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ARTICLE *in* CHEMISTRY · JULY 2006

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Deconvoluting the Memory Effect in Pd-Catalyzed Allylic Alkylation: Effect of Leaving Group and Added Chloride

Peter Fristrup, Thomas Jensen, Jakob Hoppe, and Per-Ola Norrby*[a]

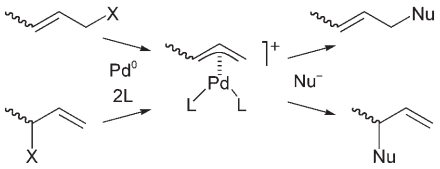
Abstract: An analysis of product distributions in the Tsuji–Trost reaction indicates that several instances of reported "memory effects" can be attributed to slow interconversion of the initially formed *syn*- and *anti*-[Pd(η^3-allyl)] complexes. Addition of chloride triggers a true memory effect, in which the allylic terminus originally bearing the leaving group has a higher reactivity. The latter effect, termed *regioretention*, can be rationalized by ionization from a palladium complex bearing a chloride ion, forming an unsymmetrically substituted [Pd(η^3-allyl)] complex. DFT calculations verify that the position *trans* to the phosphine ligand is more reactive both in the initial ionization and in the subsequent nucleophilic attack.

Keywords: allylic compounds · halide effect · homogeneous catalysis · memory effect · palladium

Introduction

The palladium-catalyzed allylic alkylation (Tsuji–Trost reaction) is a popular tool in modern organic synthesis. The reaction has been the subject of numerous reviews,[1] and in particular the asymmetric version has received much recent attention.[2] The generally accepted mechanism involves complexation with Pd(0), displacement of an allylic leaving group (X) leading to the formation of an [Pd(η^3-allyl)] species, and finally, attack by nucleophiles at either terminus of the allyl moiety, releasing Pd(0) and closing the catalytic cycle.

From this mechanism it can be predicted that two isomeric allylic substrates that can yield the same intermediate, such as the isomeric allylic substrates shown in Scheme 1, or enantiomeric substrates leading to the same symmetric intermediate, should yield the same product distribution. However, more than two decades ago, Fiaud and Malleron reported that enantioenriched cyclohexenyl acetate yields product with partial retention of the optical activity, in conflict with the accepted mechanism.[3] The experimental results were immediately questioned by Trost[4] and later also by Bosnich.[5] However, a substrate-dependent product distribution that cannot be rationalized by using a single common intermediate has been noted on several occasions, in particular for unsymmetrically substituted allyls,[6–8] and the term "memory effect" has sometimes been applied to this phenomenon. The mechanism of the memory effect has been studied,[9–12] and is in many cases well understood. Particularly clear cases can be noted in the presence of chiral ligands,[9,11,12] in which initial ionization can give different points of entry into the [Pd(η^3-allyl)] manifold for enantiotopic substrates. Another important class of memory effects is observed upon formation of unsymmetrically substituted η^3-allyls, for which the product distribution can be dependent on both the regio- and stereochemistry of the starting material. The latter class can be observed also with nonchiral ligands,[8] and is the subject of the current study. In reactions involving monosubstituted [Pd(η^3-allyl)] intermediates, three isomeric starting materials (*cis*, *trans*, and internal) can lead to two isomeric [Pd(η^3-allyl)] moieties (*syn* and *anti*) that can equilibrate and, in turn, can produce three isomeric products (Scheme 2).[8]



Scheme 1. Basic mechanism for the Tsuji–Trost reaction.

It has been suggested[5] that the fast dynamics of the [Pd(η^3-allyl)] intermediate[13] will equilibrate all allyl intermediates. However, a series of papers from the Åkermark group clearly showed that the isomerization can, in some instances,

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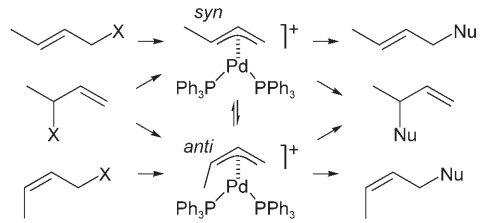


Scheme 2. Isomers in the Tsuji–Trost reaction of butenyl substrates.

be rendered slow enough to allow isolation of pure *syn* and *anti* configurations of the [Pd(η^3-allyl)] complexes, and furthermore, that the reactivities of these configurations differ considerably.[8] In short, nucleophilic attack is disfavored at *syn*-substituted positions.[8] In the reaction depicted in Scheme 2, the *anti* complex produces *cis* linear and branched products in almost equal amounts as the reactivities of the two termini are similar, whereas the *syn* complex gives predominantly the *trans* linear product.[8] Thus, it is clear that slow equilibration of the intermediate will give rise to memory effects.[14,15] A *trans* substrate must ionize initially to a *syn* complex (usually, but not always, the most stable isomer[16]) that will then give preferential formation of *trans* product, due to the inherent reactivity difference between the *syn*-substituted and -unsubstituted termini. A *cis* substrate, on the other hand, ionizes to the *anti* complex, and usually yields a mixture of products, depending on the particular substituent and the rate of isomerization. Finally, the branched substrate would be expected to give a result intermediate between that of the *cis* and *trans* substrates, entirely dependent on the initial ionization preference (*anti*/*syn*). In fact, if no memory effects beyond those implied in Scheme 2 are active, the product distribution obtained from the branched substrate must be a linear combination of the distributions obtained by using *cis* and *trans* substrates. We propose that by investigating the product distribution from each of the three isomeric substrates in Scheme 2, it is possible to elucidate the degree of isomerization of the intermediate and the ionization preference of the branched substrate, as well as to detect memory effects not included in Scheme 2 by deviations from the linear relationship between the three product distributions. Herein, we use the term *stereoretention* for unequal product distributions caused by slow isomerization between *syn* and *anti* complexes. Experimentally, this is detected by comparing the distribution of linear products from *cis* and *trans* linear substrates, respectively (any branched product can be ignored in this analysis). If the *cis* and *trans* substrates yield identical linear-product distributions, there is no stereoretention. Conversely, if there is no crossover, that is, if only *cis* linear product is obtained from *cis* substrate and *trans* linear product is obtained from *trans* substrate, we have full stereoretention. We expect additives that increase the rate of isomerization of the [Pd(η^3-allyl)] intermediate, such as halides,[13] to decrease the degree of stereoretention.

The "memory effect" has been frequently rationalized in terms of an unsymmetrical reactivity in the [Pd(η^3-allyl)] intermediate, favoring reactivity of the terminus that was connected to the leaving group before initial ionization. Many explanations for the reactivity difference between the termini have been advanced, including a tight ion pair with the leaving group,[12] reaction through [Pd(η^1-allyl)] intermediates,[17] and unequal *trans* effects arising from unsymmetrical ligation.[18] In the case in which chiral ligands are employed, the available evidence indicates that enantiotopic substrates ionize to diastereomeric [Pd(η^3-allyl)] intermediates, in which the interactions of the chiral ligand with the allyl moiety lead to differences in reactivity and, thus, to unequal product distributions.[9] In nonchiral systems, attention has focused on branched-versus-linear products, and several studies have shown that branched and linear substrates indeed give different product distributions. However, most of these studies have employed only two substrates, commonly *trans* linear and branched butenyl substrates. We note that the mechanism depicted in Scheme 2 is well able to rationalize these results, because the branched substrate is expected to ionize at least partially to an *anti*-[Pd(η^3-alkenyl)] intermediate, with a product profile markedly different from that of the *syn*-[Pd(η^3-alkenyl)] complex initially formed from the *trans* linear substrate.[8] Herein, we show that inclusion of the *cis* linear substrate in the study allows a detection of memory effects beyond those apparent from the stereoretention caused by slow isomerization between the isomeric intermediates in Scheme 2. We use the term *regioretention* exclusively for cases in which it can be proven that the intermediate Pd–allyl complex retains a "memory" of the position of the leaving group beyond the inherent reactivity difference between *syn* and *anti* complexes. Experimentally, we detect this effect by comparing the product distributions from all three isomeric substrates in Scheme 2. If the product distribution obtained from the branched substrate is a linear combination of those obtained from *cis* and *trans* linear substrates, we have *no* regioretention.[19]

Herein, we have studied the behavior of butenyl substrates that ionize to simple methyl-substituted [Pd(η^3-allyl)] intermediates (Figure 1). It is of critical importance that all three substitution patterns leading to the same [Pd(η^3-allyl)] manifold are included.[8]

Alcohols **1a–c** were synthesized and converted into substrates **2–4** by using standard methods. The substrates were reacted with two equivalents of the sodium salt of diethyl methyl malonate, in the presence of 2.5% [$Pd_2(dba)_3$] (dba = (*E*,*E*)-dibenzylideneacetone) and 10% PPh_3, to generate 5% of the catalytically active [$Pd(PPh_3)_2$] complex. The product distribution was determined by GC and NMR

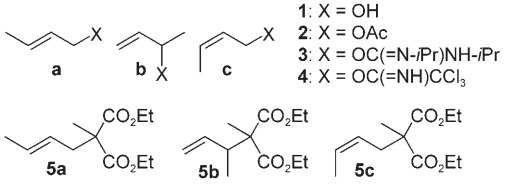


Figure 1. Allylic substrates and corresponding products studied.

spectroscopy. Halide ions were rigorously excluded in the initial part of the study to avoid complications caused by the "halide effect".[20] In the second part of the study, we wanted to investigate the influence of chloride ions, without adding a new type of countercation to the reaction. This was achieved by addition of a small amount of allyl chloride, which reacts more rapidly than the allylic acetates, liberating a controlled amount of chloride ions.

Results and Discussion

Allylic alkylation of acetates 2a–c: The acetate leaving group is expected to be only weakly coordinating to palladium. As for any coordinating anion, it will accelerate equilibration of the η^3-allyl intermediate, though not as strongly as, for example, a chloride anion.[21] The results from allylic alkylation of the acetates **2a–c** are listed in Table 1 (entries 1–3).

Table 1. Results from allylic alkylation.

Entry	Substrate	**5a** [%]	**5b** [%]	**5c** [%]	Chloride [mol %]
1	**2a**	77	16	7	–
2	**2b**	59	26	14	–
3	**2c**	15	38	47	–
4	**3a**	81	17	3	–
5	**3b**	55	30	15	–
6	**3c**	52	30	18	–
7	**4a**	67	22	11	–
8	**4b**	61	26	12	–
9	**4c**	47	34	20	–
10	**4c**	36	38	26	–
11	**2a**	76	16	8	0.5
12	**2b**	36	51	13	0.5
13	**2c**	45	21	34	0.5
14	**2a**	81	17	2	5
15	**2b**	43	46	11	5
16	**2c**	53	22	25	5

We analyze the results in terms of the mechanism depicted in Scheme 2. If nucleophilic attack is slow relative to the isomerization of the intermediate, the same product distribution should be expected from all three substrates. This is clearly not the case; *trans*-acetate **2a** yields mostly *trans* product **5a** from terminal attack on the *syn* intermediate, whereas *cis*-acetate **2c** yields almost equal amounts of branched and *cis* products, **5b** and **5c**, respectively, in good agreement with a previous study from the Åkermark group.[8] A more detailed analysis of the product distribution from **2a** and **2c** shows that under the current reaction conditions, only 12% of the *syn* complex (from **2a**) and 17% of the *anti* complex (from **2c**) isomerize before reaction with nucleophile, and that the ratio of terminal:internal attack is 88:12 for *syn*, and 57:43 for *anti*. (See Experimental Sections for the iterative formulae used to derive these ratios.) Thus, for both substrates, there is more than 80% *stereoretention*, here defined as the amount that reacts in the initially formed isomeric form of the intermediate.[19] By using the above ratios in analyzing the product distribution from branched acetate **2b**, we can conclude that the initial ionization yields approximately 70% *syn* complex. However, we also see a slight excess of internal product relative to what would be expected from the observed amounts of *cis* and *trans* product (observed: 26%, predicted: 19%). This could be a slight *regioretention*, that is, a preference for the nucleophile to attack the carbon that originally carried the leaving group.[19] The effect here is weak, and may not be significantly larger than the error in the measurements.[22]

Notably, branched products arise primarily from *anti*-[Pd(η^3-allyl)] complexes. As only branched products are chiral, it is clear that ligands that favor formation of the *anti* form of monosubstituted [Pd(η^3-allyl)] complexes[16] should have an improved chance of giving branched, chiral product in the asymmetric version of the title reaction.[2] In addition, it is clear that successful rationalization of enantioselectivity requires consideration of *anti* complexes.[23]

The strong stereoretention effect observed here, resulting from a slow interconversion of intermediates, can be used to rationalize the observed memory effects of Williams,[6] Hayashi,[7] and Faller,[10] by postulating that a significant proportion of the internal allylic substrates utilized in those studies ionized initially to the *anti* complex. As no *cis* substrates were employed, it is not possible to state if also a regioretention mechanism was operative.

Notably, a wide range of relative rates of isomerization and nucleophilic attack can be found in the literature. For example, almost complete stereoretention can be achieved by increasing the reactivity of the nucleophile,[24] whereas complete isomerization within an isolated manifold coupled with substrate-directed regioselectivity forms the basis of a recent enantioconvergent procedure.[25]

New leaving groups: Two alternative types of leaving groups were included in the current studies, isoureas and imidates. Dicyclohexylisoureas were employed previously,[26] however, in our hands, it was difficult to isolate these in pure form. The corresponding diisopropylisoureas were found to be more tractable (**3a–c**). In addition, we wanted to test trichloroacetimidates as leaving groups (**4a–c**), as these are easily synthesized from the corresponding alcohols, and could also function as bases upon liberation. For the latter substrates, a one-pot tandem procedure was developed. Thus, the sodium salt of an allylic alcohol (**1a–c**) was treated with CCl_3CN, followed by the catalyst and the malonate nucleophile in neutral form, to yield directly products **5a–c**.

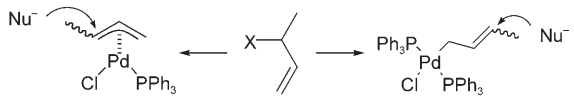
The results obtained with the new leaving groups are shown in Table 1 (entries 4–10). There are some distinct differences from the allylic acetates. First of all, it is clear that the isomerization is now faster (i.e., there is less stereoretention), as shown by the high proportion of *trans* product **5a** from the *cis* substrates **3c** and **4c** (compare entries 6 and 9 to entry 3). Furthermore, the position of the *syn*/*anti* equilibrium has clearly shifted; despite the higher rate of isomeri-

zation of the intermediate, *trans*-isourea **3a** yields only approximately 3% of *cis* product, compared to 7% for the acetate **2a**, and 11% for the imidate **4a** (entries 4, 1, and 7). This indicates that the leaving groups function to some extent as Pd ligands, influencing the equilibrium by coordination. The experiment starting from **4c** was repeated (entries 9 and 10), and it is clear that the relative rates of isomerization and nucleophilic attack are very sensitive to reaction conditions. However, none of our conclusions are sensitive to variations of this moderate magnitude.

For both new leaving groups, the degree of regioretention is negligible. The product distribution from **3b** closely matches **3c** (entries 5 and 6), whereas **4b** instead gives a result more similar to **4a** (entries 8 and 7) showing that the position of the leaving group is immaterial, and also that the two leaving groups have opposite ionization preferences. Isourea **3b**, like **3c**, forms the *anti*-allyl complex upon ionization. To our knowledge, this is the first report of a leaving group that ionizes to the thermodynamically less-favored *anti* complex. Imidate **4b**, on the other hand, gives mainly the *syn* complex and, thus, matches **4a**. As a corollary, isoureas should be better leaving groups than acetates if a branched-to-branched reaction is desired, whereas imidates should be preferred for isomerization to linear product.

Effect of chloride ions: To study the "halide effect",[20,27] the allylic alkylation of the acetates **2a–c** was also performed by the addition of small amounts of allyl chloride (either 10% or 100% relative to Pd). In the presence of Pd(0) the very reactive allyl chloride will immediately liberate a controlled amount of chloride ions into the reaction mixture. We expected the main effect of the chloride ions to be an acceleration of the *syn*/*anti* isomerization.[13] With this in mind, the product distributions from the three isomeric acetates **2a–c** should become more similar upon chloride addition. The results are shown in Table 1 (entries 11–16).

Upon observation of the product distributions, the initial expectation (i.e., faster *syn*/*anti* isomerization) is clearly fulfilled, as shown by the higher amount of *trans* product **5a** from *cis* substrate **2c**. However, the most drastic effect is a strong regioretention. The results from **2a** and **2c** show the two extremes of initial ionization, to the pure *syn* and *anti* complex, respectively. In the absence of regioretention, the product distribution from the branched substrate must be a linear interpolation between these two extremes, however, the results with **2b** show almost twice as much internal product as from either of the other substrates. This is proof that the intermediate in this case is not the symmetrically ligated [Pd(η^3-allyl)] complex shown in Scheme 2. Furthermore, the observation that the regioretention is triggered by addition of external chloride makes it very unlikely that in this case the memory effect is due to tight ion pairing with the leaving group, acetate.[12] Somehow, the chloride ion must interact with Pd to yield a less-symmetric intermediate. Two plausible possibilities have been advanced in the literature, both depending on initial reaction with anionic [$Pd^0(PPh_3)_xCl]^-$,[17,27] (Scheme 3).



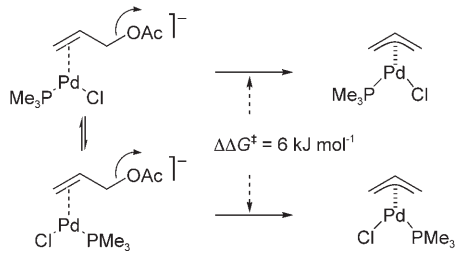
Scheme 3. Plausible intermediates rationalizing regioretention in the presence of chloride.

The first is a neutral [Pd(η^3-allyl)] complex with two unequal ligands, PPh_3 and Cl^-, in which both ionization and nucleophilic attack would be expected to occur primarily *trans* to phosphorus.[18] The second is a likewise neutral [Pd(η^1-allyl)$(PPh_3)_2$Cl] complex formed by and reacting through S_N2' reactions.[3,17] Of these, we favor the former, as recent experimental results[28] indicate that [Pd(η^1-allyl)] complexes react with electrophiles rather than nucleophiles. DFT modeling also indicates that the former explanation is well able to rationalize the observed results (see below).

The chloride effect shows an early saturation behavior. The effect is dramatic already at 0.5% Cl^- (entries 11–13), and then does not change much upon increasing to 5% Cl^- (equimolar with Pd, entries 14–16). This is a strong indication that under the present reaction conditions, the resting state of the catalyst is Pd(0), and that less than 10% of the Pd is present in Pd^{II} form at low levels of Cl^-. In addition, the ionization event must be strongly accelerated by Cl^-, as shown by Amatore, Jutand, and co-workers,[17] as an excess of Pd(0) over Cl^- has little effect.

Computational study: To verify some of the conclusions reached in the mechanistic study we undertook a computational study of the selectivity-determining features in the transition state of the title reaction, assuming that initial ionization occurs by reaction of allylic acetate with an anionic [$Pd(PR_3)X$] complex (X = chloride or carboxylate), in analogy with recent studies on oxidative addition.[29] We have shown previously that the transition state in the allylation reaction is strongly affected by solvent.[30] As in previous studies, we chose to represent the solvent with a continuum model.[30,31] For the phosphine ligand, we used Me_3P as a model. In analogy with previous studies of similar reactions,[18c,32] the nucleophile is modeled by simple ammonia. This model system is not expected to represent steric interactions well, but should be able to uncover inherent regioselectivity caused by the *trans* effect. We have also modeled the initial ionization step, with the same phosphine model, but including the full acetate leaving group. All DFT calculations were performed with the B3LYP functional[33] in combination with the LACVP* basis set[34] in Jaguar.[35] The solvent was represented by using the PB-SCRF model[36] in Jaguar, with parameters suitable for CH_2Cl_2 (dielectricity constant: epsout = 9.08; probe radius: radprb = 2.33237).

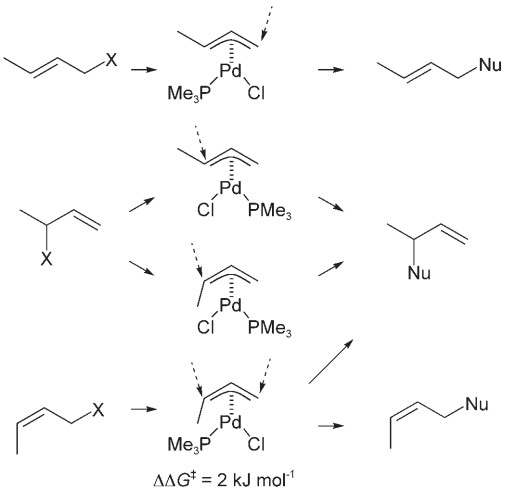
We first considered the influence of the *trans* effect on the initial ionization step. For the model system depicted in Scheme 4, ionization *trans* to the phosphine is favored by approximately 6 kJ mol^{-1}, corresponding to a 10:1 ratio of products under kinetic control at room temperature. Thus, ionization in the presence of chloride would be expected to



Scheme 4. Calculated *trans* effect in the initial ionization of allyl acetate.

give a large excess of [Pd(η^3-allyl)] complex with the phosphine ligand *trans* to the allyl terminus that was originally bonded to the leaving group.

From this result, it is clear that in the presence of chloride, branched and linear substrates will not ionize to the same [Pd(η^3-allyl)] complexes (Scheme 5). For all of the intermediates, we calculated the barrier for reaction with the model nucleophile at each allyl terminus, and in the three first cases, we found a preference for the terminus *trans* to phosphine of 11–13 kJ mol^{-1}, which would predict a regioretention of about 99% for the internal and *trans* linear substrates. Only in the *anti* complex, initially formed from the *cis* substrate, will the inherent preference for internal attack compensate the *trans* effect, and for the mismatched *anti* complex we calculate that attack at the two allyl termini are virtually isoenergetic.



Scheme 5. In all examples except the lower one, nucleophilic attack *trans* to phosphine is favored by more than 10 kJ mol^{-1}.

From the results depicted in Scheme 5, we would expect a very high degree of regioretention for the branched and *trans* linear substrates. However, as stated earlier, the presence of chloride and excess ligand will also increase the rate of isomerization of the [Pd(η^3-allyl)] complexes, reducing the regioretention from the very high level implied by Scheme 5 to the moderate 30–40% observed in the experiments (Table 1). If this isomerization could be suppressed, we expect that a very high degree of regioretention could be obtained.[18d]

Conclusion

The previously reported memory effects in the title reaction can be divided into two distinct classes that we term *regioretention* and *stereoretention.* The latter is caused by a slow isomerization of the intermediate [Pd(η^3-allyl)] complex, in combination with the inherent stereochemical preference of the initial ionization step. We also identified reaction with anionic [Pd(PR$_3$)Cl], influenced by a strong *trans* effect, as one potential source for regioretention in the title reaction.

By changing the nature of the leaving group, the fate of the initial ionization step can be controlled, directing the reaction of branched allylic substrates either to an *anti* complex with high branched preference or to a *syn* complex with high linear preference of the subsequent nucleophilic attack. This discovery holds great promise for further development of the synthetic applications of the palladium-catalyzed allylic alkylation. Also, the addition of anionic ligands, such as Cl$^-$, enhances the branched-to-branched reactivity, a fact that could be useful in future enantioselective implementations.

Experimental Section

General: All reactions were performed in glassware flame-dried under vacuum and flushed with argon, except for the synthesis of the allylic alcohols **1a–c** and the trichloracetimidates **4a–c**. Solvents were distilled prior to use. THF was distilled from Na/benzophenone and dichloromethane from CaH_2, both under N_2 atmosphere. Diethyl ether, ethyl acetate, and hexane used for flash chromatography were of HPLC grade. Commercially available reagents were used as delivered unless mentioned. TLC was performed by using alumina plates coated with silica (Merck: silica gel 60 F_{254}). The plates were visualized by using a 5% phosphormolybdic acid solution in ethanol followed by warming with a heat gun, which resulted in blue spots.

Flash column chromatography was performed by using silica gel (Amicon 85040) as described by Still et al.[37] Solvents were removed by using a rotary evaporator (about 17 mm Hg at 20–30 °C).

Products were identified by ^{1}H NMR spectroscopy. Spectra were recorded by using a Varian Mercury 300 operating at 300 MHz. Chemical shifts are given in ppm relative to $CHCl_3$ (7.27 ppm). Quartets are designated by using "q" and apparent quintets are designated by using the abbreviation "k". New compounds were characterized further by ^{13}C NMR spectroscopy (Varian Mercury 300, 75 MHz). Chemical shifts in ^{13}C NMR data are given relative to $CDCl_3$ (77.0 ppm). Microanalyses were conducted by Mikroanalytisches Laboratorium am Institut für Physikalische Chemie der Universität Wien.

Gas chromatography (GC) of allylic alcohols **1a–c** was performed by using a Hewlett–Packard 5890 Series II gas chromatograph connected to a Hewlett–Packard 3392A integrator on a 25 m × 0.25 mm Chrompack Chirasil-Dex column. H_2 was used as carrier gas in an isothermic run (50 °C, 20 min). Gas chromatography to determine the product distribution from the allylic substitutions were performed by using a Perkin–Elmer Autosystem 1020 equipped with a 25 m × 0.25 mm Chrompack CP-SIL 8CB column. He was used as carrier gas in an isothermic run

(180 °C, 10 min). IR spectra were recorded by using a Perkin–Elmer 1600 Series FTIR with AgCl plates.

(*E*)-2-Buten-1-ol (1a):[38] $LiAlH_4$ (4.5 g, 117.7 mmol) was suspended in 1,2-dimethoxyethane and cooled to 0 °C in an ice-bath. 2-Butyn-1-ol (6.9 g, 98.5 mmol) in 1,2-dimethoxyethane (30 mL) was added over a period of 15 min. After addition, the solution was left at RT for 80 h. The reaction mixture was quenched with water (6 mL), and washed with 14% NaOH (6 mL) and water (16 mL). The gray precipitate was filtered off and washed with diethyl ether. Product **1a** was isolated as a colorless oil by distillation through a Vigreaux column (yield 48%, 3.4 g). R_f = 0.25 (hexane/EtOAc 5:1); b.p. 120 °C (ref. [39] 118–122 °C); GC (50 °C, isothermic): t_R = 8.77 min, analysis did not show any traces of (*Z*)-isomer; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76–5.64 (m, 2H; CH), 4.10–4.07 (m, 2H; CH_2), 1.72 (app. dq, *J* = 3.6, 0.6 Hz, 3H; CH_3), 1.42 ppm (br s, 1H; OH).

(*Z*)-2-Buten-1-ol (1c):[40] 2-Butyn-1-ol (8.0 g, 114.1 mmol), quinoline (8 mL), and Lindlar catalyst (5% Pd mixed with $CaCO_3$ and doped with Pb, 879 mg, 0.41 mmol) was mixed in dichloromethane (72 mL). The hydrogenation was performed with 1 atm H_2 at RT under stirring for two weeks. Consumption of H_2 was 3100 mL (129 mmol). The catalyst was filtered off, and **1c** was isolated as a colorless oil by distillation through a Vigreaux column (yield 61%, 5.0 g). R_f = 0.23 (hexane/EtOAc 5:1); b.p. 119–121 °C (ref. [41] 119.8–120.5 °C, 747 torr); GC (50 °C, isothermic): t_R = 12.11 min, analysis did not show any (*E*)-product; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65–5.53 (m, 2H; CH), 4.18 (dm, *J* = 4.5 Hz, 2H; CH_2), 1.64 ppm (dm, *J* = 5.1 Hz, 3H; CH_3).

General procedure for synthesis of acetates 2a–c:[42] The allylic alcohol (4.4 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C under stirring. Acetyl chloride (0.34 mL, 4.8 mmol) and pyridine (0.38 mL, 4.7 mmol) were added and the reaction was monitored by TLC. After completion of the reaction (after 15 min) water was added (2.5 mL, 0 °C), the organic phase was separated and washed with brine (10 mL, 0 °C) and water (10 mL, 0 °C). The organic phase was dried over Na_2SO_4, filtered, and evaporated to yield the corresponding acetate as a colorless oil.

(*E*)-2-Butene-1-yl acetate (2a): Yield 96% (452 mg). R_f = 0.54 (hexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79 (dqt, *J* = 15.3, 6.6, 1.2 Hz, 1H; CH), 5.58 (dtq, *J* = 15.3, 6.6, 1.5 Hz, 1H; CH), 4.49 (app. dk, *J* = 6.3, 1.0 Hz, 2H; CH_2), 2.05 (s, 3H; CH_3), 1.71–1.75 ppm (m, 3H; CH_3).

3-Butene-2-yl acetate (2b): Yield 91% (432 mg). R_f = 0.51 (hexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (ddd, *J* = 17.3, 10.5, 6.3 Hz, 1H; CH), 5.35 (br k, *J* = 6.3, 1.3 Hz, 1H; CH), 5.25 (app. dt, *J* = 17.4, 1.3 Hz, 1H; CH), 5.15 (app. dt, *J* = 10.5, 1.2 Hz, 1H; CH), 2.07 (s, 3H; CH_3), 1.32 ppm (d, *J* = 6.6 Hz, 3H; CH_3).

(*Z*)-2-Butene-1-yl acetate (2c): Yield 98% (460 mg). R_f = 0.49 (hexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.74 (dqt, *J* = 10.8, 6.9, 1.7 Hz, 1H; CH), 5.56 (dtq, *J* = 10.8, 6.9, 1.7 Hz, 1H; CH), 4.64 (app. dk, *J* = 6.6, 0.90 Hz, 2H; CH_2), 2.07 (s, 3H; CH_3), 1.71 ppm (ddt, *J* = 6.9, 1.7, 0.8 Hz, 3H; CH_3).

General procedure for synthesis of allylic isoureas 3a–c: The literature procedure for the formation of dicyclohexylisoureas could also be used to form the diisopropylisoureas.[43] The allylic alcohol (5.0 mmol) was added to a mixture of CuCl (0.08 mmol, 7.5 mg) and diisopropyl carbodiimide (5.0 mmol, 781 μL) under stirring at RT. After about 12 h, CuCl (0.08 mmol, 7.5 mg) was added again. Before use, CuCl was purified as described by Österlöf.[44] The reaction mixture was stirred until the absorption due to diisopropyl carbodiimide (2110–2120 cm^{-1}) was no longer apparent from the IR spectrum (usually 24 h). The reaction mixture was diluted with hexane (15 mL), washed with water (10 mL), 25% NH_3 (aq) (3 × 5 mL), and water (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated by using a rotary evaporator. This procedure yielded the desired product as a colorless oil. The isoureas produced two spots on a TLC plate, in spite of high purity. For this reason, both R_f values were reported for each isourea.

***O*-((*E*)-2-Buten-1-yl)-*N*,*N*′-diisopropyl isourea (3a)**: This synthesis was performed on a 2-mmol scale. Yield 68% (270 mg). R_f = 0.25/0.44 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75 (dqt, *J* = 15.3, 6.3, 1.1 Hz, 1H; CH), 5.63 (dtq, *J* = 15.3, 5.7, 1.2 Hz, 1H; CH), 4.47 (app. dk, *J* = 5.7, 1.1 Hz, 2H; CH_2), 3.78 (sp, *J* = 6.6 Hz, 1H; CH), 3.41 (br d, *J* = 6.7 Hz, 1H; NH), 3.16 (sp, *J* = 6.1 Hz, 1H; CH), 1.72 (app. dq, *J* = 6.3, 1.2 Hz, 3H; CH_3), 1.12 (d, *J* = 6.6 Hz, 6H; CH_3), 1.09 ppm (d, *J* = 6.3 Hz, 6H; CH_3).

***O*-(3-Buten-2-yl)-*N*,*N*′-diisopropyl isourea (3b)**: The crude product was purified by Kugelrohr distillation (0.8 mm Hg, 50 °C). Yield 81% (801 mg). R_f = 0.30/0.49 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (ddd, *J* = 17.3, 10.6, 5.2 Hz, 1H; CH), 5.42 (app. qdt, *J* = 6.3, 5.2, 1.3 Hz, 1H; CH), 5.22 (app. dt, *J* = 17.3, 1.5 Hz, 1H; CH), 5.05 (app. dt, *J* = 10.6, 1.4 Hz, 1H; CH), 3.78 (sp, *J* = 6.5 Hz, 1H; CH), 3.37 (br d, *J* = 6.6 Hz, 1H; NH), 3.16 (sp, *J* = 6.2 Hz, 1H; CH), 1.12 (d, *J* = 6.4 Hz, 6H; CH_3), 1.29 (d, *J* = 6.4 Hz, 3H; CH_3), 1.07 (d, *J* = 6.2 Hz, 3H; CH_3), 1.06 ppm (d, *J* = 6.3 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6, 127.7, 126.1, 60.7, 46.2, 43.3, 24.3, 24.0, 23.9, 13.3 ppm; elemental analysis calcd (%) for $C_{11}H_{22}N_2O$: C 66.62, H 11.18, N 14.13; found: C 66.85, H 10.88, N 14.17.

***O*-((*Z*)-2-Buten-1-yl)-*N*,*N*′-diisopropyl isourea (3c)**: The use of an oil pump (0.8 mmHg, RT) for 2 h was necessary to remove traces of solvent. Yield 88% (873 mg). R_f = 0.30/0.49 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70–5.55 (m, 2H; CH), 4.62 (br d, *J* = 5.4 Hz, 2H; CH_2), 3.76 (sp, 6.5 Hz, 1H; CH), 3.40 (br d, *J* = 6.6 Hz, 1H; NH), 3.18 (sp, *J* = 6.2 Hz, 1H; CH), 1.71 (dm, *J* = 5.4 Hz, 3H; CH_3), 1.11 ppm (app. t, *J* = 5.9 Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.3, 139.4, 114.0, 69.8, 46.1, 43.2, 24.3, 24.2, 24.0, 19.7 ppm; elemental analysis calcd (%) for $C_{11}H_{22}N_2O$: C 66.62, H 11.18, N 14.13; found: C 66.34, H 10.91, N 13.94.

General procedure for synthesis of allylic trichloracetimidates 4a–c:[45] The allylic alcohol (1.96 mmol) was dissolved in dichloromethane and cooled to −15 °C. Aqueous KOH (50%, 2 mL) and tetrabutylammonium hydrogensulfate (8.8 μmol, 3 mg) were added as the temperature was maintained at −15 °C, then trichloracetonitrile (2.34 mmol, 236 μL) was added dropwise. The resulting solution was stirred for 30 min at −15 °C, followed by 30 min stirring at RT. The solution was diluted with 5 mL dichloromethane and water (10–15 mL). The organic phase was isolated, and the water phase was extracted twice with dichloromethane (7.5 mL). The combined organic phases were dried over Na_2SO_4, concentrated to about 10 mL, and filtered through silica gel (2 cm). The silica gel was eluted with 10–15 mL of dichloromethane, and the product was isolated as a colorless oil by evaporation of solvent.

((*E*)-2-Butene-1-yl)trichloracetimidate (4a): Yield 75% (319 mg). R_f = 0.59 (hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (br s, 1H; NH), 5.90 (dqt, *J* = 15.3, 6.3, 1.2 Hz, 1H; CH), 5.72 (dtq, *J* = 15.3, 6.2, 1.5 Hz, 1H; CH), 4.74 (app. dk, *J* = 6.3, 1.1 Hz, 2H; CH_2), 1.77 ppm (dm, *J* = 6.4 Hz, 3H; CH_3).

(3-Butene-2-yl)trichloracetimidate (4b): Yield 14% (61.4 mg). R_f = 0.56 (hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (br s, 1H; NH), 5.95 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H; CH), 5.47 (br k, *J* = 6.2 Hz, 1H; CH), 5.37 (app. dt, *J* = 17.3, 1.3 Hz, 1H; CH), 5.21 (app. dt, *J* = 10.6, 1.2 Hz, 1H; CH), 1.45 ppm (d, *J* = 6.5 Hz, 3H; CH_3).

((*Z*)-2-Butene-1-yl)trichloracetimidate (4c): Yield 79% (335 mg). R_f = 0.55 (hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (br s, 1H; NH), 5.82 (dq, *J* = 10.8, 6.9 Hz, 1H; CH), 5.69 (dtq, *J* = 10.8, 6.3, 1.4 Hz, 1H; CH), 4.87 (br d, *J* = 6.3 Hz, 2H; CH_2), 1.76 ppm (br d, *J* = 6.3 Hz, 3H; CH_3).

General procedure for allylic alkylation of acetates 2a–c: NaH (60% suspension in oil, 1.0 mmol) was dissolved in THF (1 mL) and degassed with argon. Diethyl methyl malonate (1.2 mmol, 200 μL) was added and the solution was stirred for 30 min. Triphenylphosphine (13.2 mg, 0.05 mmol) was dissolved in THF (0.5 mL) and degassed with argon. $[Pd_2(dba)_3]\cdot CHCl_3$ (13 mg, 0.0125 mmol) was then added at which point the solution turned brownish. The solution was stirred for 30 min and the allyl acetate (0.5 mmol) was added, followed by the sodium enolate of diethyl methyl malonate (1 mmol) in dry, degassed THF (1 mL). After stirring for 24 h at RT the solution was diluted with diethyl ether (10 mL) and washed with 1 M HCl (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed. This gave a pale-yellow oil, which was purified by flash column chromatography

(hexane/Et_2O 9:1). The product was a mixture of three isomers and the components were identified and characterized by GC (180 °C, isothermic) and ^1H NMR spectroscopy. The yield and composition from each allylic alkylation is given below (Table 2).

Table 2. Yield and product distributions from allylic alkylation of **2a–c**.

Substrate	Isolated yield [%]	**5a** [%]	**5b** [%]	**5c** [%]
2a	77	77	16	7
2b	65	59	26	14
2c	68	15	38	47

Diethyl-((*E*)-2-butene-1-yl)methyl malonate (5a): GC: $t_R = 5.50$ min; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.53$ (dqt, $J = 15.1$, 6.3, 1.1 Hz, 1H; CH), 5.31 (dtq, $J = 15.1$, 7.3, 1.5 Hz, 1H; CH), 4.19 (q, $J = 7.1$ Hz, 1H, CH), 4.18 (q, $J = 7.1$ Hz, 2H; CH_2), 2.54 (app. dk, $J = 7.3$, 1.1 Hz, 2H; CH), 1.65 (app. dq, $J = 6.3$, 1.1 Hz, 3H; CH_3), 1.37 (s, 3H; CH_3), 1.25 ppm (t, $J = 7.1$ Hz, 6H; CH_3).

Diethyl-(3-butene-2-yl)methyl malonate (5b): GC: $t_R = 5.24$ min; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.79$ (ddd, $J = 17.1$, 10.3, 8.1 Hz, 1H; CH), 5.08 (ddd, $J = 17.1$, 1.9, 1.1 Hz, 1H; CH), 5.04 (ddd, $J = 10.3$, 1.9, 0.8 Hz, 1H; CH), 4.17 (q, $J = 7.1$, 4H; CH_2), 3.01 (app. k, $J = 7.0$, 1.9, 1.0 Hz, 1H; CH), 1.35 (s, 3H; CH_3), 1.25 (t, $J = 7.1$ Hz, 6H, CH_3), 1.07 ppm (d, $J = 6.9$ Hz, 3H; CH_3).

Diethyl-((*Z*)-2-butene-1-yl)methyl malonate (5c): GC: $t_R = 5.76$ min; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.62$ (dqt, $J = 10.9$, 6.8, 1.5 Hz, 1H; CH), 5.30 (1H, dtq, $J = 11.0$, 7.5, 1.8 Hz), 4.18 (q, $J = 7.1$ Hz, 4H; CH_2), 2.64 (ddq, $J = 7.6$, 1.4, 0.8 Hz, 2H; CH_2), 1.63 (dq, $J = 6.0$, 0.9 Hz, 3H; CH_3), 1.39 (s, 3H; CH_3), 1.25 ppm (t, $J = 7.1$ Hz, 6H; CH_3).

General procedure for allylic alkylation of isoureas 3a–c: NaH (60% suspension in oil, 24 mg, 0.6 mmol) was dissolved in THF (0.3 mL). The solution was degassed with argon. Diethyl methyl malonate was added (120 μL, 0.70 mmol) and the solution was stirred for 30 min. $[Pd_2(dba)_3]\cdot CHCl_3$ (7.8 mg, 0.0075 mmol) and triphenylphosphine (7.9 mg, 0.03 mmol) were dissolved in THF (0.6 mL), which gave a brownish solution. The solution was purged with argon and stirred for 30 min. The allylic isourea (0.3 mmol) was added followed by the sodium enolate of diethyl methyl malonate (0.6 mmol) in dry, degassed THF (0.3 mL). The solution was stirred for 24 h (RT), then diluted with diethyl ether (10 mL) and washed with 1 M HCl (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed. This gave a pale-yellow oil, which was purified by flash column chromatography (hexane/Et_2O 9:1). The product was a mixture of three isomers and the components were identified and characterized by GC (180 °C, isothermic) and ^1H NMR spectroscopy. The yield and composition from each allylic alkylation is given below (Table 3).

Table 3. Yield and product distributions from allylic alkylation of **3a–c**.

Substrate	Isolated yield [%]	**5a** [%]	**5b** [%]	**5c** [%]
3a	57	81	17	3
3b	61	55	30	15
3c	54	52	30	18

General procedure for alkylation of in situ generated trichloroacetimidates 4a–c: The allylic alcohol (36.1 mg, 0.5 mmol), trichloroacetonitrile (72.2 mg, 0.5 mmol), and NaH (60% suspension in oil, 40 mg, 1.0 mmol) were dissolved in dry THF (1.0 mL). Triphenylphosphine (13.3 mg, 0.05 mmol) and $[Pd_2(dba)_3]\cdot CHCl_3$ (13.1 mg, 0.0125 mmol) were dissolved in dry THF (0.5 mL), and the solution was degassed with argon, during which it turned brownish. After stirring for 30 min the solution containing the allylic imidate was added. After another 30 min of stirring diethyl methyl malonate (202.6 mg, 1.16 mmol) was added. The solution was stirred for 24 h (RT) and then diluted with diethyl ether (10 mL) and washed with 1 M HCl (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed. This gave a pale-yellow oil, which was purified by flash column chromatography (hexane/Et_2O 9:1). The product was a mixture of three isomers and the components were identified and characterized by GC (180 °C, isothermic) and ^1H NMR spectroscopy. The yield and composition from each allylic alkylation is given below (Table 4).

Table 4. Yield and product distributions from allylic alkylation of **1a–c** via **4a–c**.

Substrate	Isolated yield [%]	**5a** [%]	**5b** [%]	**5c** [%]
1a	46	67	22	11
1b	38	61	26	12
1c	35	47	33	20

General procedure for allylic alkylation with chloride ions: Two experiments was performed with each of the three acetates **2a–c**, the only difference being the amount of added allyl chloride (0.5 and 5 mol%).

NaH (60% suspension in oil, 1.0 mmol) was dissolved in THF (1 mL) and degassed with argon. Diethyl methyl malonate (1.2 mmol, 200 μL) was added and the solution was stirred for 30 min. Triphenylphosphine (13.2 mg, 0.05 mmol) was dissolved in THF (0.5 mL) and degassed with argon. $[Pd_2(dba)_3]\cdot CHCl_3$ (13 mg, 0.0125 mmol) was then added, during which the solution turned brownish. The solution was stirred for 30 min and allyl chloride (0.0025 or 0.025 mmol) was added followed by 10 min of stirring. The allylic acetate (0.5 mmol) was added, followed by the sodium enolate of diethyl methyl malonate (1 mmol) in dry, degassed THF (1 mL). After stirring for 24 h at RT the solution was diluted with diethyl ether (10 mL) and washed with 1 M HCl (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed. This gave a pale-yellow oil, which was purified by flash column chromatography (hexane/Et_2O 9:1) in the case of 0.5 mol% allyl chloride. The product was a mixture of three isomers and the components were identified and characterized by GC (180 °C, isothermic) and ^1H NMR spectroscopy. After the reaction was run with 5 mol% allyl chloride the product distribution was determined by GC on the crude product. The yield and composition from both experiments are given below (Table 5).

Table 5. Yield and product distributions from allylic alkylation of **2a–c** in the presence of chloride ions.

Substrate	Isolated yield [%]	**5a** [%]	**5b** [%]	**5c** [%]
2a[a]	49	76	16	8
2b[a]	59	36	51	13
2c[a]	62	45	21	34
2a[b]	–	81	17	2
2b[b]	–	43	46	11
2c[b]	–	53	22	25

[a] 0.5 mol% allyl chloride. [b] 5 mol% allyl chloride.

Iterative determination of terminal:internal reactivity ratios: The ratio of internal-to-terminal attack on each intermediate is denoted *f*. In the complete absence of regioretention (the initial assumption), we have two such ratios, one for the *syn* intermediate, f_s, and one for *anti* intermediate, f_a. Furthermore, we use brackets with indices "*t*" to label reactions starting from *trans* substrates **2a–4a**, "*c*" for *cis* substrates **2c–4c**, and "*i*" for internal substrates **2b–4b**. We obtain initial estimates of all fractions f^0 by assuming complete stereoretention, that is, by assuming that *trans* substrates react completely via *syn* complexes, and *cis* substrates via *anti* complexes:

$$f_s^0 = [\mathbf{5b}/\mathbf{5a}]_t$$
$$f_a^0 = [\mathbf{5b}/\mathbf{5c}]_c$$

We know that the final proportion of branched product **5b** arises both from *syn* and *anti* complexes, whereas *trans* product **5a** must arise exclusively from the *syn* complex, and *cis* product **5c** can come from the *anti* complex only. Thus, for all reactions:

$$\mathbf{5b} = f_s\ \mathbf{5a} + f_a\ \mathbf{5c}$$

For each set of three reactions, we then get a simple set of refinement equations by using the ratios from the preceding iteration:

$$f_s^{n+1} = [(\mathbf{5b} - f_a^n\ \mathbf{5c})/\mathbf{5a}]_t$$
$$f_a^{n+1} = [(\mathbf{5b} - f_s^n\ \mathbf{5a})/\mathbf{5c}]_c$$

The above expressions converge to the final ratios in a few iterations. With the final ratios in hand, the expected amount of branched product can now be calculated also for the reaction employing branced substrates **2b**–**4b**. The excess observed branched-to-branched reactivity x_b is then given by:

$$x_b = [(f_s\ \mathbf{5a} + f_a\ \mathbf{5c} - \mathbf{5b})/(\mathbf{5a} + \mathbf{5b} + \mathbf{5c})]_i$$

With this definition, x_b (in %) is a measure of the degree of regioretention in the reaction. In all experiments, x_b is found to be positive, although in the experiments without chloride, it is small, possibly within experimental uncertainty (2–7%). In the experiments with added chloride, it is significant, 33–40%.

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Received: February 3, 2006
Published online: April 25, 2006

