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Catalytic activation of hydrogen, silicon, and fluorine by transition-metal complexes*,**

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Abstract: The remarkable versatility of palladium catalysis is exemplified by recent work in two distinct areas. Firstly, coupling chemistry is discussed, in which the reactive entity is generated by cleavage of a C–H or C–Si bond. The second part concerns the activation of allylic C–F bonds, where divergence from the normal stereochemical pattern of the reaction was observed.

Keywords: allylic alkylation; C–H activation; fluoride; palladium; silyl transfer.

INTRODUCTION

Palladium catalysis is rightly seen as a highly versatile method for making carbon–carbon and carbon–heteroatom bonds by an array of coupling reactions. The contents of this lecture define two of these. Firstly, a variant on the well-established Heck reaction (C–X electrophile plus alkene nucleophile) leads to an oxidative coupling (Fig. 1), an early example using a boronic acid as nucleophile [1]. The equally well established but more sparsely applied Fujiwara–Moritani reaction [2] is formally an oxidative Heck reaction with the initial step driven by C–H rather than C–X activation. The work re-

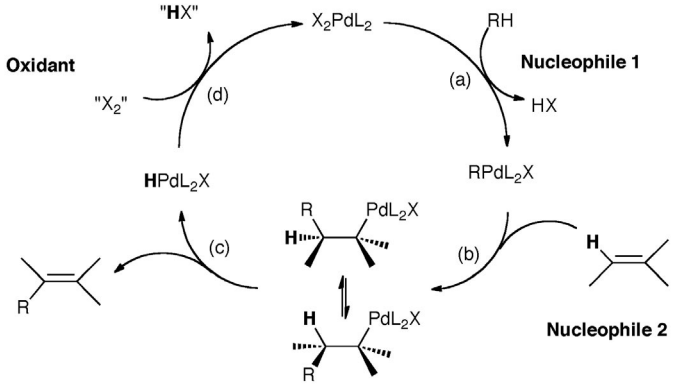

Fig. 1 Alternative Heck-type procedure involving initial nucleophile addition; each cycle requires a reoxidant. With a C–H activated reactant as Nucleophile 1, the process is formally classified as a Fujiwara–Moritani reaction.

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**Dedicated to the memory of Keith Fagnou, a leader in CH activation catalysis.
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ported here arose from a study designed to gain further understanding of the reaction mechanism. Unexpected observations led to a switch of emphasis from C–H to C–Si activation, leading to a more general appraisal of the latter case.

The second topic involved an effort to develop both the catalytic formation and cleavage of C–F bonds. Site-specific catalytic introduction of fluorine into organic compounds is of considerable current interest, both in the context of novel aryl fluoride syntheses and in developing routes to ^{18}F-labeled compounds for imaging purposes [3]. At the time this work commenced, there were no examples of Tsuji–Trost allylic alkylation using allyl fluorides in the literature. The objectives of our work are summarized in Fig. 2, first demonstrating how to labilize allylic C–F, with the intention of utilizing this information to discover how an allylpalladium cation can capture fluoride ion under turnover conditions.

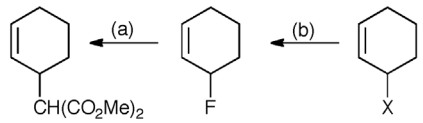


Fig. 2 Allyl fluorides as (a) the reactant and (b) the product in allylic alkylations.

MECHANISTIC STUDIES OF C–H ACTIVATION ALKENYLATION REACTIONS

Consider step (a) in Fig. 1 above, in which a C–Pd bond is formed. When a directing group facilitates reaction, there are two possible ways in which the activation could occur, as outlined in Fig. 3 below. The formal process is replacement of C–H by C–Pd, and this could occur in at least two ways. The directing group could permit the approach of palladium to form a Wheland-type intermediate (PATH 1), or it could function by acting as a base in the proton-abstraction step (PATH 2). The second pathway might bypass formation of a palladacycle in the turnover-limiting step. There is also support in the literature for a concerted pathway embracing both events, which could apply here [4]. In earlier work, we had noted that *N*-indolyl substituents that were effective in stabilizing palladacycle formation at the 2-position were ineffective in catalysis, and in the specific case of *N*-(2-pyridylmethyl) substitution, catalysis was efficient but it proved impossible to characterize any palladacyclic intermediate [5]. This led us to seek a formal proof of the existence of palladacyclic intermediates along the catalytic reaction pathway, assaying one of the now classic cases of Fujiwara–Moritani catalysis [6].

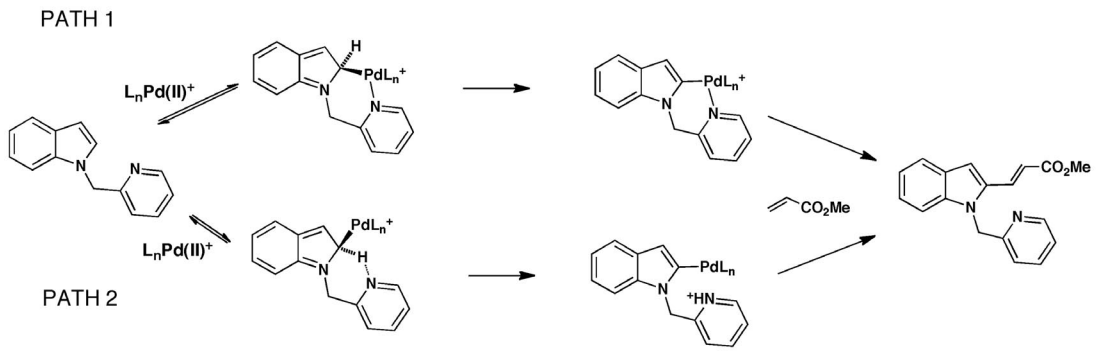


Fig. 3 Alternative pathways for activation of the 2-position of an N-substituted indole.

In the course of the mechanistic work, an interesting regiochemical effect was noted [7]. Intuitively, a C–Pd bond should be stabilized by an *ortho*-fluorine substituent. In practice, for the examples shown in Fig. 4, alkenylation reaction occurs completely at the site remote from fluorine, and is not observed at the 2-position. By starting with the 2-iodo derivative (for the case of X = H), the disfavored coupling product could be prepared by a conventional Heck coupling process, and this reaction occurred with reasonable facility. The small ionic radius of fluorine discourages any explanation based on steric hindrance to reagent approach. In order to gain further insight, the two alternative regioisomers of the palladacycle were prepared for X = F. The 6-isomer was prepared by direct palladation under stoichiometric conditions, and recrystallization from acetonitrile gave X-ray quality crystals of the ionic structure shown. The analogous 2-substituted regioisomer could not be prepared directly, but was accessed through a related electrophilic route. There are precedents for Pd(II) displacements of silicon from an arylsilane, and synthesis of the 2-$SiMe_3$ derivative followed by reaction with palladium acetate promoted by acid afforded an efficient palladadesilylation route to the desired product, also forming X-ray quality crystals on reaction with excess acetonitrile—tosylate is the counterion. The two crystal structures are shown in Fig. 5, together with a superimposition. This demonstrates that the 3-F substituent in the 2-isomer creates significant steric pressure on the C–Pd bond, and ensuing in-plane distortion. This observation could provide a specific explanation for the high level of regiocontrol observed in the oxidative Heck procedure, and perhaps more generally in square–planar substituted aryl complexes where an adjacent ring-substituent is enforced into coplanarity with the adjacent *cis*-substituent on the metal.

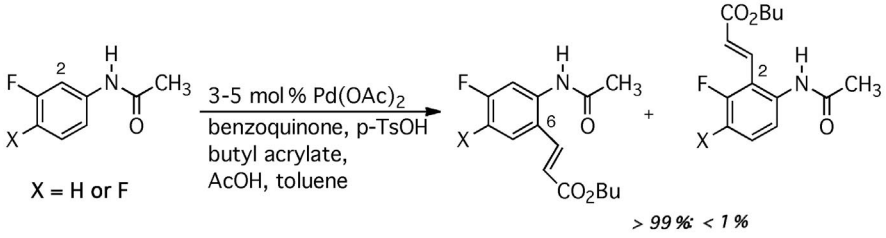


Fig. 4 The high level of regiochemical control observed in alkenylation of 3-fluoroacetanilides.

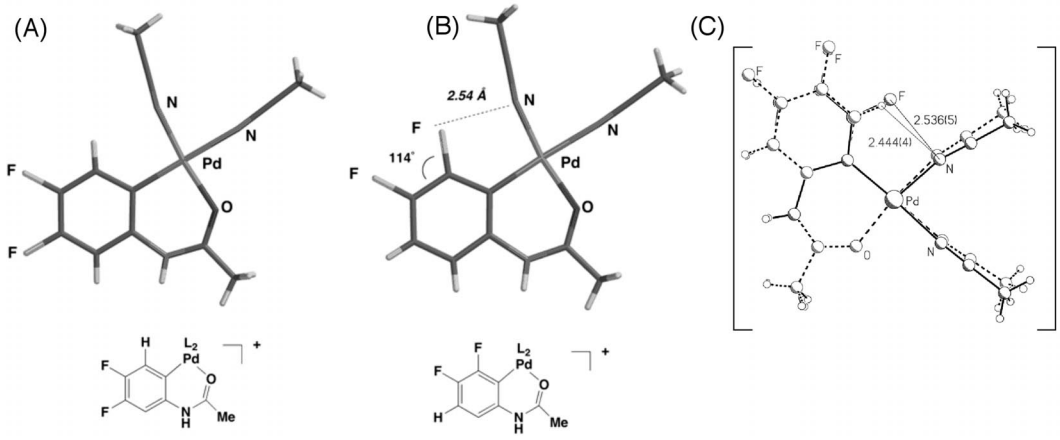


Fig. 5 X-ray structures of the two cationic palladacycles (A) formed directly from 3,4-difluoroacetanilide and (B) formed via palladation of its 2-TMS derivative, and showing the short F...N contact. In (C) the two structures have been superimposed so that the distortion of the square plane introduced by the 2-fluoro substituent in (B) (full bonds) is directly compared with the isomer (A) (dashed bonds).

The ease of palladation of the trimethylsilyl (TMS) derivative evidenced in the route to (B) led to a further development. If Me_3Si can function as the electrophilic leaving group in a stoichiometric reaction, is it feasible to carry out catalytic alkenylation by the same route? This was readily tested according to the procedure of Fig. 6a, under similar conditions to the C–H activation-based examples described above. A general method for the introduction of a TMS group would require prior lithiation of the aromatic ring aided by a directing group that was also capable of activating the palladation step. The parent acetanilides are unsuitable because of the potential for competing deprotonation of the acetyl methyl group. *ortho*-Silylation by this protocol is however successful for a phenolic *t*-Boc group, but then the product is unstable to the conditions of palladium catalysis, the Boc group being competitively removed. A successful balance of the requirements for both lithiation and palladation was achieved when the related urea was employed, the desired reactant being readily prepared by addition of a secondary amine to the appropriate aromatic isocyanate. The urea may then be lithiated smoothly and trapped with Me_3SiCl to give the corresponding silyl derivative. As will be seen, the availability of silylated ureas for palladation chemistry did not provide a general route to regiocontrolled couplings, but enjoyed modest success in one specific area of application. In addition to that, two interesting and unexpected outcomes were achieved, as follows. With an *ortho*-silylated urea on hand, a direct comparison was made with the corresponding silylated amide in oxidative alkene coupling. Catalytic reaction between the amide and butyl acrylate (Fig. 6a) was carried out under conventional conditions, and the desired product of desilylation/alkenylation was observed. It was accompanied, however, by a significant quantity of an isomer. This is best explained by a competing acid-induced desilylation process, followed by a C–H activation induced alkenylation of the product. When the silylurea reacted under similar conditions, three coupling products were formed (Fig. 6b). The reaction was rapid, but the yield of the product formed via direct silyl replacement was only modest. Clearly, desilylation followed by the "normal" reaction pathway was more important in this instance. A more unusual feature was the appearance of the disubstituted product, not previously seen in our own work, or more generally. This indicated that the urea possessed a greater activating power than the acetamido group in directed C–H activation.

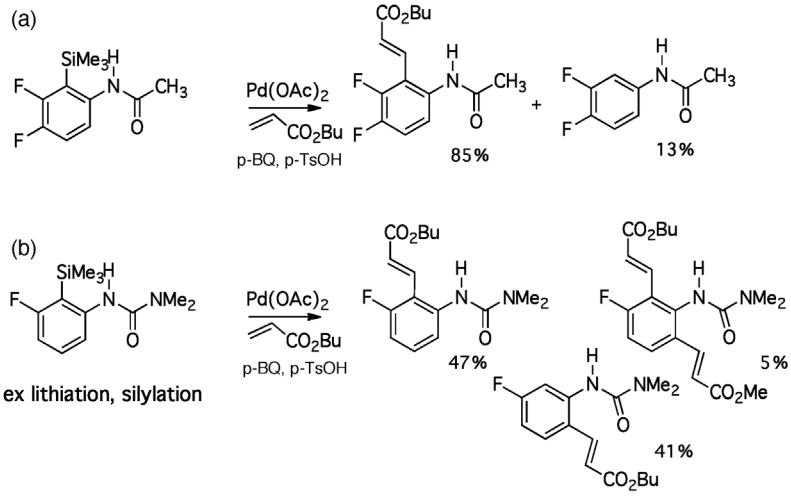


Fig. 6 (a) Alkenylation through desilylation, with an amide directing group. The reaction requires 10 mol % Pd catalyst to minimize competing desilylation; (b) as (a) with a urea directing group, leading to a higher level of side-reactions in a more rapid reaction.

This set of observations indicated that urea direction might be interesting in its own right. Indeed, work by Booker–Milburn and Lloyd–Jones in particular has demonstrated their utility in palladium chemistry [8]. The overall course of an oxidative Heck reaction can be followed by in situ ^{1}H NMR, and an experiment with both urea and anilide reactants present is revealing. The experimental details and the results obtained are shown in Fig. 7. The urea dominates the reaction, and independent work shows that the reactivity of the anilide is suppressed. This indicates that formation of the palladacycle is turnover-limiting and that it is the formation of the urea that is the step enabling its kinetic dominance.

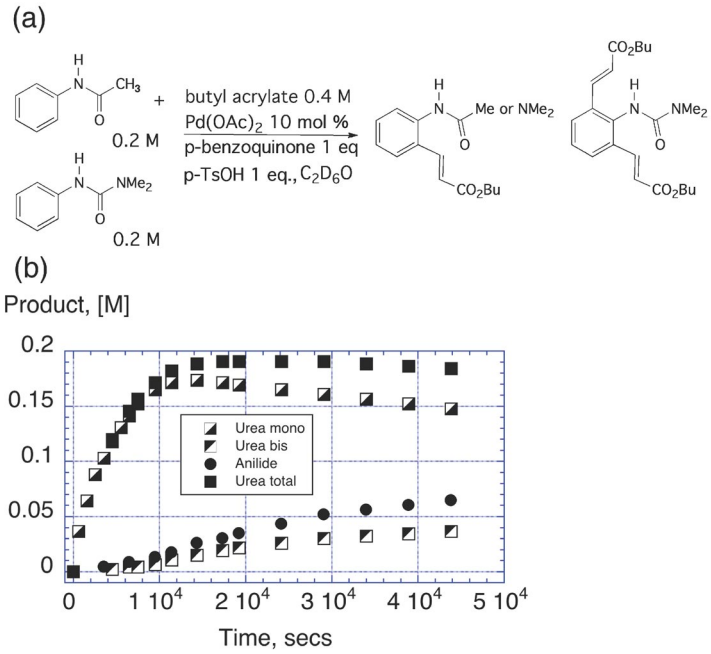


Fig. 7 (a) Internal competition for butyl acrylate between acetanilide and *N*-phenyl-*N*,*N*'-dimethylurea via palladacycle formation; (b) ^{1}H NMR monitoring of the concentrations of the individual products over time.

The results indicated the potential utility of urea activation in catalytic alkenylation reactions, but also demonstrated their tendency to react twice, a trend not shown by the anilides. This indicated that the main application of urea activation, at least within the domain of oxidative Heck reactions, would involve reactants of depressed activity where the first C–C bond-forming step was already difficult. An appropriate series of compounds was already available since Lee and co-workers had already shown that acetanilides bearing halogen at *meta*- or *para*-positions were difficult substrates for this catalyic procedure [9]. In addition, *ortho*-substituted anilides reacted in lower yields. Following these observations, closely corresponding ureas were subjected to standard alkenylation conditions, with the proportion of $Pd(OAc)_2$ limited to 2 mol %. Figure 8 shows that in several cases the results are better than those obtained with amide directing groups. To some extent, the urea overrides the need for an electron-rich reactant in a process that is basically an electrophilic substitution. The disubstitution process was verified as a preparative reaction starting with acetanilide and reacting with 2 equiv of reactant butyl acrylate and the standard reagents. Alternatively, the isolated monosubstitution product was isolated and reacted a second time, leading to the desired double *ortho*-substituted dialkene. In both cases, the yield was ca. 35 %. More generally, rapid alkenylation of ureas was noted, the drawback as stated being a decreased regioselectivity. The increased flexibility of the urea functionality arising from the lower bar-

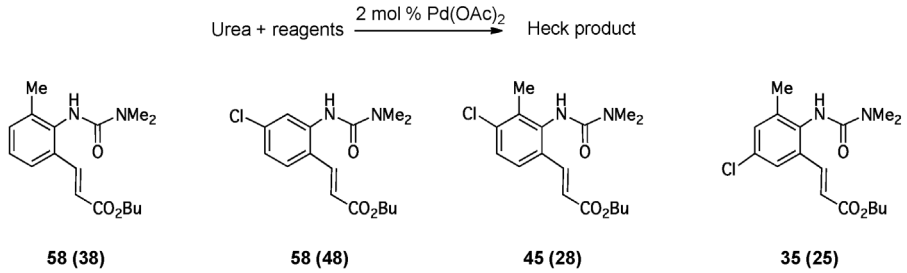


Fig. 8 Comparison between ureas and anilides in directed alkenylation. The numbers refer to isolated yields in the urea case with 2 mol % catalyst; the numbers in brackets refer to the literature isolated yield from anilides with 5 mol % catalyst.

rier to rotation about the HN–CO bond [10] may be a strong factor in promoting palladacycle formation in the urea case.

PALLADACYCLIC INTERMEDIATES IN THE CATALYTIC ALKENYLATION OF ARYLTRIALKYLSILANES

The experiments described in Fig. 6 indicate that formation of a palladacycle by displacement of C–Si is easier than by C–H displacement. In the example shown, formation of the alkenylation product under Heck conditions by silyl displacement was accompanied by competing protodesilylation. In order to gain a cleaner discrimination between these two pathways, an optimization screen was carried out, starting with TMS as the electrophilic leaving group. Benzanilide was chosen to demonstrate the reaction, since this is known to react in the anilide ring under standard oxidative Heck conditions, and also to be substituted in the amide ring following lithiation and trapping with TMS chloride. As a general observation, palladacycles formed from electron-poor aromatic precursors are not so common, and few examples of carbonyl-bonded 5-ring palladacycles have been crystallographically characterized. It was found (Fig. 9a) that alkenylation did indeed occur but that it was accompanied by loss of the silyl group promoted by acid. The most favorable conditions are shown and required fine-tuning of promoting acid with the best results obtained with $PhPO_3H_2$; the reaction was impracticably slow under these conditions. Since the lithiation of benzanilide is straightforward and also there are many chlorosilanes readily available, substitution at silicon was the preferred variable. The product from phenyldimethylsilyl chloride presents an interesting question. The sp^2-Ph group could compete with the desired endocyclic desilylation through an exocyclic process. Related activation of phenyl groups is well established, especially through the work of Hiyama where the activating group is a benzylic alkoxide *ortho* to the aryl–Si bond [11]. In practice, both of these pathways occur and the competition between them is quite even. At this stage, due consideration was made of the requirements for successful alkenylation by the endocyclic route. Protodesilylation probably requires access of a nucleophile to silicon to facilitate the cleavage process. The key to palladacycle formation is access of the palladium electrophile to the adjacent carbon. If attack at silicon is inhibited, then the desired reaction could be facilitated. This analysis encouraged an attempt to carry out the reaction with a *tert*-butyldimethylsilyl (TBDMS) group attached to the aromatic ring. Applications of the TBDMS functionality have been pioneered by Corey. He demonstrated that its reduced lability, when compared to TMS, made it a superior protecting group for alcohols. When this was applied to the alkenylation of benzanilide the desired reaction pathway occurred without competition from protodesilylation (Fig. 9c). This proved sufficient to demonstrate the potential of palladadesilylation as a synthetic procedure, albeit in a limited domain, and provides an addition to the range of leaving groups accessible to oxidative Heck reactions [12].

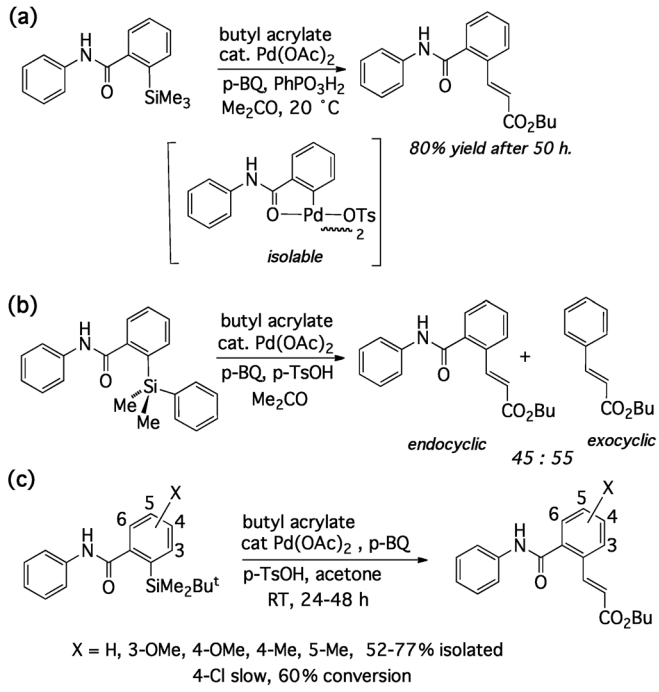


Fig. 9 (a) The optimum conditions for an oxidative Heck reaction involving displacement of a TMS group; (b) the competition between exocyclic and endocyclic pathways in the reaction with butyl acrylate, and (c) the preferred method for alkenylation using TBDMS as the electrophilic leaving group.

CATALYTIC TRANSFER OF METHYL GROUPS BY PALLADIUM ACTIVATION OF TRIMETHYLSILYL-SUBSTITUTED ARENES

In the course of studying the endocyclic activation of the C–Si bond as a means to promote alkenylation, side-reactions were observed to varying degrees. Protodesilylation has already been discussed, but a further unexpected pathway was sometimes evident. On varying the reaction conditions for the transformation of Fig. 9a, a further side-product involving ring methylation was observed. This was more apparent in the related reaction employing the corresponding *N*-methylbenzamide shown in Fig. 10. In this case, side-reactions involving methyl transfer dominate over the C–C bond-forming pathway. In ad-

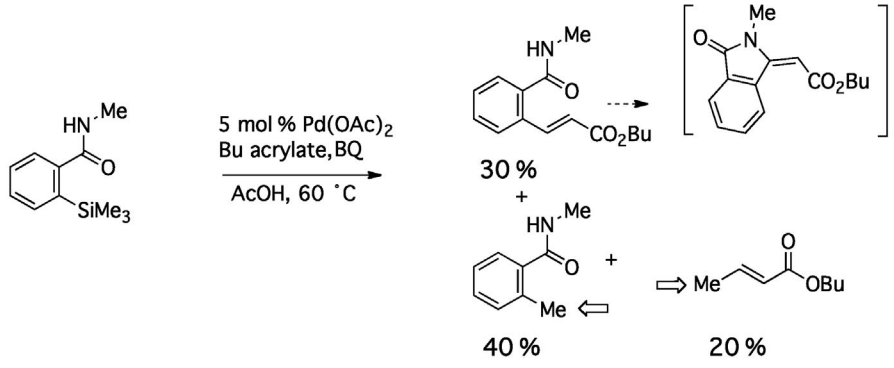


Fig. 10 Anomalous reaction pathways in the attempted alkenylation of 2-TMS-*N*-methylbenzamide.

dition to ring methylation, some of the butyl acrylate is transformed into butyl crotonate. The TMS group is the source of the transferred methyl group, but neither pathway is precedented to our knowledge. The C–Si bond in a TMS group is generally considered robust, although there are scattered examples in the literature reporting its lability toward a neighboring nucleophile [13]. At this stage, it was not known whether the ring methylation process is intramolecular or intermolecular, since attention was then focused on the transfer of a methyl group to butyl acrylate.

The reaction pathway in Fig. 10 that leads to methyl crotonate is formally a Heck reaction in which a methyl group is transferred. Intermolecular Heck reactions involving alkyl transfer are unprecedented, either from Pd(0) or Pd(II) catalysts. Since an isolated $SiMe_3$ group is robust, activation of silicon by the neighboring amide toward methyl transfer was thought to be the likely cause. This encouraged further work on surveying the generality of the reaction and discovering the most favorable precursor. A number of amides, ureas, and an ester, all possessing the potential for a formal 5-ring chelate between the carbonyl oxygen and silicon, were prepared or obtained, and reacted with butyl acrylate according to Fig. 11. In this way, an effective procedure for oxidative methylation of alkenes was developed [14]. Both amides and ureas are effective, the latter marginally more so, and the one ester examined was far less efficient. The synthetic route to ureas via lithiation produced a disubstituted product preferentially and this was generally employed. Ethyl transfer was less effective than methyl trans-

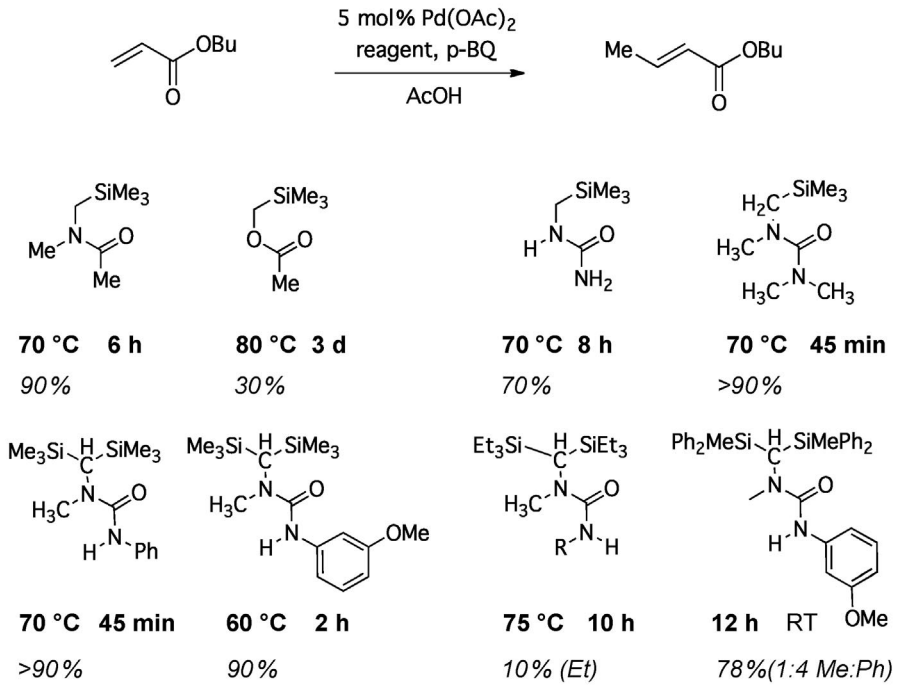


Fig. 11 Carbonyl-induced transfers of a methyl group from TMS to butyl acrylate, under palladium catalysis.

fer by far, and the internal competition between methyl and phenyl transfer showed a preference for the latter, but only to a modest extent.

The success observed in these experiments encouraged a broader extension to synthesis. As a general rule, Heck reactions with neutral catalysts, whether based on Pd(0) or Pd(II), are most effective with lightly substituted alkenes, preferably carrying electron-withdrawing substituents. For this reason, our efforts were concentrated on the reactions of monosubstituted and α,α-disubstituted alkenes. As can be seen from Fig. 12, the chemistry worked well within this range. Overall, the product from mono-

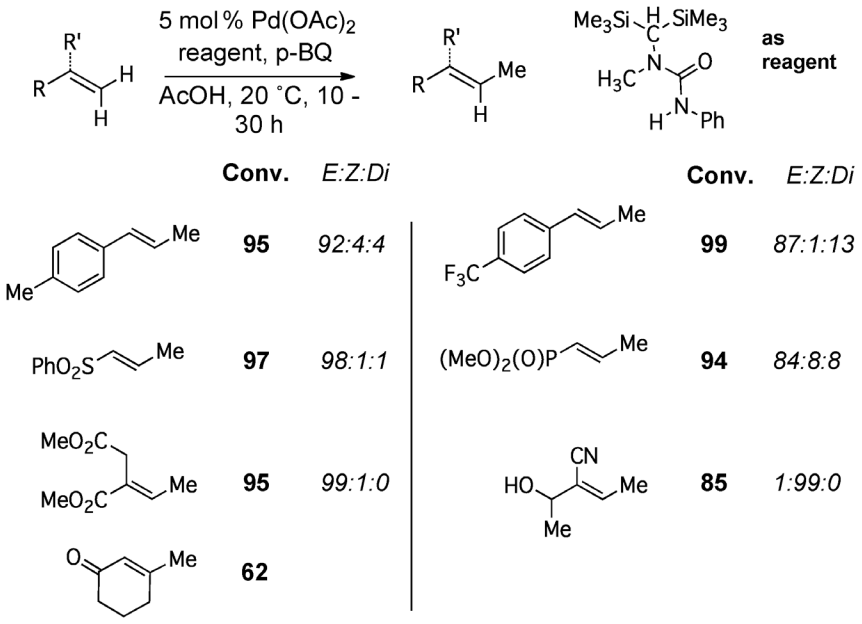


Fig. 12 Synthetic development of catalytic methyl transfer from silylureas.

substituted alkenes was predominantly of *trans*-configuration with a tendency for competing disubstitution. With methyl itaconate, a single diastereomer of the product was formed analogous to the course of a reported Heck reaction involving arylation of the same reactant [15]. The Baylis–Hillman product from acrylonitrile gave the opposite alkene diastereomer in a slow reaction, indicating the possibility that the free hydroxyl group was responsible for stereocontrol. The reactions were carried out with a *bis*-silane as shown and up to 6 equiv of silyl-bound methyl groups are transferable, in principle. In practice, the reaction with butyl acrylate and 0.18 equiv of the *bis*-silane demonstrated that the first 2 equiv are transferred quickly, the second two moderately rapidly and the final two quite slowly.

At this stage, it is worthwhile to consider how methyl transfer could arise and how a catalytic cycle may be constructed (Fig. 13), The key component must be the proximity of the urea or amide component of the reagent to silicon, allowing it to act as an internal nucleophile. The closest analogy in the literature comes from the work of Bassindale and co-workers, through X-ray and NMR studies of the effect of a neighboring carbonyl group on the properties of an Si–X bond [16]. Depending on the electronegativity of X, bond lengthening and structural movement from tetrahedral to trigonal bipyramidal Si is observed. A survey of the crystal structures of compounds with a carbonyl in proximity to TMS, reveals a couple of structures that show a short Si–O bond and distortion of the Si tetrahedron. This suggests methyl transfer occurs as in step (a) with subsequent formation of reactive intermediates in steps (b) and (c). Alternatively, the process may involve alkene coordination from an early stage. When the reactant is *p*-methoxystyrene, the product is not the corresponding arylpropene but the benzylic acetate, and the simplest explanation for this is carbocation involvement by PdOAc solvolysis, leading to the side-reaction of step (f). The remainder of the catalytic cycle follows convention for an oxidative Heck reaction.

In conclusion, the study of regiochemistry in directed oxidative Heck reactions has led to the application of arylureas as directing groups, the discovery of a silane-based analog of the alkenylation reaction and the activation of silicon-bonded methyl groups in palladium coupling catalysis. None of these were planned at the outset.

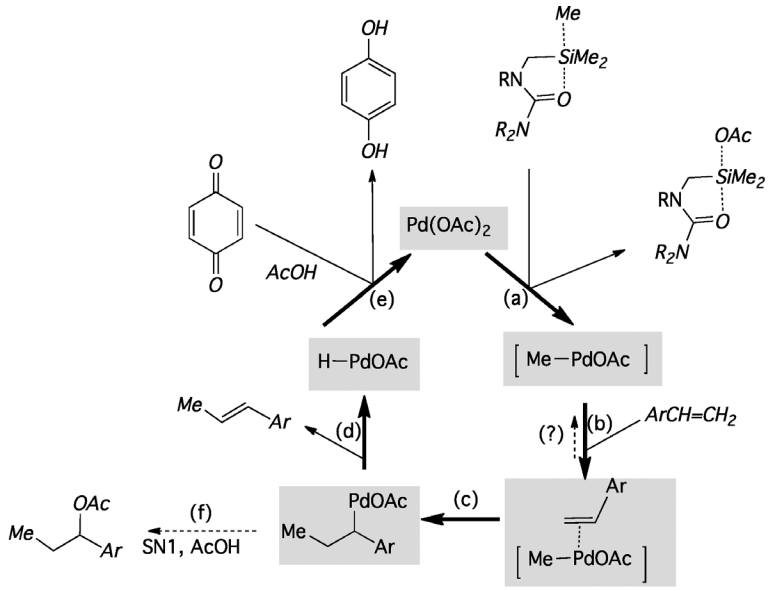


Fig. 13 Proposed catalytic cycle for the Pd-catalyzed methylation of alkenes mediated by silylureas.

ACTIVATION OF CARBON FLUORINE BONDS; C–F AS THE LEAVING GROUP IN ALLYLIC ALKYLATION

In recent years, there has been a revival in organofluorine chemistry, in part driven by the need for access to aryl fluorides and other fluoroorganic species in drug development, and equally by the increasing importance of ^{18}F-labeled compounds in medical imaging. Since ^{18}F has a half-life of under 2 h, catalytic methods that provide rapid access to the desired fluorinated products are desirable, and much recent work has been devoted to their development [17]. Allylic substitution has been one of the mainstays of palladium coupling chemistry, but when our work commenced there were no successful reports either of fluorine as the leaving group or as incoming nucleophile in allylic alkylation chemistry. The ultimate goal was fluorine incorporation, but it was realized that valuable information would accrue from study of the reverse reaction, using allylic fluorides as the reactive substrate.

Our first experiments tested the feasibility of the procedure by palladium-catalyzed reaction of a simple allylic fluoride with nucleophiles derived from dimethyl malonate. The success in these trials encouraged a more detailed study. A central characteristic of palladium-catalyzed allylic substitutions is their stereochemical course. The reaction involves a palladium catalyst that binds the alkene on the opposite face to the leaving group—in this case, fluoride. The nucleophile then attacks on the face of the allyl from which the leaving group departs. The overall result is retention of configuration. 5-Substituted esters of cyclohex-3-enecarboxylic acid were central to the development of stereochemical rules for the reaction [18], and this seemed an appropriate starting point for detailed study (Fig. 14). Conventional methods for the introduction of the allylic fluoride moiety from either of the diastereomerically pure alcohols using DAST (diethylaminosulfur trifluoride) gave a mixture of stereoisomers; an alternative procedure involving a percursor allylsilane was more successful [19]. The products were reactive toward allylic alkylation under a variety of conditions, with a surprising result; the allylic alkylation was not stereoselective! The proportions of product diastereomers depended on the catalyst, with PPh_3 favoring *syn*-product and BIPHEP marginally favoring *anti*-product. The results are out of line with all related reactions that employ different leaving groups.

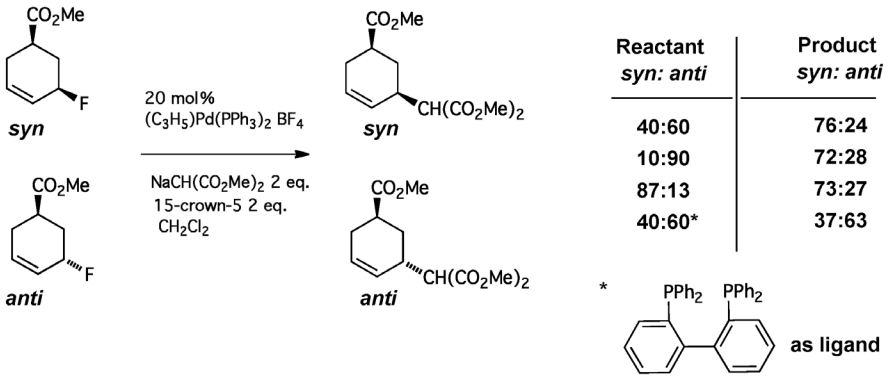


Fig. 14 Allylic alkylations starting with stereoisomeric mixtures of methyl 5-fluorocyclohex-3-enecarboxylate.

Having established that a model allyl fluoride is responsive toward the conventional conditions for allylic alkylation, the next step was to determine the reactivity of fluoride relative to conventional leaving groups. The recently developed stereoselective synthesis of acetoxycyclohexenyl fluorides provided an ideal test [20]. Under several different conditions allylic alkylation occurred, and in every case, fluoride was preferred over acetate as the leaving group (Fig. 15).

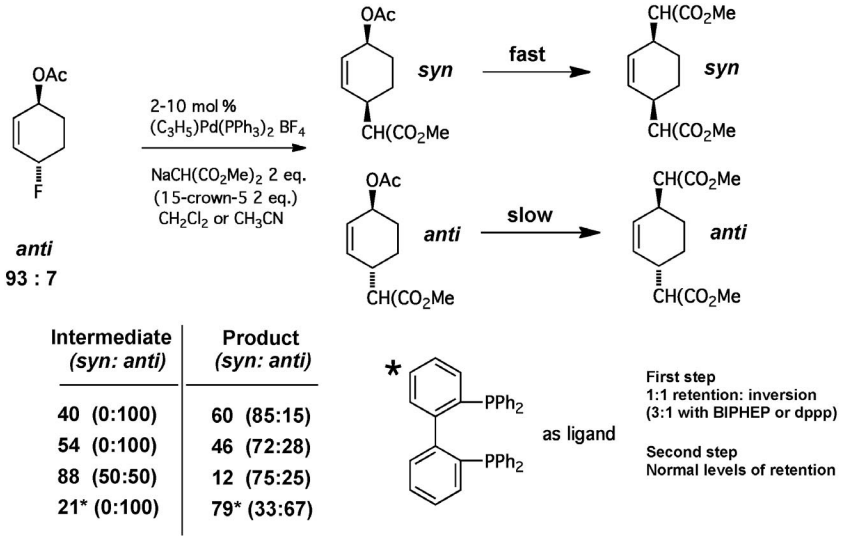
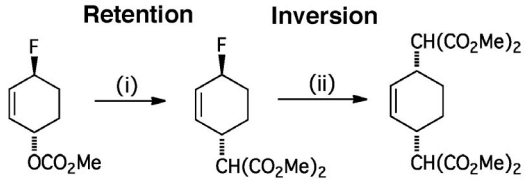


Fig. 15 Comparative reactivity of fluoride and acetate in allylic alkylation catalyzed by palladium complexes.

Just as before, both stereoisomers of the resulting allylic acetate were formed from a single stereoisomer of the reactant. Subsequently, a second allylic displacement of acetate occurred, although the two diastereomeric intermediates reacted at different rates. Quantitative analysis of the reaction is complicated by the fact that under reasonable conditions, both the allylic acetate intermediate (predominantly the slow reacting *anti*-isomer) and the fully substituted product were both present on completion. It was also demonstrated that the proportion of *anti*-acetate produced in the first step increased in proportion to the concentration of added tetrabutylammonium fluoride, although not to the point of stereospecificity. The leaving group potential of acetate is lower than that of other carboxylates, notably benzoate, and far lower than that of an alkylcarbonate [21]. Indeed, both the related benzoate and

methyl carbonate esters reacted to retain fluoride in the first step of allylic alkylation. This provided information on the stereochemical course of the first step with conventional leaving groups, and in each case retention of configuration was demonstrated. For the carbonate case, the intermediate fluorocyclohexenyl malonate was isolable (Fig. 16i). When the intermediate was subjected again to the conditions of allylic alkylation, fluoride was displaced, and in this case predominant inversion of configuration was observed, reinforcing the anomalous role of fluoride leaving groups.



(i) $[Pd(allyl)Cl]_2$ plus 2 PPh_3 2.5 mol %; $NaCH(CO_2Me)_2$, 15-crown-5, THF; 40 % isolated.
(ii) $[(Ph_3P)_2Pd(allyl)][BF_4]$ 20 mol %; s $CH_2(CO_2Me)_2$/BSA

Fig. 16 (i) The first step in reaction of a fluorocyclohexenyl carbonate, showing preferential displacement of the carbonate moiety; (ii) allylic alkylation of the isolated fluoromalonate intermediate demonstrating predominant inversion in the second step.

Interpretation of the stereochemical course of fluoride displacement is hampered by the lack of precedents. Bäckvall and co-workers have shown that inversion of the intermediate palladium allyl is observed in the presence of additional phosphine-bound Pd(0), and suggested that this occurs by a direct displacement of one PdP_2 entity by another [22]. Given that the initial ion-pair formation is likely to lead to a tight association of the allyl with fluoride ion and perhaps extend its lifetime under catalytic turnover conditions. This could encourage higher levels of inversion. Alternatively, fluoride ion could be a ligand for palladium, leading to a neutral complex capable of dissociating to an ion-pair. The formation of an intermediate of this type, although not previously characterized, could explain the increased tendency toward retention of configuration in the presence of excess fluoride ion where the concentration of the intermediate (A in Fig. 17) would be enhanced. This intermediate could also give rise to inversion in appropriate conditions through the ion-pair stereomutation shown as $B \rightleftharpoons \bar{B}$ in Fig. 17. Further experiments are needed to determine the precise origin of the unusual stereochemistry of fluoride displacements in allylic alkylation by palladium catalysts.

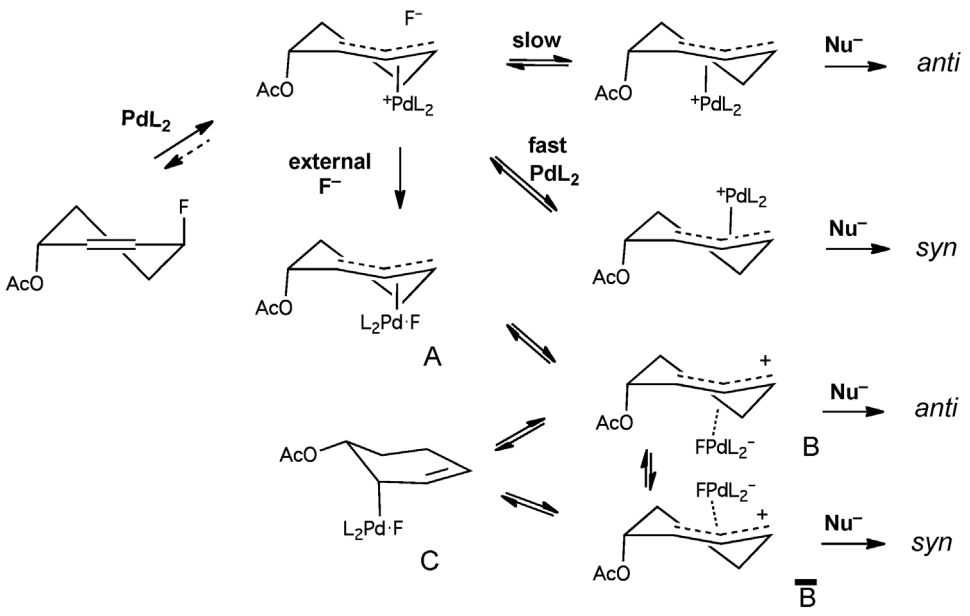


Fig. 17 Possible explanations for the unusual stereochemical course of allylic alkylations involving displacement of fluoride ion.

A summary of the results obtained from the reaction of malonates with bifunctional allyl fluorides is shown in Fig. 18 [23]. The most useful conclusion is that it is possible to tune the reactivity of different leaving groups in allylic alkylation, such that a fluoride substituent may be the reactive or the passive component. The clear preference for methyl carbonate over fluoride as leaving group indicates the possibility for fluoride incorporation through allylic alkylation under the appropriate conditions.

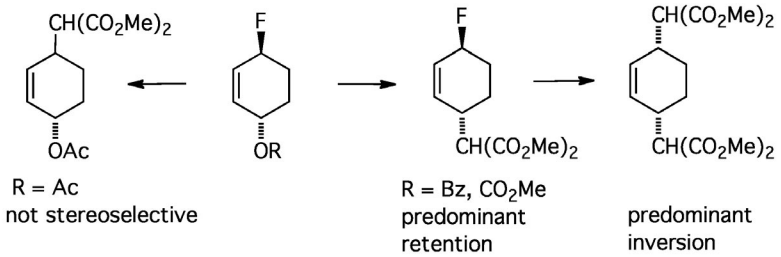


Fig. 18 Summary of the relative reactivities observed in Pd-catalyzed allylic alkylation of bifunctional reactants by malonate.

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