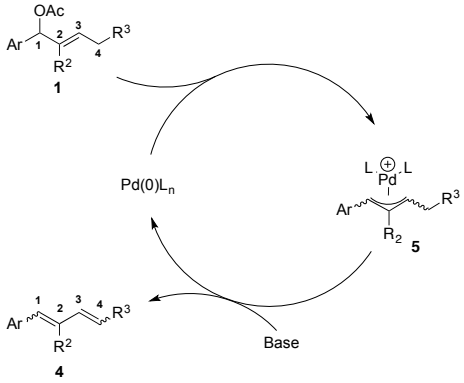
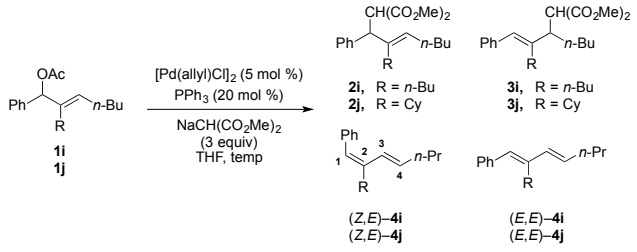


Table 4. Palladium-Catalyzed 1,4-Elimination of Allylic Acetates **1i** and **1j**



entry	acetate	R	temp (°C)	allylic substitution yield[a] (%)	allylic substitution **2**:**3**[b]	elimination yield[a] (%)	elimination (*Z*,*E*):(*E*,*E*)[b]
1	**1i**	*n*-Bu	40	83	81:19	17	24:76
2	**1i**	*n*-Bu	70	20	81:19	67	27:73
3	**1j**	Cy	40	61	84:16	22	85:15
4	**1j**	Cy	70	15	N/A	70	86:14

[a] Yield of purified and isolated products. [b] Ratios determined by ^{1}H NMR spectroscopy of unpurified reaction mixtures.

Inspired by these observations, allylic acetates **1i** and **1j** were reexamined in the allylic substitution reaction and 1,3-dienes were isolated at 40 °C in 17 and 22% yield, respectively (Table 4, entries 1 and 3). The ratios of dienes were determined by ^{1}H NMR spectroscopy of unpurified reaction mixtures and the stereochemistry of the dienes was confirmed by comparison to similar known compounds. In the reactions above, the ratios of (*Z*,*E*) and (*E*,*E*) isomers were 24:76 for **4i** and 85:15 for **4j**. At 70 °C little change in the regioselectivity of allylic substitution products or ratio of (*Z*,*E*) to (*E*,*E*) elimination products were observed. However, at 70 °C 1,3-dienes **4** were the major products. At 70 °C, 2-*n*-butyl allylic acetate **1i** provided the allylic substitution product in 20% isolated yield with the same regioselectivity (81:19). The 1,4-elimination product was isolated in 67% yield with similar diene ratio to reaction at 40 °C [(*Z*,*E*)-**4i** : (*E*,*E*)-**4i** = 27 : 73, Table 4, entry 2]. The 2-cyclohexyl allylic acetate **1j** resulted in formation of 15% of allylic substitution products and 70% yield of 1,4-elimination product also with a similar ratio of isomers [(*Z*,*E*)-**4j** : (*E*,*E*)-**4j** = 86:14, Table 4, entry 4]. It is noteworthy that only two geometric isomers of 1,3-dienes were observed among four possible isomers.

Very importantly, the observation of 1,2-(*Z*)-configured diene indicates the presence of a 1-*anti*-η^3-allyl complex as a reactive intermediate.[44h] Irrespective of the mechanism of elimination (E2 or β-hydride elimination), the (*Z*,*E*)-product can arises from an intermediate with the phenyl substituent in the *anti*-position of the (η^3-allyl)Pd intermediate. This observation lends further support to our interpretation that *anti*-configured intermediates are important in the nucleophilic attack. The newly formed double bond in 3,4-position can be formed from either intermediate, with a configuration controlled by preferred orientation of the 3,4 single bond in the intermediate.[45] Allylic strain would thus favor the 3,4-(*E*)-configuration of the diene products, in full agreement with our observations.

3. Summary and outlook

We have investigated the unusual regioselectivity of the palladium-catalyzed Tsuji-Trost allylic substitution reaction with 1,2,3-trisubstituted allylic substrates. With 1,3-unsymmetrically substituted 2-B(pin)-allylic acetates, the boryl group plays a pivotal role in determining the regioselectivity of the allylic substitution reaction. The unsymmetrical 2-B(pin)-substituted allylic acetates show preference for nucleophilic attack at the *benzylic site*, which is opposite to the expected regioselectivity in Tsuji-Trost allylic substitution reactions with (η^3-1-aryl-3-alkyl-allyl)Pd intermediates. A computational study of the mechanism responsible for regioselectivity with cationic (η^3-1-Ph-2-B(pin)-3-Me-allyl)Pd(PPh_3)$_2$ indicates that the unusual regioselectivity is controlled by the relative reactivity of the *syn*- and *anti*-oriented allylic termini. Through systematic studies involving variation of the size of the C-2 substituent, we demonstrated that the bulkier the group at the 2-position of 1-aryl-2,3-disubstituted η^3-allyl intermediates, the greater propensity for nucleophilic attack at the benzylic position. The use of Charton steric parameters led to a strong correlation between the size of the C-2 substituent and the regioselectivity of nucleophilic attack at the corresponding η^3-allyls. Based on the working models garnered from computational and experimental studies, we attribute this selectivity to the repulsion between the 1- and 2-substituents, forcing the 1-aryl group into a reactive *anti*-position through rapid *syn*-*anti* isomerization.

Finally, palladium-catalyzed 1,4-elimination reactions of allylic acetates also support the presence of the *anti*-oriented allyl palladium intermediates. These results contribute to our fundamental understanding of regioselectivity in Tsuji-Trost allylic substitution reactions and will be useful in their predictive power in the application of this chemistry to synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details, full characterization of new compounds, and calculated structures and energies]. See DOI: 10.1039/b000000x/

1 (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

2 (a) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (c) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Ed.; Springer: Berlin, Germany, 1999; Vol. 2, p 833. (e) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (f) Hegedus, L. S.; Söderberg, B. C. G. *Transition Metals in the Synthesis of Complex Organic Molecules*; 3rd ed.; University Science Books: Sausalito, 2009.

3 (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1997. (b) Trost, B. M.; Fandrick, D. R. *Aldrichim. Acta* **2006**, *40*, 59.

4 (a) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3416. (b) Norsikian, S.; Chang, C. W. *Current Organic Synthesis* **2009**, *6*, 264. (c) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C. In *Top. Organomet. Chem.*; Kazmaier, U., Ed.; Springer-Verlag: Berlin, Heidelberg, 2011; Vol. 38, p 1.

5 Hartwig, J. F. *Organotransition Metal Chemistry – From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010.

6 (a) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769. (b) Zhang, J.; Stanciu, C.; Wang, B.; Hussain, M. M.; Da, C.-S.; Carroll, P. J.;

Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 20552. (c) Fiaud, J.-C.; Legros, J. Y. *J. Org. Chem.* **1987**, *52*, 1907.

7 (a) Granberg, K. L.; Baeckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (b) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417.

8 Pedersen, T. M.; Hansen, E. L.; Kane, J.; Rein, T.; Helquist, P.; Norrby, P.-O.; Tanner, D. *J. Am. Chem. Soc.* **2001**, *123*, 9738.

9 (a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

10 (a) Poli, G.; Scolastico, C. *Chemtracts* **1999**, *12*, 822. (b) Ogasawara, M.; Takizawa, K.-i.; Hayashi, T. *Organometallics* **2002**, *21*, 4853. (c) Faller, J. W.; Wilt, J. C. *Organometallics* **2005**, *24*, 5076. (d) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem. Eur. J.* **2006**, *12*, 5352.

11 Gouriou, L.; Lloyd-Jones, G. C.; Vyskocil, S.; Kocovský, P. *J. Organomet. Chem.* **2003**, *687*, 525.

12 Svensen, N.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Adv. Synth. Cat.* **2007**, *349*, 2631.

13 Sjögren, M.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954.

14 (a) Åkermark, B.; Zetterberg, K.; Hansson, S.; Krakenberger, B.; Vitagliano, A. *J. Organomet. Chem.* **1987**, *335*, 133. (b) Branchadell, V.; Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *Organometallics* **1999**, *18*, 4934. (c) Malet, R.; Moreno-Mañas, M.; Parella, T.; Pleixats, R. *Organometallics* **1995**, *14*, 2463. (d) Moreno-Mañas, M.; Pajuelo, F.; Parella, T.; Pleixats, R. *Organometallics* **1997**, *16*, 205.

15 (a) Tanikaga, R.; Jun, T. X.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1185. (b) Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 4351.

16 Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.

17 Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015.

18 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

19 (a) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (b) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683. (c) Kazmaier, U.; Zumpe, F. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 1468. (d) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Williams, J. M. J. *Org. Lett.* **1999**, *1*, 1969. (e) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Mosconi, E.; Tolomelli, A. *Org. Lett.* **2008**, *10*, 2425.

20 (a) Li, H.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 3521. (b) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516. (c) Hernández Toribio, J.; Hussain, M. M.; Cheng, K.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 6094. (d) Hussain, N.; Hussain, M. M.; Ziauddin, M.; Triyawatanyu, P.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 6464. (e) Hussain, M. M.; Hernández Toribio, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 6337.

21 Hussain, M. M.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 1834.

22 (a) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, *48*, 3305. (b) Touchet, S.; Carreaux, F.; Molander, G. A.; Carboni, B.; Bouillon, A. *Adv. Synth. Cat.* **2011**, *353*, 3391. (c) Kukkadapu, K. K.; Ouach, A.; Lozano, P.; Vaultier, M.; Pucheault, M. *Org. Lett.* **2011**, *13*, 4132.

23 Kleimark, J.; Norrby, P.-O. In *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*; Kazmaier, U., Ed.; Springer-Verlag Berlin: Berlin, 2012; Vol. 38, p 65.

24 Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem. Eur. J.* **1999**, *5*, 902.

25 Jaguar, v., Schrodinger, LLC, New York, NY, **2011**. For current versions, see: http://www.schrodinger.com.

26 Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.

27 (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Chem. Phys.* **1994**, *98*, 11623.

28 Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

29 (a) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Chem. Phys.* **1996**, *100*, 11775. (b) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Honig, B.; Ringnalda, M.; Goddard, I. I. I. W. A. *J. Am. Chem. Soc.* **1994**, *116*, 11875.

30 Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

31 Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem. A* **2008**, *112*, 12862.

32 Goodman, J. M.; Silva, M. a. A. *Tetrahedron Lett.* **2003**, *44*, 8233.

33 (a) Farrar, D. H.; Payne, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 2054. (b) Togni, A.; Rihs, G.; Pregosin, P. S.; Ammann, C. *Helv Chim Acta* **1990**, *73*, 723.

34 Burckhardt, U.; Gramlich, V.; Hofmann, P.; Nesper, R.; Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1996**, *15*, 3496.

35 (a) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. (b) Faller, J. W.; Tully, M. T.; Laffey, K. J. *J. Organomet. Chem.* **1972**, *37*, 193. (c) Faller, J. W.; Tully, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 2676.

36 Tonogaki, K.; Itami, K.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2006**, *128*, 1464.

37 Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, 2008.

38 Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.

39 Two types of control experiments were investigated. There were no detectable change of the ratio of 2h and 3h in the presence of $[Pd(allyl)Cl]_2/4PPh_3$ with or without 3 equiv of $NaCH(CO_2Bn)_2$.

40 Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471.

41 Sigman, M. S.; Miller, J. J. *J. Org. Chem.* **2009**, *74*, 7633.

42 (a) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615. (b) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552. (c) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3691. (d) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3694.

43 (a) Tsuji, J. *Palladium Reagents and Catalysts : Innovations in Organic Synthesis*; Wiley, John & Sons, Incorporated: Chichester, 1995. (b) Shimizu, I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2002; Vol. 2.

44 (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075. (b) Trost, B. M.; Verhoeven, T. B.; Fortunak, J. M.; McElvain, S. M. *Tetrahedron Lett.* **1979**, *20*, 2301. (c) Takashi, T.;

Naoshi, N.; Tooru, M.; Hisao, Y.; Jiro, T. *Tetrahedron Lett.* **1990**, *31*, 4333. (d) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513. (e) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151. (f) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1. (g) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956. (h) Schwarz, I.; Braun, M. *Chem. Eur. J.* **1999**, *5*, 2300. (i) Takenaka, H.; Ukaji, Y.; Inomata, K. *Chemistry Letters* **2005**, *34*, 256. (j) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Dalton Transactions* **2007**, 3710.

45 Hauser, F. M.; Tommasi, R.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1988**, *53*, 4886.