Activation of Allyl Alcohols as Allyl Cations, Allyl Anions, and Amphiphilic Allylic Species by Palladium

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Palladium/Et_3B induces allyl alcohols to undergo electrophilic allylation of soft carbonucleophiles (pK_a 5–14), alkyl aldehydes at the α-position, and amines, indoles, and tryptophan at the 3-position. The same catalyst, and also Pd/Et_2Zn, also effect the generation of allyl anions from allyl alcohols, which react with aromatic and aliphatic aldehydes and imines to furnish homoallyl alcohols and homoallylamines, respectively, in good yields. 2-Methylenepropane-1,3-diol undergoes a sequential amphiphilic activation, generating an allyl cation and an allyl anion, and reacts with aldehydes to furnish 3-methylenecyclopentanols. The amphiphilic activation has been extended to 1,3-bis(alkoxy)-2-methylenepropanes and vinyl epoxides.

1. Introduction

Alkylation of carbonyl compounds, both at the carbonyl carbon (C1, nucleophilic alkylation) and at the α-carbons (α to the carbonyls; C2, electrophilic alkylation), is the most fundamental and useful transformation in organic synthesis. In particular, *allylation* has been employed most widely, thanks to its good performance in terms both of reactivity and yields. Allyl alcohols would be ideal allylating agents because of their availability and stability, but their hydroxy groups are too unreactive to effect the C1 and C2 allylations.

C2 allylation has generally been performed by conversion of allyl alcohols into allyl halides (Scheme 1, pathway c). Allyl acetates and carbonates, like allyl alcohols themselves, are reluctant to undergo heterolytic C–O bond cleavage. However, palladium(0) complexes activate these esters well; π-allylpalladium intermediates, generated in situ through oxidative addition of Pd^0 species to allyl acetates and carbonates, serve as allyl cation equivalents and react with a wide range of nucleophiles (path e; the Tsuji–Trost reaction).[1]

C1 allylation has usually been achieved by use of allylmetals and -metalloids, generated by the metallation of allyl halides (path d, Scheme 1).[2] Bis-π-allylpalladium species, generated by the reaction of π-allylpalladiums and allyltins, also serve as allyl anion equivalents (path f).[3]

An overview of palladium–catalyzed activation of allyl alcohols as allyl cations (pathway a) and as allyl anions (pathway b), as well as a sequential amphiphilic activation of a bis-allyl alcohol as a zwitterionic allylating agent (pathway g), is presented here. These methods, developed by us, may have many advantages over the existing methods (pathways c–f) from practical and economical points of view. A

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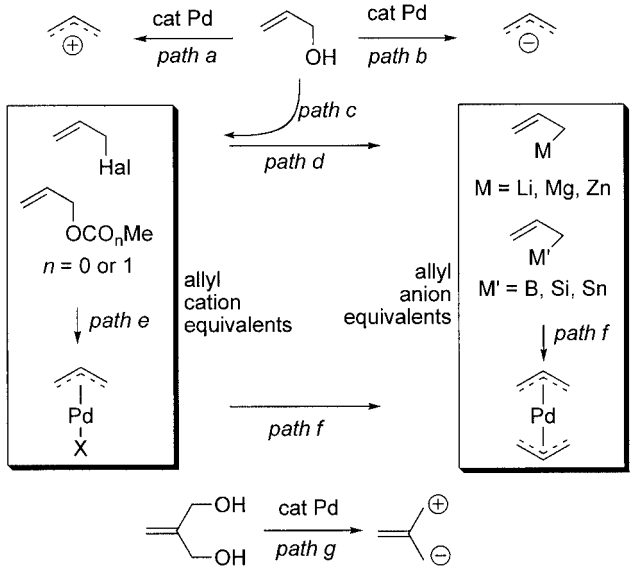
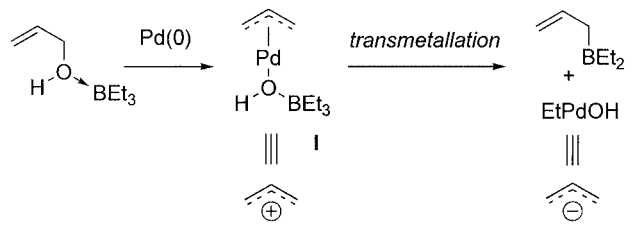
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1. Generation of allyl cations and allyl anions. Traditional methods (pathways c–f) and new methods based on palladium catalysis (pathways a, b, and g).

wide structural variety of allyl alcohols are commercially available and abundant in nature, frequently in a chiral form. They are stable towards many purification procedures (e.g., distillation, column chromatography), making large-scale experiments viable, and may be stored at ambient temperature and under ambient atmosphere. Furthermore, the methods described here are environmentally benign, not requiring either strong, hazardous acids (as required for the preparation of allyl halides and esters) or toxic reagents (e.g., organotins) and only producing water as a side product.[4] In fact, some reactions can be performed even in the presence of water, conditions never allowed for reactions using allylmetal reagents (pathway d).

The most probable reaction mechanism responsible for the generation of both allyl cation and allyl anion species is outlined in Scheme 2, with pivotal roles being played by Et_3B. Unlike other organometallics, Et_3B resists hydrolysis by water and alcohols.[5] Rather, it activates alcohols toward oxidative addition of a Pd^0 species by coordination to the hydroxy group. A thus formed π-allylpalladium species **I** serves as an allyl cation toward a variety of nucleophiles. Provided that no appropriate nucleophiles were present, **I** would be subject to an allyl–ethyl exchange reaction, providing allyldiethylborane and ethylpalladium^{2+} hydroxide. The former works as an allyl nucleophile and the latter might decompose in many ways, eventually regenerating a Pd^0 species (e.g., ethylene, water, and Pd^0).

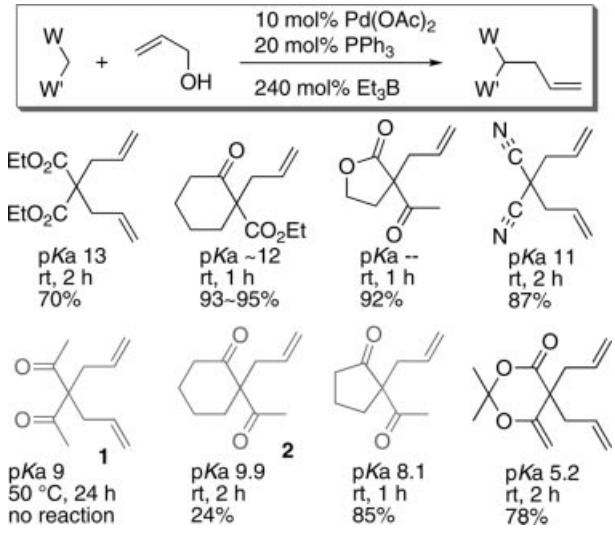


Scheme 2. Pd-catalyzed, Et_3B-promoted generation of an allyl cation (**I**) and an allyl anion species.

2. Activation of Allyl Alcohols as Allyl Cations

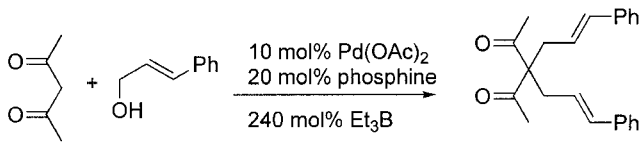
As early as the 1970s it was noted that some soft carbon-nucleophiles (acetylacetone, β-keto esters, malonates) would undergo direct allylation with allyl alcohols with palladium catalysis, though under harsh conditions (e.g., 100 °C).[6] Meanwhile, many methods based on in situ activation of allyl alcohols with inorganic acids such as AsO_3,[7] B_2O_3,[8] or CO_2[9] or with Lewis acids such as Ti(O-*i*Pr)$_4$[10] have been devised. A breakthrough has been brought about by employing palladium complexes with sp^2-hybridized bidentate phosphane ligands; with catalysis by these complexes, alkylation of amines, malonates, and β-keto esters with allyl alcohols proceeds at 50 °C and provides the expected products in excellent yields.[11]

Scheme 3 summarizes Et_3B-promoted alkylation of soft nucleophiles with varying pK_a values.[12] Most reactions, except for those of acetylacetone (AA, e.g., **1**) and 2-acetylcyclohexanone (AC, e.g., **2**), are complete within a few hours at room temperature, and the yields are satisfactory.



Scheme 3. Alkylation of soft nucleophiles (pK_a, 5–14) with allyl alcohol.

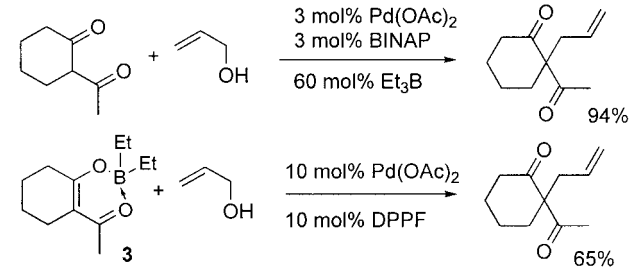
Et_3B withstands hydrolysis by water and alcohols, but it readily undergoes hydrolysis when exposed to organic acids with chelating ability (e.g., 2-hydroxypyridine, AA, AC) to form cyclic diethylboric acid esters (e.g., **3**, Scheme 5).[13] This, however, is not the main reason for the reluctant reactivity of AA and AC, because the structurally similar 2-acetylcyclopentanone is similarly reactive to other soft nucleophiles (Scheme 3). At the moment the reason is not clear, but as is shown in Schemes 4 and 5, the reactivity of AA and AC is recovered by use of a bidentate phosphane ligand with a large bite angle. There seems to be a good correlation between the isolated yields and bite angles (Scheme 4): the larger the bite angles, the better the yields of the alkylation products.



phosphine	bite angle (°)	% yield
PPh_3	---	trace
DPPE	85	36
DPPP	95	32
DPPB	99	65
DPPF	106	78

Scheme 4. Dependence of yields on the bite angles of bidentate phosphane ligands. DPPE, DPPP, DPPB, and DPPF stand for 1,2-bis(diphenylphosphanyl)ethane, 1,3-bis(diphenylphosphanyl)propane, 1,4-bis(diphenylphosphanyl)butane, and 1,1′-bis(diphenylphosphanyl)ferrocene, respectively.

The first example in Scheme 5 demonstrates that, through the use of BINAP as a ligand, the loading amounts of $Pd(OAc)_2$ and Et_3B can be reduced to ca. one third of those employed under the standard conditions. This implies that a subcatalytic amount of Et_3B is sufficient to bring the reaction to completion. The second example in Scheme 5, undertaken with an isolated borate **3** as the starting material, indicates that not only Et_3B, but also the apparently less Lewis acidic **3** is effective enough to activate allyl alcohol to generate π-allylpalladium. In the absence of Et_3B or palladium, of course, no allylation takes place.



Scheme 5. Reactions of 2-acetylcyclohexanone (AC) and its Et_3B complex **3** with allyl alcohol in the presence of bidentate phosphane ligands with large bite angles. BINAP stands for 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

Figure 1 shows that alkylation under standard conditions is quite satisfactory for a wide structural variety of allyl alcohols, encompassing primary and secondary alcohols. Unsymmetrical allyl alcohols predominantly tend to furnish straight-chain isomers (γ) over branched ones (α). Cinnamyl alcohol exclusively provides a straight-chain isomer in good yield.

In order to accomplish α-alkylation of ketones through palladium catalysis, the existing methods require both reaction partners to be preactivated: allyl alcohols as their esters, ketones as their enol ethers.[14] In sharp contrast, the Pd/Et_3B catalytic system can successfully be applied to the alkylation of *o*-hydroxyacetophenone (Scheme 6).[15] The reaction proceeds at room temperature and is complete within 24 h. The table in Scheme 6 clearly indicates that the second alkylation proceeds much more rapidly then the first

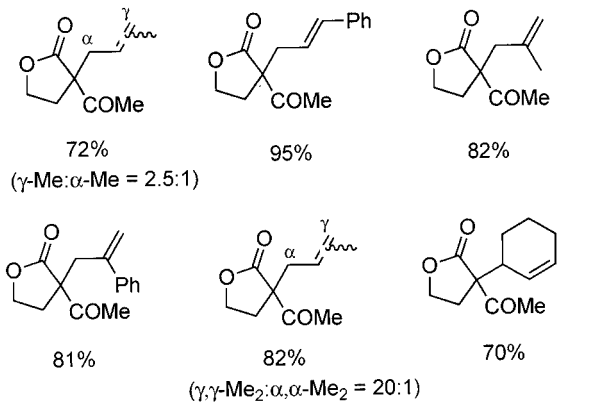
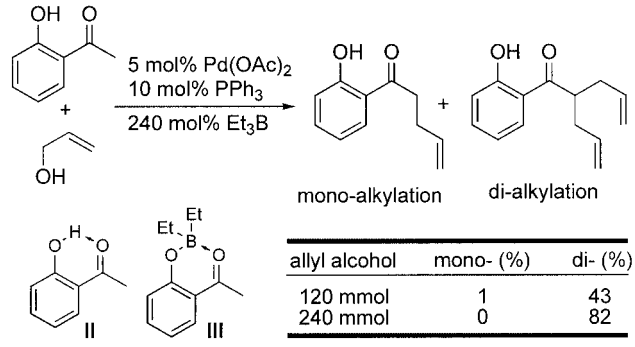


Figure 1. Alkylation of α-acetyl-γ-butyrolactone with a wide structural variety of allyl alcohols under the standard conditions (see Scheme 3).

one. The third alkylation proceeds much more slowly than the two preceding processes, and no trialkylation product is formed even in the presence of a large excess of allyl alcohol.



allyl alcohol	mono- (%)	di- (%)
120 mmol	1	43
240 mmol	0	82

Scheme 6. Pd-catalyzed alkylation of *o*-hydroxyacetophenone with allyl alcohol.

Unfortunately, the reaction is limited to *o*-hydroxyphenyl alkyl ketones. None of the acetophenone derivatives listed in Figure 2 are reactive, which suggests that promotion of the enolization of the α-carbon either by an intramolecular hydrogen-bonding process (**II**) or by coordination of B to carbonyl oxygen (e.g., **III**, vide infra) is essential for the reaction to proceed.

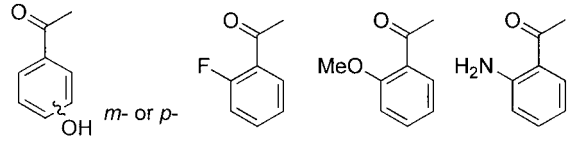


Figure 2. Acetophenones unreactive toward alkylation under the conditions shown in Scheme 6.

The reaction tolerates primary, secondary, and tertiary allyl alcohols with a wide variety of substitution patterns on the double bond. A few examples examined with *o*-hydroxypropiophenone (**4**) are listed in Figure 3.

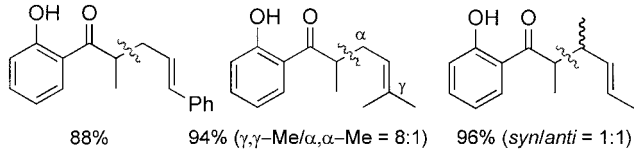
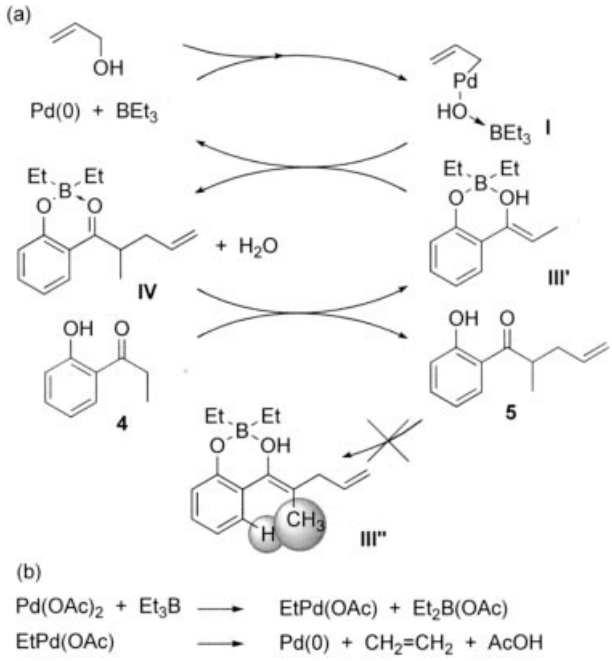


Figure 3. Alkylation of *o*-hydroxypropiophenone (**4**) with a variety of allyl alcohols.

Scheme 7 outlines the most probable catalytic cycle of the reaction with **4** as a substrate, with Et_3B acting to promote the reaction in many ways. First of all, Et_3B may reduce $Pd(OAc)_2$ to a Pd^0 species in a few steps [Scheme 7(b)]. Ethyl group transfer from B to Pd^{2+}, followed by β-H elimination, might provide a mixture of Pd^0, ethylene, and acetic acid. Diethyl(acetoxy)borane, a mixed acid anhydride of a boric acid and acetic acid, would react with **4** to form a phenolic ester, which would equilibrate with its enol form **III′**. A π-allylpalladium species **I** and **III′** would collapse to yield **IV**, water, Et_3B, and Pd^0; the latter pair would be utilized for a new catalytic cycle. An intermediate **IV** then undergoes transesterification with **4** and yields a final product **5** and an intermediate **III′**.



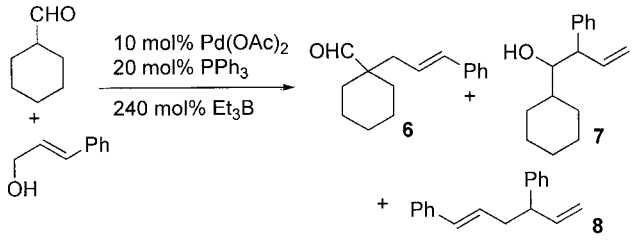
Scheme 7. a) Catalytic cycle with respect to Pd^0 and Et_3B for alkylation of **4** with allyl alcohol. b) Generation of catalytically active species, Pd^0 and $Et_2B(OAc)$.

The catalytic cycle suggests that the reaction should also be catalytic with respect to Et_3B. In fact, the reaction between **4** and allyl alcohol performed in the presence of Et_3B (60 mol%) was complete in 5 h at room temperature and provided **5** in 96% yield. Of course, no reaction takes place in the absence of Et_3B.

Lack of further alkylation of **5** may be ascribed to difficult availability of a tetrasubstituted enol (e.g., **III′′**), which suffers from steric repulsion between the groups indicated by gray circles ($A^{1,3}$-allylic strain).[16]

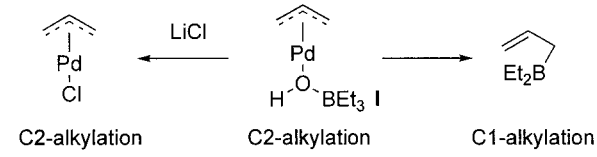
Traditional stoichiometric α-alkylation of ketone enolates (e.g., lithium enolates) has in some cases been performed successfully at lower temperatures. This method has hardly been extended to aldehydes, however, since aldehyde enolates are prone to undergoing many side reactions: aldol condensation, the Cannizaro reaction, the Tishchenko reaction, and so on. Palladium catalysts effect the C2-allylic alkylation of aldehydes with combinations of enol ethers or enamines of aldehydes and allyl esters or allyl halides.[17]

In this context, the alkylation recorded in Run 4 in Scheme 8, directly with an aldehyde and an allyl alcohol, is remarkable.[18] Under the usual Pd/Et_3B conditions (Run 1), cyclohexanecarbaldehyde provides a mixture of C2 alkylation (**6**) and C1 alkylation (**7**) products, together with a cinnamyl alcohol homocoupling product **9**. In this reaction, additives play decisive roles: Et_3N increases the yield of **6**, while LiCl impedes the reaction. Surprisingly, however, a combination of Et_3N and LiCl works effectively to yield **6** selectively. Triethylamine may serve to increase the enol content and to facilitate the formation of **6**. On the other hand, lithium chloride may act to transform **I** into the π-allylpalladium chloride, an active C2 alkylation species, and hence interrupt the formation of allylborane, an active C1 alkylation species (Scheme 9).



run	additive (mol%)	temp/ time (h)	% isolated yield 6	7	8
1	none	rt/4	30	39	20
2	Et_3N (120)	rt/18	70	23	0
3	LiCl (120)	50 °C/36	0	0	0
4	Et_3N (120) + LiCl(120)	rt/40	92	4	0

Scheme 8. Additives, Et_3N and LiCl, effecting the selective C2 alkylation of an aldehyde.



Scheme 9. The role of LiCl in effecting C2 alkylation.

Representative results for the alkylation of secondary aliphatic aldehydes are summarized in Figure 4 and should suffice to demonstrate the generality of the reaction. Especially rewarding is the last example, of a dienyl aldehyde being produced in good yield. The starting material, divinyl carbinol, is notorious for its thermal instability and tends to undergo polymerization under conditions generating carbocation species.

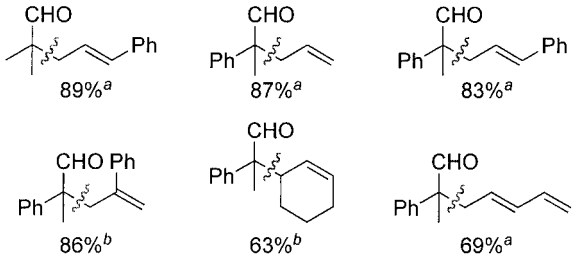
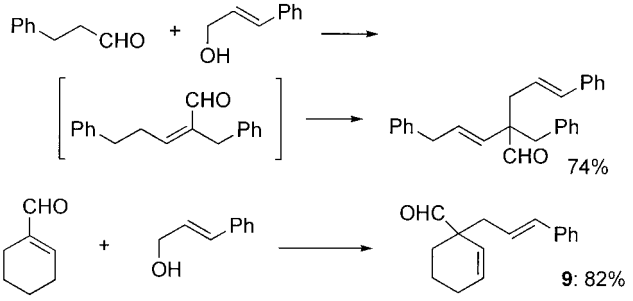


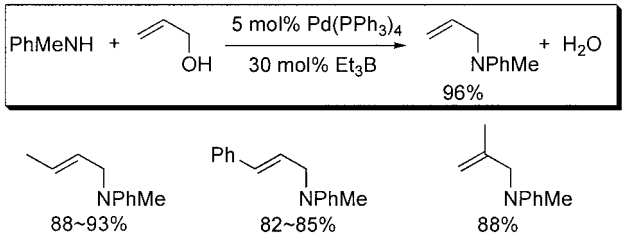
Figure 4. C2 Alkylation of *sec*-aldehydes with a variety of allyl alcohols. a) 10 mol% $Pd(OAc)_2$/20 mol% PPh_3. b) 5 mol% $Pd(OAc)_2$/10 mol% PPh_3.

Primary aldehydes first undergo aldol condensation and then α-alkylation of the aldol products (Scheme 10). 1-Cyclohexenecarbaldehyde, which might be regarded as an aldol product of heptanedial, reacts in an expected way with cinnamyl alcohol and provides 1-*trans*-cinnamyl-2-cyclohexenecarbaldehyde (**9**) in excellent yield.



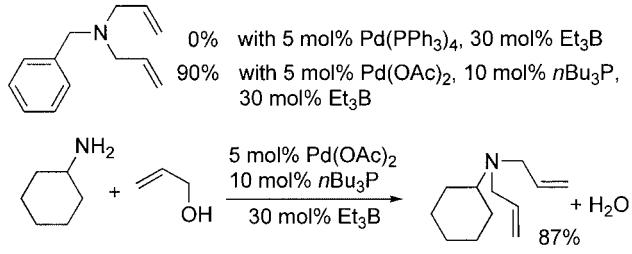
Scheme 10. C2 alkylation of primary aldehydes accompanied by aldol condensation.

The Pd/Et_3B catalyst system has also been successfully applied to the alkylation of amines with allyl alcohols.[19] The reaction displays remarkable ligand effects: alkylation of aromatic amines is effected by $Pd(PPh_3)_4/Et_3B$ and is successful for a variety of allyl alcohols (Scheme 11), while the catalyst fails completely in the alkylation of aliphatic amines (Scheme 12). Benzylamine, for example, remained intact under the conditions. On the other hand, the $Pd(OAc)_2/P(nBu)_3/Et_3B$ system effects alkylation and provides *N*,*N*-di(allyl)benzylamine in quantitative yield. Although the reason is not clear at the moment, these contrasting results might be primarily attributable to the stereoelectronic effects of amines on the binding strength (or binding mode) to Et_3B.



Scheme 11. Alkylation of aromatic amines with a variety of allyl alcohols.

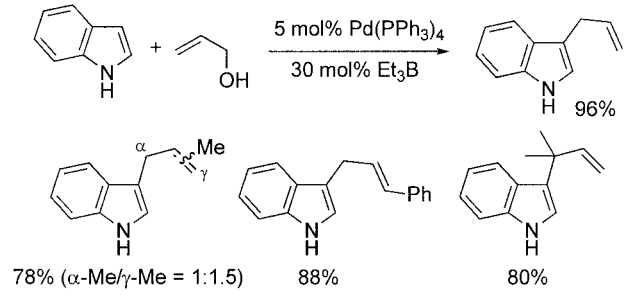
It is noteworthy that large excesses of amine – ca. threefold with respect to Et_3B – are present under the conditions



Scheme 12. Alkylation of aliphatic amines with allyl alcohol, showing remarkable phosphane ligand effects.

shown in Scheme 11 and Scheme 12, and hence no free Et_3B seems to be available. Even under such conditions, however, the activation of allyl alcohols still takes place smoothly. ^{11}B NMR studies indicate that primary amines such as cyclohexylamine form tight 1:1 complexes with Et_3B. All these results suggest that free Et_3B, present only in very tiny amounts in the acid–base equilibrium, still works as an activator of allyl alcohols.

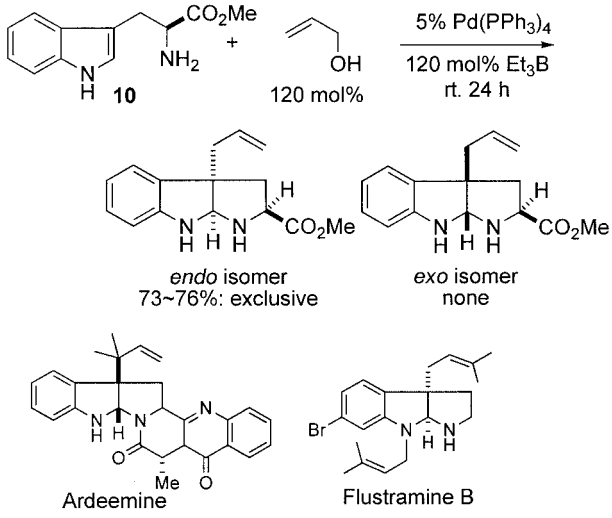
Indole is an ambident nucleophile, reacting at *N* and C3, and its regioselective alkylation is a matter of concern for synthetic organic chemists.[20] The Pd/Et_3B system is able to promote the selective C3 alkylation of indole with a wide structural range of allyl alcohols;[21] yields are excellent in all cases (Scheme 13). The reaction shows unusual regioselectivity: crotyl (and α-methylallyl) and cinnamyl (and α-phenylallyl) alcohols react as usual, providing straight-chain isomers as the major products (e.g., cf., Figure 1), while prenyl alcohol and α,α-dimethylallyl alcohol each react to furnish a branched isomer exclusively and in good yield. These data indicate that the reaction might be more complicated than would be expected of a simple Friedel–Crafts-type alkylation.



Scheme 13. C3-selective alkylation of indole with a variety of allyl alcohols, showing contrasting regioselectivity.

Tryptophan methyl ester (**10**) is a good substrate for Pd/Et_3B-catalyzed alkylation (Scheme 14).[21] Remarkably, the reaction not only takes place exclusively at C3, two kinds of amino nucleophiles remaining intact, but is also stereoselective, exclusively providing an *endo* isomer in excellent yield.

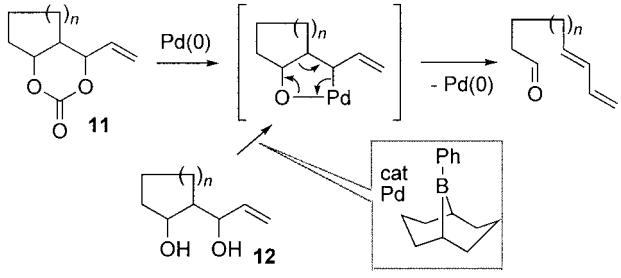
The origin of the stereoselectivity is not clear at present, but it should be noted that an *N*-Boc derivative of tryptophan methyl ester gives an *exo* isomer, the opposite diastereomer to the present alkylation, with high diastereoselectivity (20:1) upon treatment with *N*-phenylselenyl-suc-



Scheme 14. The C3 regioselective and *endo*-stereoselective alkylation of tryptophan methyl ester (**10**).

cinimide (amino-selenyl cyclization at C2 and C3).[22] The utility of the reaction may be apparent from the close structural similarity to many alkaloids, such as the ardeemine and flustramine families.[23]

In 1997 we reported a novel palladium-catalyzed C–C bond cleavage reaction of bicyclic carbonates **11** (Scheme 15), in which 2-oxapalladacyclopentanes, formed by oxidative addition of a Pd^0 species to an allylic C–O bond and decarboxylation, undergo β-C elimination to yield ω-dienyl aldehydes.[24] The reaction can be performed with direct use of diols **12**, precursors of bicyclic carbonates **12**, as the starting materials.[25] The key stage in the reaction is the activation of the allyl alcohol moiety of **12** to generate π-allylpalladium, which could be achieved by use of a rather special borane reagent, 9-phenyl-9-borabicyclononane (9-Ph-9-BBN), as a Lewis acid catalyst. Et_3B shows only marginal success, tending to undergo hydrolytic decomposition, giving rise to cyclic ethylboric acid esters of **12**.[26] Once formed, such cyclic esters are robust and would no longer react further under the conditions.

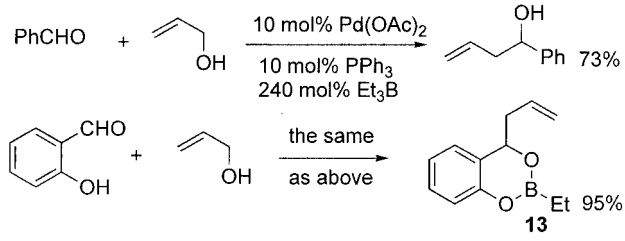


Scheme 15. ω-Dienyl aldehyde synthesis through a novel β-C elimination of 2-oxapalladacycles.

3. Activation of Allyl Alcohols as Allyl Anions

Nucleophilic alkylation of carbonyl compounds with allyl alcohols was first achieved by Masuyama et al., who used a $Pd/SnCl_2$ catalytic system.[27] At first glance, the heterolytic cleavage of an allyl alcohol into an allyl anion and a hydroxy cation species (CH_2=$CHCH_2OH$ → CH_2=$CHCH_2^-$ + OH^+) seems to be formidable, but proved to be achievable by virtue of the capability of a Pd^0 species to undergo oxidative addition at the C–O bond of an allyl alcohol and the capability of $SnCl_2$ to reduce a cationic π-allylpalladium species to an anionic allyltin species, *Umpolung* of a cation to an anion.

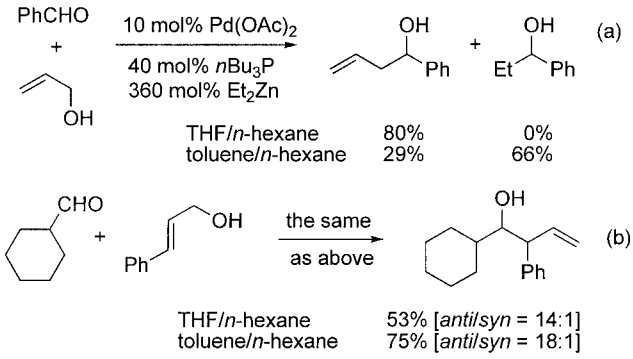
Our Umpolung method for π-allylpalladium, from an allyl cation to an allyl anion, is based on transmetallation between π-allylpalladium and Et_3B (Scheme 2), so both electrophilic and nucleophilic alkylation can be achieved under almost the same reaction conditions (cf., Scheme 3 and Scheme 16).[28] Provided that carbonyl compounds did not possess enolizable protons, they would wait for **I** to change to allylborane and would then react with it to form homoallyl alcohols (Scheme 2).[29] Salicylaldehyde is a particularly good substrate for this allylation and provides products such as cyclic ethylboric esters **13** in excellent yields.



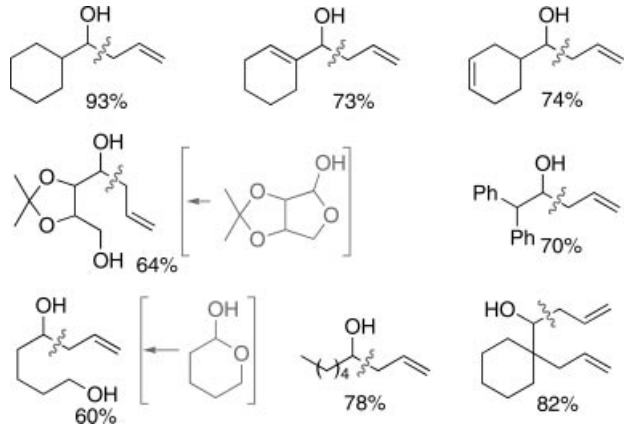
Scheme 16. C1 alkylation of aromatic aldehydes with allyl alcohol.

To perform nucleophilic alkylation, it is desirable to facilitate the transmetallation process (Scheme 2). For this purpose, one can utilize organometallics of more electropositive metals than B (e.g., Et_2Zn, Et_3Al). However, these organometal species react with carbonyl compounds in their own right under certain conditions. Scheme 17 (a), for example, demonstrates Et_2Zn working as an ethyl nucleophile as well as as an Umpolung reagent for π-allylpalladium. The extent of the contributions of these two processes depends both on the solvents and on the carbonyl compounds. For the reaction of benzaldehyde, for example, ethylation predominates over allylation in toluene/*n*-hexane (*n*-hexane, solvent for Et_2Zn), while in THF/*n*-hexane, allylation takes place overwhelmingly. For the reactions of less reactive aldehydes, such as aliphatic aldehydes, ethylation becomes negligible and both solvent systems suffice to perform allylation [see (b) in Scheme 17]. Nonpolar toluene/*n*-hexane is the solvent system of choice for the alkylation of aliphatic aldehydes. This solvent system generally records the better yields and better diastereoselectivities (Scheme 18).[30]

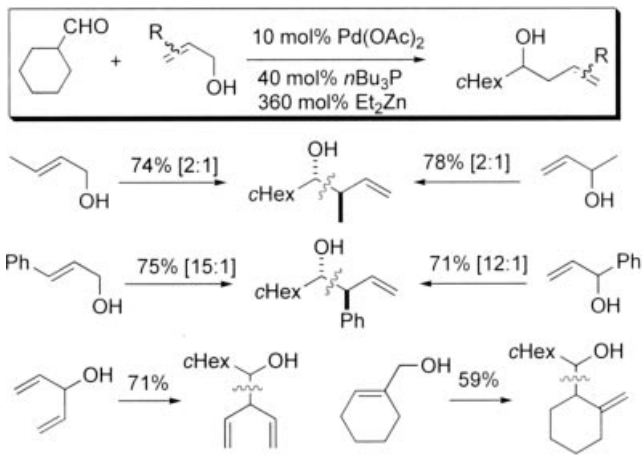
Scheme 18 summarizes some typical examples of allylation reaction of aliphatic aldehydes, demonstrating that all primary, secondary, and tertiary aldehydes are C1 alkylated in reasonable yields. Cyclic hemiacetals also behave in an expected way.[30] The nonpolar solvent system may work



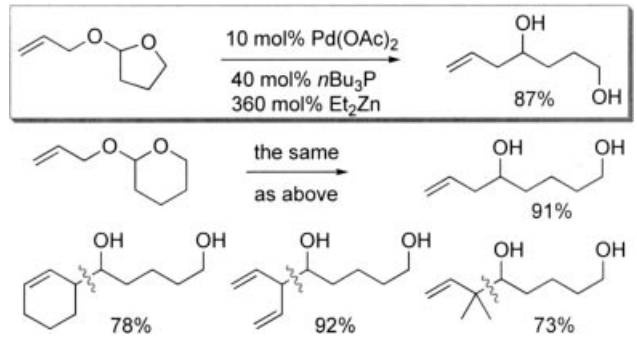
Scheme 17. Solvent effects on allylation vs. ethylation of benzaldehyde (a) and on the yields and diastereoselectivities for the C1 allylation of an aliphatic aldehyde (b).



Scheme 18. C1 allylic alkylation of aliphatic aldehydes in toluene/*n*-hexane at room temperature [$Pd(OAc)_2$ (10 mol%), nBu_3P (40 mol%), Et_2Zn (360 mol%)].



Scheme 19. Regio- and stereoselectivities for the C1 allylation of cyclohexanecarbaldehyde with a variety of allyl alcohols. The structures of major isomers are shown, and the *anti*:*syn* ratios are shown in square brackets.



Scheme 20. Use of protecting groups as useful carbon sources.

to suppress zinc alkoxides to catalyze the aldol and the other side reactions. In fact, during the reaction, zinc alkoxides appear as copious white precipitates, and the reaction mixture becomes very sludgy.

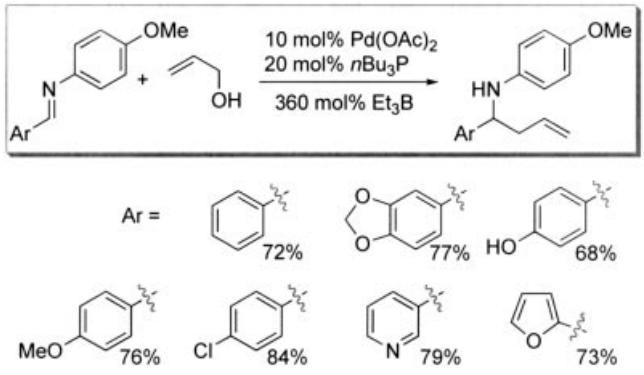
Scheme 19 illustrates the applicability of the reaction to substituted allyl alcohols.[30,31] As usual, allylation takes place at the most substituted allylic termini and provides *anti* isomers as the major products. The observed difference in diastereoselectivity for cinnamyl and α-phenylallyl alcohols is small but significant and suggests that structurally different allylating species participate in this pair of reactions.

Allyl ethers, 2-tetrahydrofuryl ethers, and 2-tetrahydropyranyl ethers have been utilized as protecting groups for alcohols. This means that these groups will eventually have to be removed. In contrast, in our strategy, these ether groups can be utilized as useful C_3, C_4, and C_5 carbon sources (Scheme 20).[30,31] Generation of allyl anions from allyl ethers is energetically more favorable than from allyl alcohols, so these reactions proceed with greater ease and record much better yields.

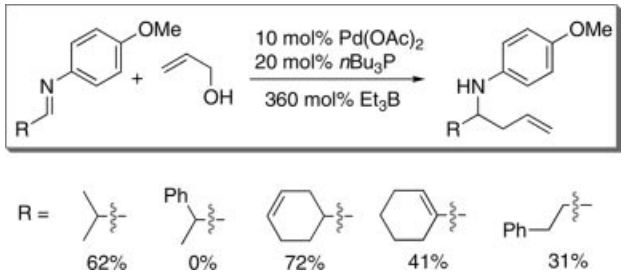
Despite their reduced reactivities, imines prepared in situ from aldehydes and anisidine (and other aromatic amines) smoothly undergo allylation under the Pd/Et_3B conditions.[32] Both aromatic (Scheme 21) and aliphatic aldehyde (Scheme 22) imines are good substrates for the reaction, which tolerates heteroaromatics, phenolic OH and aromatic C–Cl groups (Scheme 21). However, imines with highly enolizable protons fail (e.g., the second example in Scheme 22). The success of the reaction is not due to the increased reactivity of allylboranes toward imines. Rather, it may owe its origin to minimization of the side reactions suffered from by aldehydes, especially to the reduced capability of imines to undergo enolization (cf., Run 1, Scheme 8).

The reaction displays unique stereoselectivity. For example, the reaction between benzaldehyde-anisidine imine and α-methylallyl alcohol furnishes the allylation product as an 8:1 *anti*/*syn* mixture (Scheme 23). To the best of our knowledge, this is the first example demonstrating *anti* selectivity for the allylation of imines from *trans*-crotyl-type (and α-methylallyl-type) substrates; all precedents starting with *trans*-crotyl substrates provide *syn* isomers as the major products, and a transition state like **V** has been proposed to explain the *syn*-selective allylation.[33]

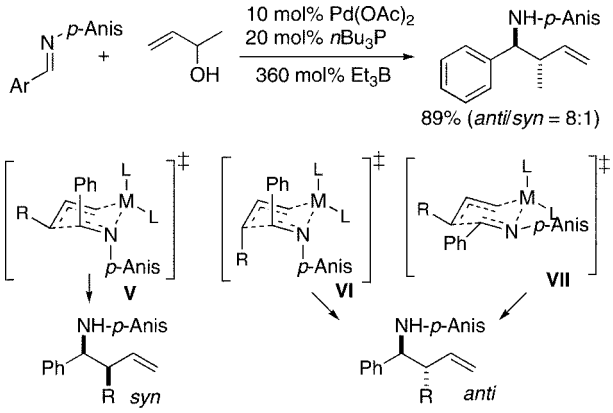
Under these reaction conditions allylboranes would be expected to react with an imine as soon as it was formed,[34] so the *anti* selection suggests that (*Z*)-allylboranes are formed selectively by transmetallation between Et_3B and π-



Scheme 21. C1 allylation of imines from aromatic aldehydes and anisidine with allyl alcohol.



Scheme 22. C1 allylation of imines from aliphatic aldehydes and anisidine with allyl alcohol.

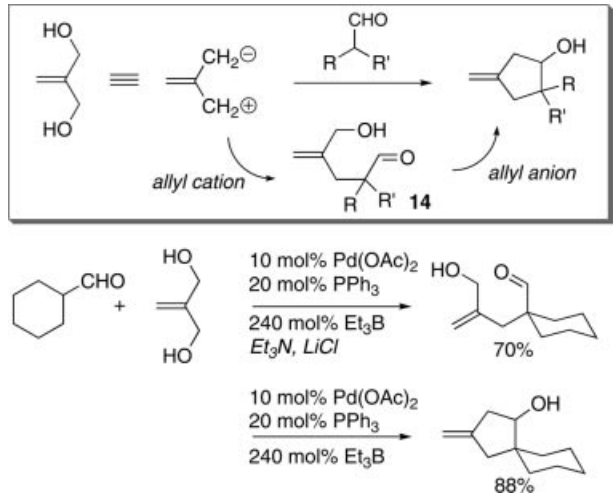


Scheme 23. Unique *anti*-selective alkylation of imines from anisidine and benzaldehyde with α-methylallyl alcohol. *p*-Anis stands for *p*-methoxyphenyl.

allylpalladium species (*syn* or *anti* isomers, which might equilibrate with one anther) and react with *trans*-imine through a transition state **VI** (ML_2 = BEt_2). These transition states **V** and **VI** share a common structural feature, both *trans*-aldimine substituents being oriented in quasi-diaxial positions in cyclic six-membered chair-like conformations. The conformation may be preferred over the corresponding quasi-diequatorial conformation (e.g., **VII**) because the latter should experience severe gauche repulsion between *p*-anisyl and the ligands on the metal (in this case, two Et groups on B).

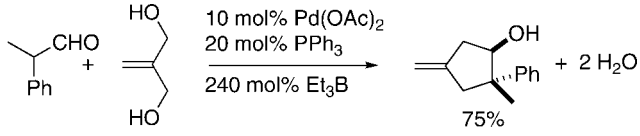
4. Amphiphilic Activation of Allyl Alcohols as Zwitterionic Allylic Species

As reported in the two preceding sections, allyl alcohols can be activated either as allyl cation or allyl anion equivalents. Here it is reported that the two allyl alcohol moieties in 2-methylenepropane-1,3-diol are activated selectively in different ways, one as an allyl cation and the other as an allyl anion (Scheme 24).[35] According to the mechanism discussed in Section 2, one of the allyl alcohols selectively undergoes C2 alkylation catalyzed by Pd/Et_3B *in the presence of* Et_3N *and LiCl*. The remaining allyl alcohol, in turn, serves as an allyl nucleophile under conditions that are the same except for *the absence of* Et_3N *and LiCl*. The intermediate, a hydroxyaldehyde **14**, present mostly in a hemiacetal form, no longer has enolizable protons, so for this particular substrate there is no need to worry about C2 alkylation.



Scheme 24. Sequential amphiphilic (electrophilic–nucleophilic) activation of 2-methylenepropane-1,3-diol.

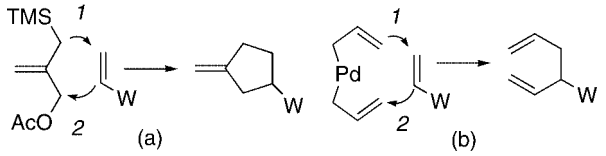
Some aldehydes possessing highly enolizable α-protons, and hence being prone to undergoing C2 alkylation rather than C1 alkylation, achieve sequential C2 and C1 alkylation with a single operation (Scheme 25). The C1 alkylation shows high stereoselectivity, placing the bulkier substituent *anti* to the OH group.



Scheme 25. One-pot amphiphilic activation of 2-methylenepropane-1,3-diol.

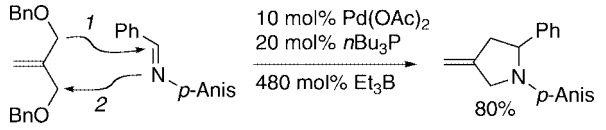
The reaction appears reminiscent of Trost's trimethylenemethane–palladium chemistry [Scheme 26, (a)][36] and Yamamoto's bis-π-allylpalladium chemistry [Scheme 26, (b)],[3] especially Trost's work, because of the close structural similarity of the methylenecyclopentane products. However, the reaction sequences portrayed in Schemes 24 and 25 and those in Scheme 26 are completely opposite to each other in the order of the electrophilic and the nucleo-

philic alkylations, with the nucleophilic allylation (*1*) preceding the electrophilic allylation (*2*) in the latter case.



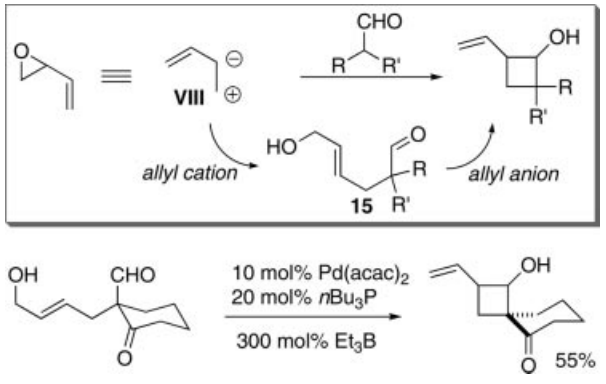
Scheme 26. Sequential nucleophilic allylation (*1*)–electrophilic allylation (*2*) via trimethylenemethane-palladium (a) and bis-π-allylpalladium (b).

Although not being successful yet with 2-methylene-1,3-propanediol (ca. 10%), as illustrated in Scheme 27, the corresponding bis-benzyl ether undergoes sequential amphiphilic alkylation with aldimines, with nucleophilic (*1*)–electrophilic alkylation (*2*) furnishing 3-methylenepyrrolidines in good yield.[37] It should be noted that, despite the similarity of the reaction conditions, the order of reaction sequences shown in Scheme 24 and Scheme 25 and Scheme 27 are opposite to each other.



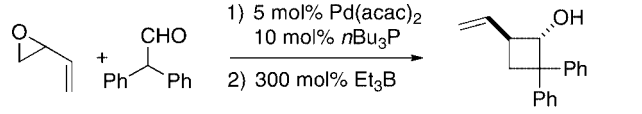
Scheme 27. One-pot amphiphilic [nucleophilic (*1*)–electrophilic (*2*)] activation of 1,3-bis(benzyloxy)-2-methylenepropane promoted by $Pd(OAc)_2/Et_3B$.

Vinyl epoxides are good substrates for nucleophilic allylic substitution with enolizable aldehydes in the presence of a Pd^0 species,[38] providing 6-hydroxy-4-hexenals **15** in good yields, with these then undergoing intramolecular C1 alkylation with Pd^0/Et_3B catalysis (Scheme 28). In this reaction, the vinyl epoxide acts overall as a zwitterionic species: 3-butenyl 2-anion-1-cation **VIII**.[39] The reaction is remarkable in many respects: firstly, the product is a strained aldol, yet no retro-aldol process takes place under the conditions, and secondly, this is probably the first example of palladium-catalyzed cyclobutanol formation. The reverse process, C–C bond cleavage (activation) through ring-opening of cyclobutanols, is currently a popular topic in palladium chemistry.[40]



Scheme 28. Amphiphilic activation of vinyl epoxide as 3-butenyl 2-anion-1-cation **VIII**.

The reaction can be performed in one-pot style, as demonstrated for the reaction between vinyl epoxide and diphenylacetaldehyde. Exposure of the organic substrates to $Pd(acac)_2/nBu_3P$ at room temperature for 3 h, followed by injection of Et_3B and stirring for 3 days at room temperature, furnishes a 2-vinylcyclobutanol derivative **16** in 55% isolated yield (Scheme 29).[39]



16: 55% [*cis*/*trans* = 10:1]

Scheme 29. One-pot synthesis of a 2-vinylcyclobutanol derivative **16** by amphiphilic activation of vinyl epoxide as 3-butenyl 2-anion-1-cation **VIII**.

5. Conclusions

Thanks to their good performance in C–C bond formation reactions, both allyl cation and allyl anion species have been utilized, probably most frequently, in synthetic organic chemistry. As illustrated in Scheme 1, traditional methods generating allyl cations rely on activation of allyl alcohols in the forms of the corresponding halides or acid esters, and the methods generating allyl anions make good use of allylmetals or allylmetalloids with high polarizability.

This microreview outlines methodologies for activating allyl alcohols directly as allyl anions and allyl cations. These activations can be achieved under palladium catalysis conditions in the presence of Et_3B or Et_2Zn as a promoter. The reaction conditions are mild and tolerate a wide variety of functionalities, so the methodologies may find wide applications to the synthesis of complex natural and unnatural products.

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