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Deacylative allylation: allylic alkylation via retro-Claisen activation

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Abstract

A new method for allylic alkylation of a variety of relatively non-stabilized carbon nucleophiles is described herein. In this process of "deacylative allylation" the coupling partners, an allylic alcohol and a ketone pronucleophile, undergo *in situ* retro-Claisen activation to generate an allylic acetate and a carbanion. In the presence of palladium, these reactive intermediates undergo catalytic coupling to form a new C–C bond. In comparision to unimolecular decarboxylative allylation, a commonly utilized method for allylation of carbon anions, deacylative allylation is an intermolecular process. Moreover, deacylative allylation allows the direct coupling of readily available allylic alcohols. Lastly, the full utility of deacylative allylation is demonstrated by the rapid construction of a variety 1,6-heptadienes via 3-component couplings.

Introduction

Decarboxylative allylation (DcA)[1] has emerged as a convenient method for the generation and allylation of carbon nucleophiles including ketone enolates,[2a,b] nitrile stabilized anions,[2c] α-sulfonyl anions,[2d,e] 2-aza-allyl anions,[2f,g] and nitronates[2h] (Scheme 1). In comparison to more classical couplings, DcA reactions are distinguished by the use of C–C bond cleavage (decarboxylation) to generate the nucleophile.[3] One hallmark of decarboxylative metalation is that it has been shown to allow the site-specific generation of a variety of carbon nucleophiles.[2c,d,4] A second hallmark of DcA reactions is the ease with which the reactants are synthesized and derivatized via mild acetoacetic estertype substitution.[5] As a testament to DcA's utility, there has been significant interest in using the reaction for the synthesis of natural products (Scheme 1).[1,6] Despite the demonstrated utility of DcA in natural product synthesis,[6a,b] the sensitivity of allyl esters often necessitates late-stage introduction of the allylic ester via transesterification using excessive amounts of an allylic alcohol and Otera's catalyst (Scheme 1).[7,8] Thus, a clear disadvantage of DcA is the necessity to covalently link the nucleophilic and electrophilic coupling partners through an ester linkage prior to decarboxylative coupling (e.g. in **1**). Ultimately, it would be advantageous if the same C–C bond formation could occur in an intermolecular fashion. Such a process could obviate the need for the two-step transesterification/decarboxylative allylation sequence and facilitate more rapid production of analogs.[9]

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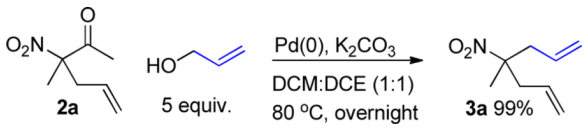
Supporting Information
Experimental procedures and complete compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

We recently communicated the development of "deacylative allylation" (DaA) of nitroacetone derivatives, where intermolecular C–C bond formation was facilitated by a retro-Claisen condensation.[10] As shown herein, the DaA process maintains several hallmarks of decarboxylative allylation. Specifically, it A) allows the site-specific generation of carbanions via C–C cleavage, B) allows rapid synthesis of precursors via acetoacetic ester-like chemistries, and C) forms both nucleophilic and electrophilic reactive intermediates *in situ*. While the literature is replete with reactions that proceed by C–C bond cleavage via retro-Claisen condensation, these reactions typically utilize the acetyl unit only as a readily cleavable activating group.[11,12] In DaA reactions, the transfer of an acyl group has a functional role in activating the allylic alcohol toward reaction with Pd(0) catalysts. Thus, our approach is unique since both the nucleophile and the electrophile are activated by a single C–C bond cleavage event.[10,12] In addition to facilitating intermolecular allylations, DaA is attractive since it results in alkylation of carbanions directly from allylic alcohols.[13] Herein, we wish to report our findings that many ketone pronucleophiles can undergo intermolecular deacylative allylation (Scheme 2). The utility of deacylative allylation is further demonstrated by the rapid construction of 1,6-heptadienes via 3-component bisallylation; such products have significant utility as precursors for cycloisomerizations and cycloadditions.[14]

Development of Deacylative Allylation

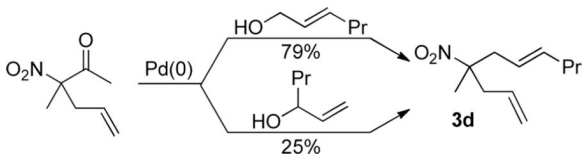
Our driving hypothesis for deacylative allylation is that an allylic alkoxide can induce a retro-Claisen condensation of an appropriately substituted ketone (Scheme 2). The retro-Claisen reaction should produce a carbanion nucleophile and an allylic acetate that can be coupled via palladium catalysis. A survey of the literature showed that there is a plethora of examples of retro-Claisen cleavage reactions of α,α-disubstistuted nitroacetone derivatives.[15] The retro-Claisen condensation of nitroketones is generally facile because the nitronate leaving group is more thermodynamically stable than the alkoxide nucleophile.[16] Nitronates are also known to undergo facile allylic alkylation under standard Tsuji-Trost conditions.[17] Thus, α-nitroketones were ideal substrates for our preliminary investigations and our desire to pursue efficient synthesis of 1,6-heptadienes led us to utilize α-allyl nitroacetone (**2a**) as a model substrate. Initially it was observed that **2a** underwent the desired deacylative allylation quantitatively (eq. 1). However, the reaction conditions (5 equiv. K_2CO_3 and allyl alcohol, 2.5 mol % $Pd(PPh_3)_4$) were unattractive because excessive amounts of alcohol and base were required and the method was not applicable to coupling of substituted allylic alcohols.



(1)

Fortunately, by simply switching from K_2CO_3 to Cs_2CO_3 base, both the base and the alcohol could be used in stoichiometric quantities. Moreover, the simple change in base additive led to facile coupling of many other allylic alcohol derivatives with α,α-disubstituted nitroacetone substrates (Table 1). For example, various commercially available allylic alcohols including cinnamyl (**3b**), crotyl (**3c**), and 1-hexenyl (**3d**) alcohols were successfully utilized as coupling partners. The cinnamyl and the hexenyl alcohols both gave exclusively the linear regioisomeric product as expected for reactions proceeding via π-allyl palladium intermediates.[1,2h] However, when crotyl alcohol was utilized, a mixture of linear/branched regioisomers was isolated (*l*:*b* = 3.8:1) and the linear isomer was obtained as a

mixture of *E* and *Z* isomers (*E:Z* = 5.6:1).[1,18] The allylic alcohol coupling partner can also contain substitution at the internal carbon, as was determined by the successful DaA of β-methylallyl alcohol (**3e**). In addition to simple allylic alcohols, the dienyl allylic alcohol underwent DaA to form product **3f** in 78% yield; such products are potential substrates for the elegant metal-catalyzed intramolecular [4+2] cycloaddition reactions of unactivated dienes and dienophiles that have been developed by Livinghouse and others.[19] While primary allylic alcohols were compatible reaction partners in DaA, a secondary allylic alcohol (1-hexen-3-ol) produced the desired product in just 25% yield (eq. 2). This suggests that deacylative allylation exhibits a steric selectivity for coupling of primary allylic alcohols.



(2)

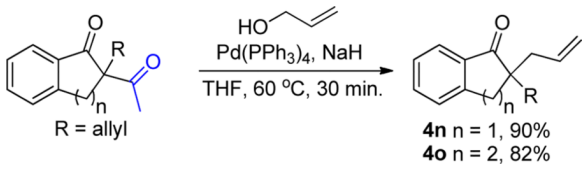
In addition to nitroacetone derivatives, nitrophenylacetylacetone derivatives also underwent smooth coupling with various allylic alcohols to produce allylated nitroarylketones (Table 1, **4a–d**). However, attempts to allylate the more basic *p*-acetylarylketone enolate showed that only allyl alcohol gave product in high yield (**4e**). Furthermore, an unsubstituted phenylketone product was allylated in low yield (**4f**, Table 1). Thus, it was apparent that relatively high enolate stability (pK_a < 20 in DMSO) was required for C–C bond formation under these conditions.

Deacylative Allylation of Ketone Enolates

With the goal of developing a more broadly applicable deacylative allylation, we screened reaction conditions to improve the yield of product **4f** (Table 2). A screen of solvents indicated that, in nonpolar solvents such as toluene, deacylation was sluggish and the desired C–C bond formation was ineffective (entry 1). The somewhat more polar solvent, THF, did promote deacylation but did not lead to substantial allylation (entry 3). Finally, good yields of the DaA product could be isolated in various polar aprotic solvents (entries 4–7), with the best conversion to **4f** occurring in *N*-methylpyrrolidinone (entry 7). Subsequently, a brief screening of bases revealed that strong bases such as potassium *tert*-butoxide or sodium hydride gave excellent results (entries 8–10). Not only is NaH a much less expensive base than Cs_2CO_3, but reaction completion using NaH was realized in a shorter time-frame at a lower temperature of 60 °C. Thus, further studies of reaction scope were done primarily under conditions similar to that of entry 10.

Next, a variety of α-aryl 1,3-diketones were prepared by facile copper-catalyzed enolate arylations followed by mild alkylation.[20] Subsequent treatment under the reaction conditions for deacylative allylation showed that the optimized reaction conditions worked well for the DaA of many different α-aryl acetylacetone derivatives (Table 3). As expected, aryl ketones that contain an electron withdrawing group worked quite well in the deacylative allylation reaction, giving high yields of the desired products **4e–k**. For example, the reaction was compatible with electron deficient aryl ketones (**4e** and **4h**) and benzonitriles (**4g**) as well as with *meta*-nitro (**4i–j**) and fluoro (**4k**) substituents. It was particularly gratifying to find that challenging electron rich aromatic ketones and dialkyl ketones that lack an α-aryl group could be allylated cleanly (**4m–4p**).

Next, we examined the regioselectivity of deacylation in unsymmetric 1,3-diketone substrates that have the potential for reaction at two different carbonyl groups. For indanones and α or β-tetralone, DaA was completely regioselective for cleavage of the exocyclic acetyl over the cyclic ketone (eqs. 3 and 4). While exocyclic acetyl groups can be selectively cleaved, there is little selectivity for cleavage of an acetyl vs. a benzoyl group (eq. 5). Given the lower electrophilicity of esters vs. ketones, it is not surprising that the cleavage of an acetyl group is preferred over the cleavage of an ethyl ester (eq. 6). Nonetheless, this reaction does illustrate that the retro-Claisen reaction is faster than transesterification of the ethyl ester to the allyl ester. Finally, an *aryl* β-ketoester substrate did not react chemoselectively when Cs_2CO_3 was utilized as the base (Scheme 3); the DaA product (**4s**) and a decarboxylative allylation product were formed in a ~1:1 ratio. Interestingly, switching to NaH as the base resulted in complete selectivity for deacylative allylation.



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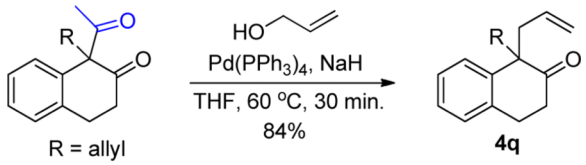

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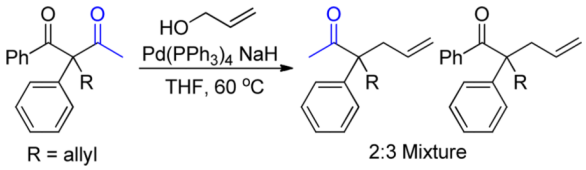

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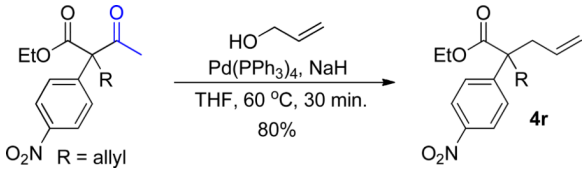


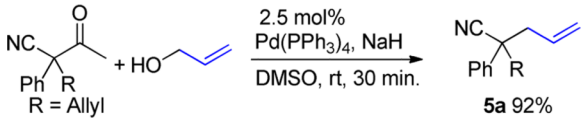
(6)

Having identified β-diketones that undergo deacylative allylation with allyl alcohol, we turned our attention to varying the allylic alcohol coupling partner (Table 4). In general, these reactions were as robust as with simple allyl alcohol but often required longer reaction times for reaction completion. β-Methallyl alcohol underwent deacylative allylation with

similar rates to that of allyl alcohol (**4t–4w**, Table 4), while hexenyl alcohol generated good to high yields of products in 3 hours (**4aa–4dd**). Cinnamyl alcohol was generally the slowest reacting allylic alcohol, usually requiring 8–12 h for reaction completion (**4x–z**). Prenyl alcohol was also a viable coupling partner, although it gave a noticeably lower yield than the other allyl alcohols used (**4ee**). It was particularly exciting that 3-cyclopropyl allyl alcohol was also an excellent coupling partner (**4ff–gg**). The inclusion of the vinyl cyclopropane onto these allylated compounds represents an efficient synthesis of chiral [5+2] precursor substrates (Scheme 4).[21]

In addition to the coupling of ketone enolates via deacylative allylation, we wished to demonstrate the potential utility of deacylation for the generation and allylation of other nucleophiles. α-Aryl cyanocarbonyl compounds are versatile chemical building blocks that can be readily elaborated via classic alkylation (such as K_2CO_3/MeI), palladium-catalyzed α-arylation[22] and allylic alkylation (Scheme 4).[23] Thus, a deacylative allylation of cyanoacetones could lead to a broad array of α-quaternary allylated nitriles.[2a,24,25]

To begin, we investigated the reaction of an α-phenyl cyanoacetone derivative under the conditions that were previously developed for the DaA of 1,3-diketones (eq. 7). Under these conditions, the α-cyanoketone underwent high yielding DaA to generate **5a** rapidly at room temperature.



(7)

As table 5 shows, deacylative allylations of a variety of phenylacetonitriles with allyl alcohol were successful. As before, deacylative allylation provides a straightforward route to 1,6-heptadienes (Table 5, **5a–c**). While these targets were our focus, DaA of simple alkyl-substituted nitriles was also feasible (**5d, 5h**). In addition, a variety of aryl substituents including heteroaromatic, polyaromatic, and electron rich aromatics were compatible with the coupling conditions (**5e–g**). That said, longer reaction times were necessary to couple electron-rich aryl acetonitrile derivatives (**5g, 5h**).

Following the successful coupling of allyl alcohol via deacylative allylation, the DaA reactions of quaternary α-aryl cyanoacetones with various allyl alcohols were investigated (Table 6). Cinnamyl and hexenyl alcohol gave good yields of a single regioisomer (**5i–j**) and β-methallyl alcohol reacted cleanly (**5j**). Prenyl alcohol was also a viable coupling partner; however, it underwent coupling without significant regioselectivity, giving a 55:45 mixture of prenylation (**5l**) and reverse-prenylation (**5m**).[26] A potential explanation for this regiochemical outcome involving inner-sphere vs. outer-sphere allylation has been previously discussed.[2c]

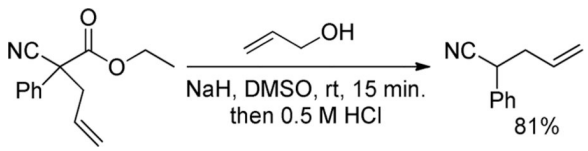
The ability to allylate electron rich α-aryl nitriles via DaA suggested that we might be able to demonstrate the utility of DaA via the production of a key intermediate in the synthesis of verapamil (Scheme 5).[25,27,28] The required precursor **5o** was synthesized in 2-steps from the commercially available homoveratronitrile by acetylation and substitution with isopropyl idodide (Scheme 6).[29] Here the use of an α-cyanoketone provided significant synthetic advantages. First, the substitution of isopropyl iodide with the relatively non-basic α-cyanoenolate allowed the construction of a sterically hindered quaternary carbon center. Second, the acetyl group acts as a blocking group, allowing only a single alkylation. Next, we chose to initiate our pursuit of **5o** using the DaA conditions that successfully coupled

allyl alcohol and the *para*-methoxy substrate corresponding to product **5g** (Table 5, NaH, DMSO, 60 °C, 12h). Unfortunately, the requisite isopropyl containing substrate gave < 5% yield of the desired product **5o**. However, use of an additional equivalent of NaH allowed the synthesis of the verapamil intermediate (**5o**) in good yield (Scheme 6). Moreover, the deacylative allylation was performed on a gram-scale, suggesting that the DaA reaction is reasonably scalable.[30] From this intermediate, verapamil can be synthesized following Nelson's 3-step protocol.[27a]

While DaA worked well for the synthesis of **5o**, the need to acylate the substrate prior to deacylation was clearly synthetically inefficient. To fully realize the synthetic utility of DaA, we thought it may be possible to construct the same compound beginning with readily available α-cyano*esters* (Scheme 7). We further expected that α-cyanoester reactants would enable introduction of the arene using Hartwig's arylation method,[22] which does not work well with α-cyanoketones. However, for this process to be a success, an allylic alcohol would need to induce a retro-Claisen condensation of an ester carbonyl. This process was expected to be challenging since ester carbonyls have a reduced electrophilicity in comparison to their acetyl analogs (eq 6).

To begin, we investigated the deacylative allylation of several α-aryl cyanoacetic ester derivatives. We were pleased to find that ethyl cyanoacetate derivatives (synthesized by Hartwig's arylation) could be utilized in deacylative allylation reactions.[22] As table 7 shows, not only could cyanoacetic esters be used to access the previously synthesized compounds such as **5a**, but they also allowed extension of the methodology to deacylative allylation of substrates that were prepared by cyanoacetate bisarylation (**5p–q**). [22] Related quaternary diarylacetonitrile derivatives often exhibit interesting biological activity.[31]

There are two possible pathways for formation of allylated products from α-cyanoesters. First, a retro-Claisen condensation could be initiated by the allylic alkoxide, producing a nitrile stabilized anion and allylic carbonate, which subsequently undergo Pd-catalyzed coupling (path A, Scheme 8). Second, the allylic alkoxide could induce transesterification to produce an allyl ester which could undergo decarboxylative allylation (path B, Scheme 8).[2c] To examine which pathway is followed, an α-cyano ethyl ester was treated under our reaction conditions in the absence of palladium. After 15 minutes, the reaction was quenched by the addition of acid. These conditions led to the formation of the protonation product in 81% yield (eq. 8). Moreover, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the ~80 % of the allyl alkoxide converted to allyl ethyl carbonate.[32] The formation of this nitrile in high yield indicates that the reaction likely proceeds via preferential retro-Claisen activation (path A).



(8)

Interestingly, the retro-Claisen allylation reactions of ethyl esters required an excess of the allylic alcohol. We hypothesized that higher concentrations of allyl alkoxide were required due to the build-up of ethoxide as the allylation progresses (via decarboxylation of the byproduct ethyl carbonate). This ethoxide can perform a competing retro-Claisen fragmentation, which funnels the reaction down an unproductive pathway toward diethyl carbonate formation (Scheme 9). Therefore, we posited that the higher concentration of allyl

alcohol was necessary to more effectively compete with ethoxide for the requisite retro-Claisen activation.

Since we previously showed that 2° alkoxides are ineffective at inducing retro-Claisen fragmentation (eq. 2), we envisioned that isopropyl cyanoacetates, which would produce isopropoxide, would obviate the need for excess allyl alcohol. Indeed, a single equivalent of allylic alkoxide can effectively out-compete the byproduct isopropoxide in the retro-Claisen activation, allowing the allylation to occur in good to excellent yields (Table 8).

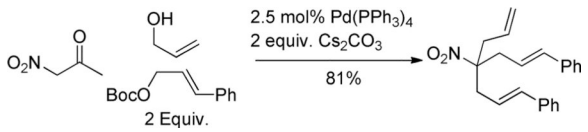
To demonstrate the synthetic flexibility of cyanoester reactants, the verapamil precursor **5o** was synthesized in 91% overall yield, via palladium-catalyzed nitrile anion arylation,[22] alkylation of the stabilized enolate,[5] and DaA (Scheme 10).

3-Component Unsymmetric Bisallylation

As detailed above, a variety of 1,6-heptadienes can be prepared in good to excellent yields via DaA of α-allyl ketones. Such ketones were readily prepared by palladium-catalyzed Tsuji-Trost allylation of stabilized enolate nucleophiles. Since both of these processes utilized a palladium-metal catalyst to effect the transformation, we hypothesized that the process could be done in a single tandem operation that would synthesize these important cycloisomerization substrates via a one-pot, 3-component coupling (Scheme 11). [14,19,21,33]

Our strategy for 3-component bisallylation is highlighted in scheme 11. An intial Tsuji-Trost allylation of the stabilized enolate should produce a substrate that is poised to undergo deacylative allylation. For selective 3-component bisallylation to produce chiral products containing two different allyl groups, it is desirable that the two allylation events are kinetically distinct. Since the Tsuji-Trost allylation of nitroketones is usually complete within minutes at room temperature[34] and DaA was anticipated to proceed more slowly, unsymmetric bisallylation should be possible.

To investigate the 3-component coupling, the general conditions developed for deacylative allylation were utilized; however, an extra equivalent of base was added to facilitate the initial Tsuji-Trost allylation. In the 3-component coupling, nitroacetone derivatives were coupled with allyl *tert*-butyl carbonates and allylic alcohols in the presence of 2.5 mol% $Pd(PPh_3)_4$ and 1 equivalent of Cs_2CO_3; a second equivalent of base is provided by the $^tBuCO_3^-$ leaving group (Table 9). As shown in table 9, **2b** was synthesized in one pot from methyl nitroacetone, cinnamyl carbonate, and allyl alcohol in an 89% yield (Table 9); the same product can be derived from cinnamyl acetate in 81% yield. Comparison of products **2b**/**2b'**, **2d**/**2d'**, and **2f**/**2f'** demonstrates that the allylic carbonate and alcohol coupling partners can be interchanged with little effect on the transformation. Aside from coupling methyl nitroacetone (**2b–f**), α-aryl (**2g**), α-benzyl (**2h**), and more functionalized nitroacetone derivatives (**2i–2k**) underwent bisallylation in good yield. As noted *vida supra*, even potentially base sensitive methyl esters were compatible with the reaction conditions (**2i–2k**). In addition to bisallylation, starting from unsubstituted nitroacetone and utilizing 2 equivalents of cinnamyl carbonate and 1 equivalent of allyl alcohol, 3 new C–C bonds can be made in single operation in an 81% yield (eq. 9). Finally, cyclic α-nitroketones can be utilized in our bisallylation and lead to products with a pendant carboxylic acid (eq. 10).



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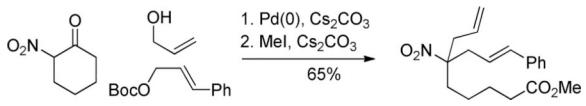


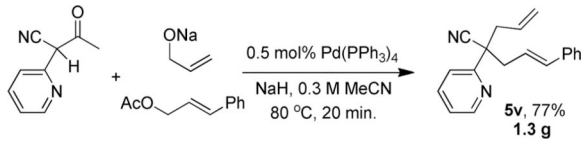
(10)

Next, we turned our attention to developing a 3-component bisallylation of ketones (Table 10). In this instance, we investigated the scope of the transformation using commercially available allylic acetates and allylic alcohols as coupling partners. In contrast to the nitroacetone substrates, higher yields of 3-component bisallylation of the diketones were obtained if reagents were added sequentially and if the alcohol was injected as its corresponding alkoxide. A lag-time between the addition of allylic acetate and allylic alcohol of 5–10 minutes gave the best results. Presumably, this is due to the necessity to complete the Tsuji-Trost allylation with cinnamyl acetate before a second allylic acetate is generated via acyl transfer to allyl alkoxide. Nonetheless, the procedure is operationally simple and the yields of unsymmetrically bisallylated ketones are good.

Simple α-phenyl acetylacetone was shown to couple in good yield with cinnamyl acetate and allyl or β-methyl allyl alcohol (Table 10). α-Aryl acetylacetone derivatives with various electron-withdrawing substituents were shown to couple nicely in this 3-component reaction, with ketones (**4ii**), nitriles (**4jj**), and nitro groups (**4kk**, **4t**) all providing products in good yield. Finally, β-tetralone was an excellent substrate for bisallylations utilizing allyl alcohol or hexenyl alcohol (**4z** and **4ll**).

The same protocol that was used to perform bisallylations of acetylketone derivates was applied to the 3-component bisallylation of α-cyanoacetones (Table 11). Under these conditions, α-phenyl cyanoacetone underwent bisallylation with cinnamyl acetate as well as hexenyl acetate (**5b** and **5c**, respectively). An α-pyridyl cyanoketone was also bisallylated in good yield (**5u** and **5v**, Table 11); **5v** was also synthesized on gram scale using just 0.5 mol % Pd without a substantial drop in yield (eq. 11).[30] Finally, other α-aryl cyanoacetones, including 2-naphthyl and *ortho*-chlorobenzene reacted cleanly to give bisallylated products in good yield.

In addition to α-aryl cyanoacetones, substrates that are derived from the arylation of cyanoacetates were also competent coupling partners for bisallylation (eq. 12). As before, the ethyl substrate required an excess of the allylic alcohol and the isopropyl acetate could be used in a near stoichiometric amount.



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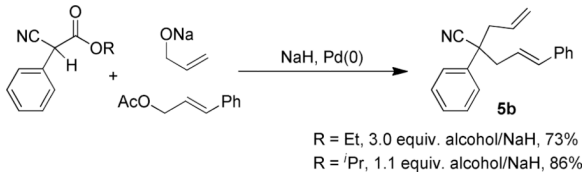

Conclusions

We have developed deacylative allylation as a method for the intermolecular allylic alkylation of carbon nucleophiles using readily available allylic alcohols. DaA is made possible by the high energy of allylic alkoxides in DMSO (pK_a~30), which leads to a facile retro-Claisen activation to produce nitronates (pK_a ~ 17), enolates (pK_a ~ 18–25), and nitrile stabilized anions (pK_a ~ 23).[16,35] Thus, the retro-Claisen activation is currently limited to the generation of nucleophiles with a pK_a(DMSO) < 25. Moreover, the retro-Claisen activation is only facile with 1° allylic alkoxides. In addition to producing reactive nucleophiles, the retro-Claisen reaction also results in acylation of the allylic alcohol to produce an allylic acetate. This acylation event activates the allyl alcohol toward formation of palladium-π-allyl electrophiles. Thus, the retro-Claisen condensation activates both the nucleophile and electrophile toward Pd-catalyzed C–C coupling. A further benefit of DaA is the use of activated ketone substrates that are readily functionalized. Thus, one can readily construct the desired nucleophiles prior to DaA. These features allow three-component couplings of ketones, allylic acetates, and allylic alcohols to produce useful 1,6-heptadienes in one pot. It is anticipated, that intermolecular deacylative allylation will be a powerful complement to intramolecular decarboxylative allylations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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32. In addition to allyl ethyl carbonate, a small quantity (~10%) of diallyl carbonate is formed. The observed diallyl carbonate can arise from transesterification followed by retro-Claisen condensation or from retro-Claisen condensation followed by transesterification.
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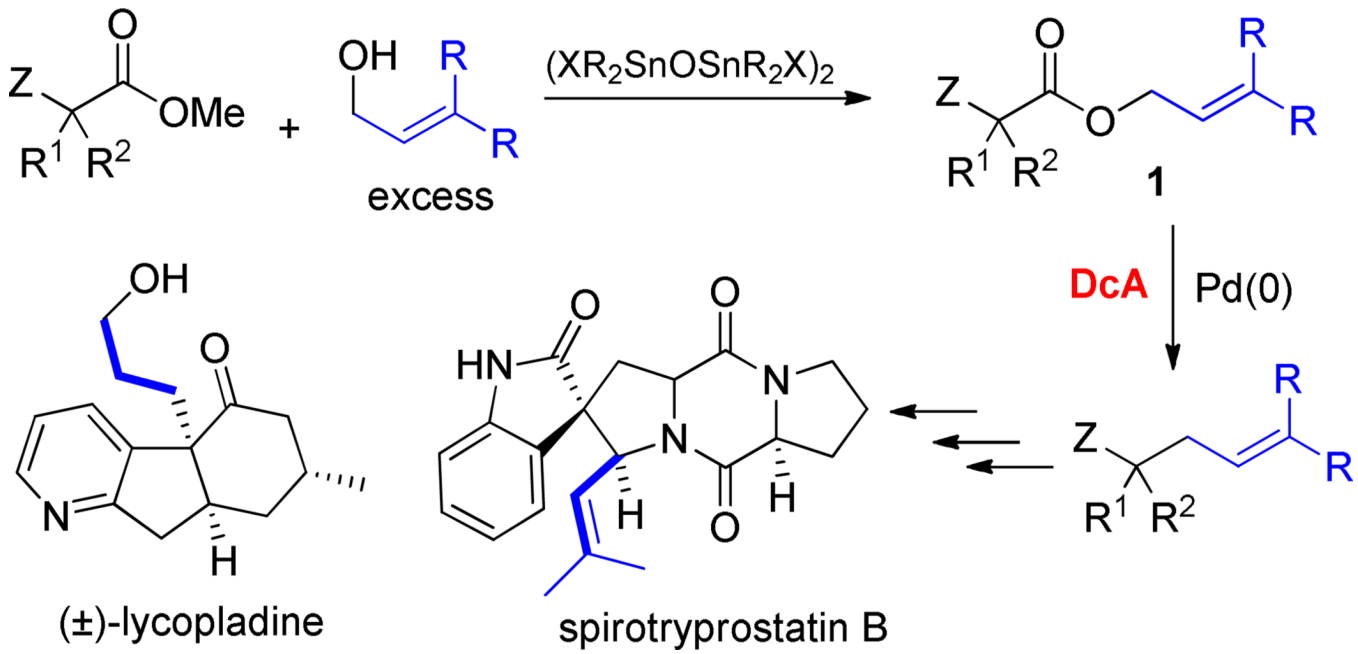
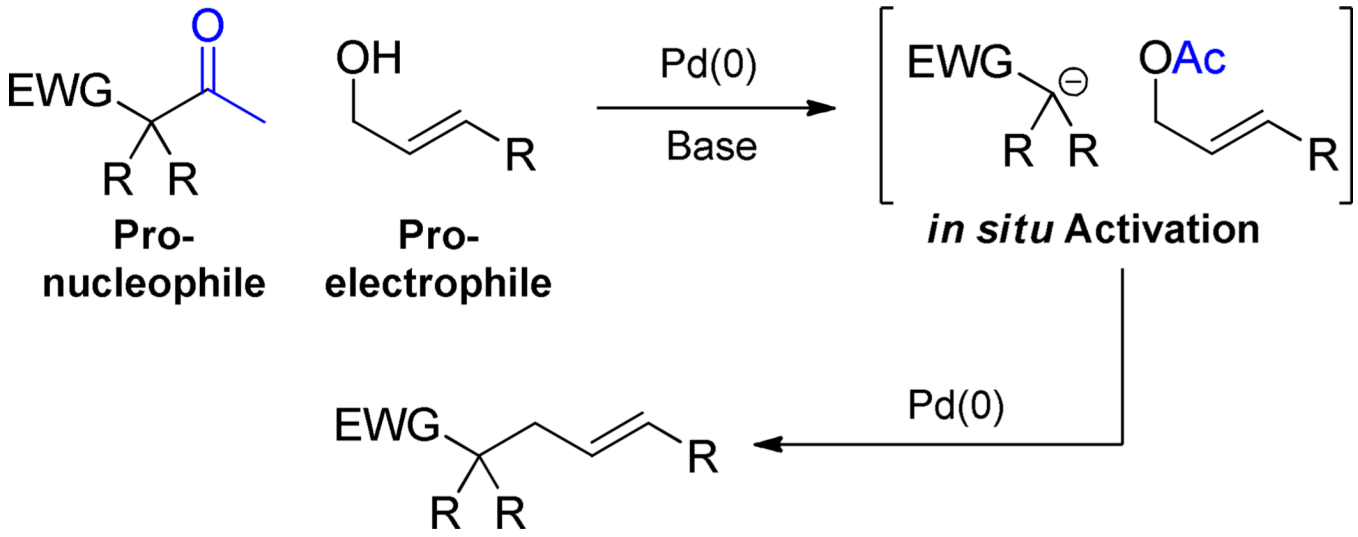
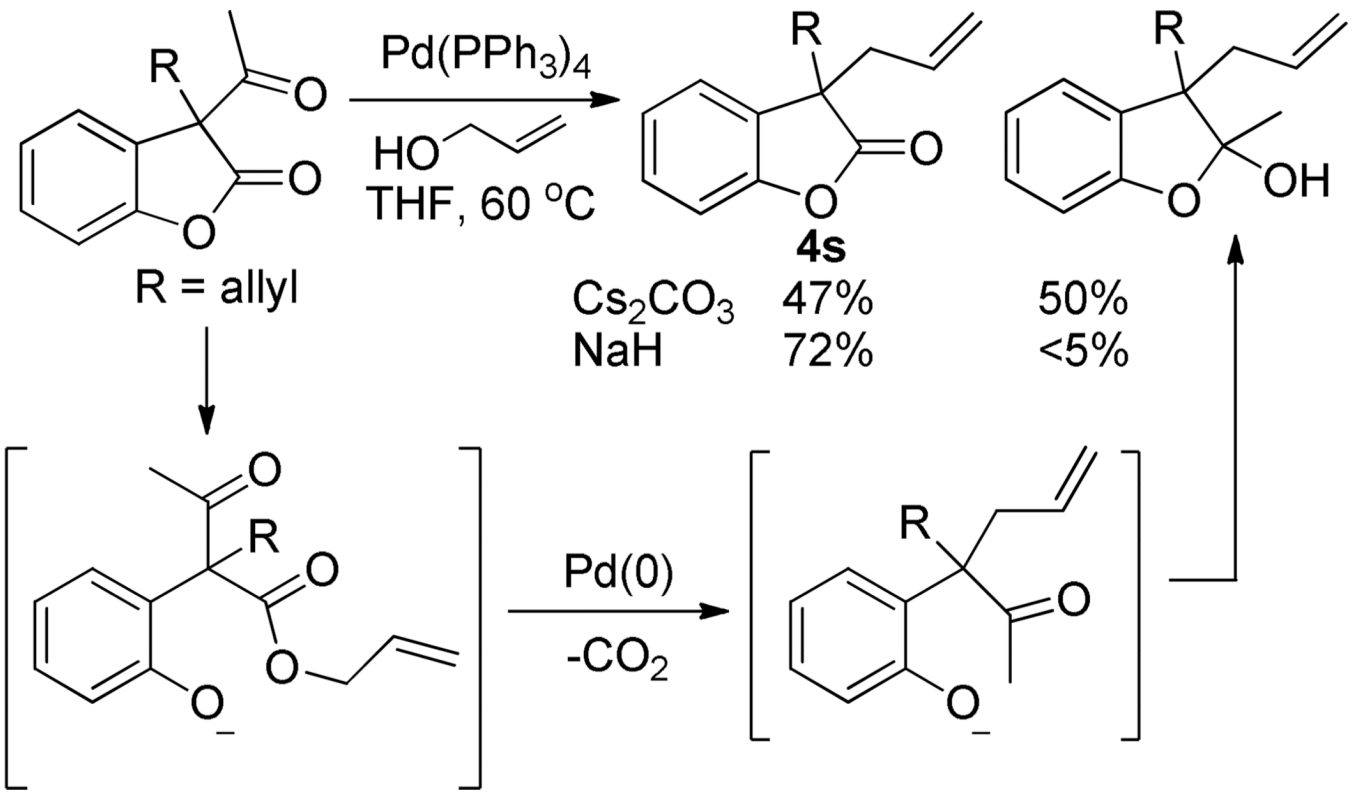


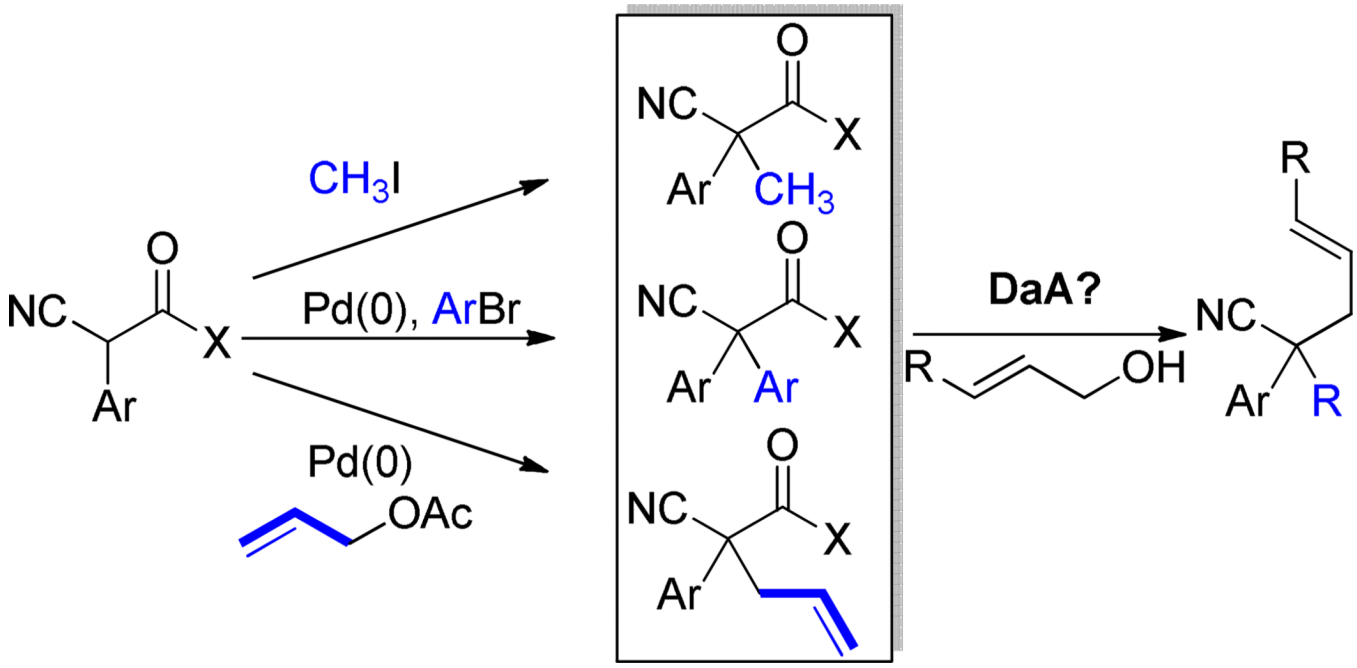
Scheme 1.
Decarboxylative Allylation



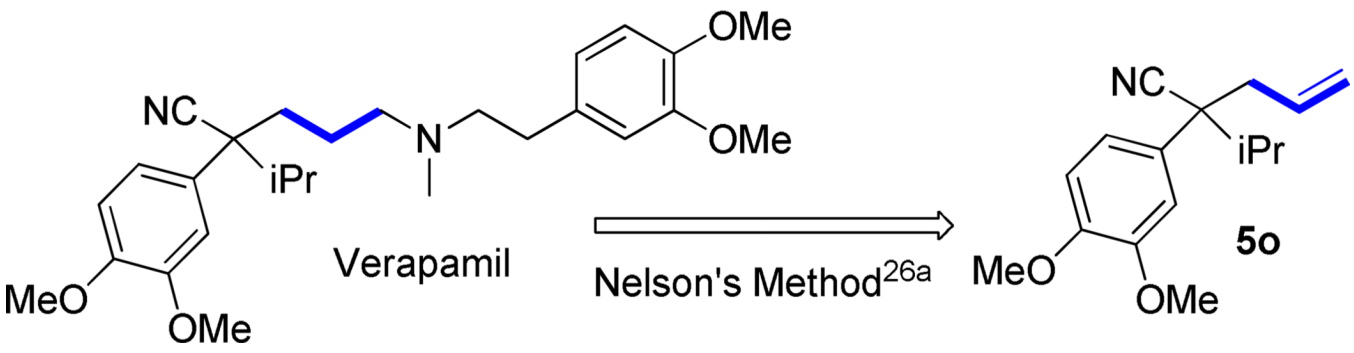
Scheme 2.
Deacylative Allylation



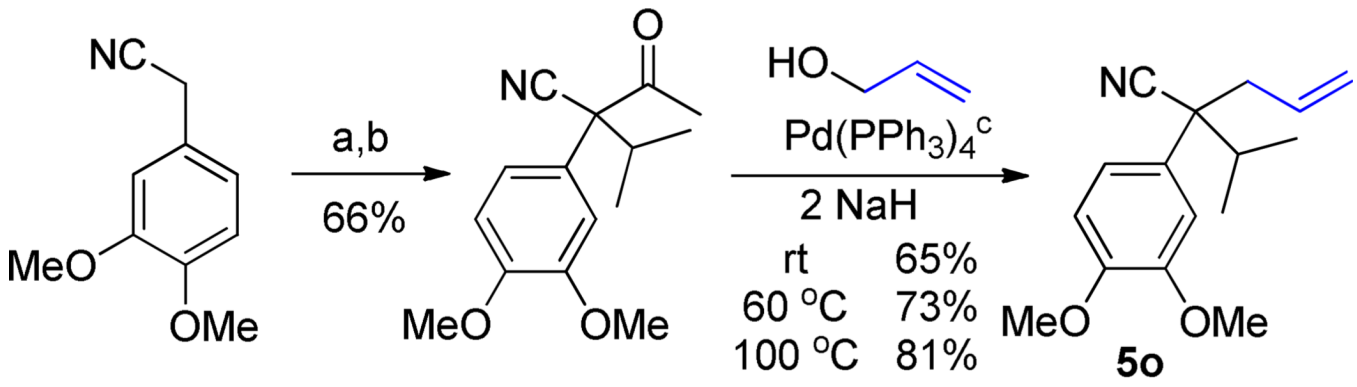
Scheme 3.



Scheme 4.
DaA of α-cyanoketones and esters

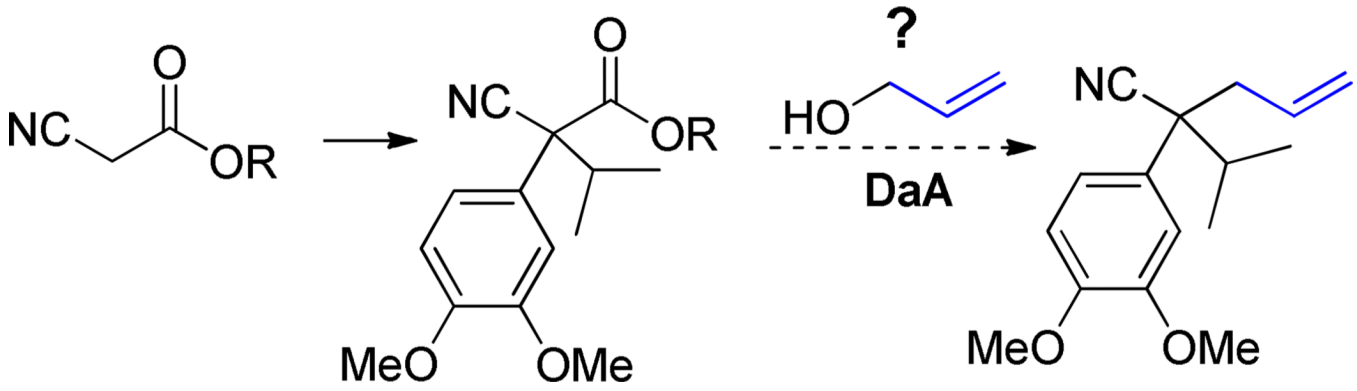


Scheme 5.
Verapamil intermediate

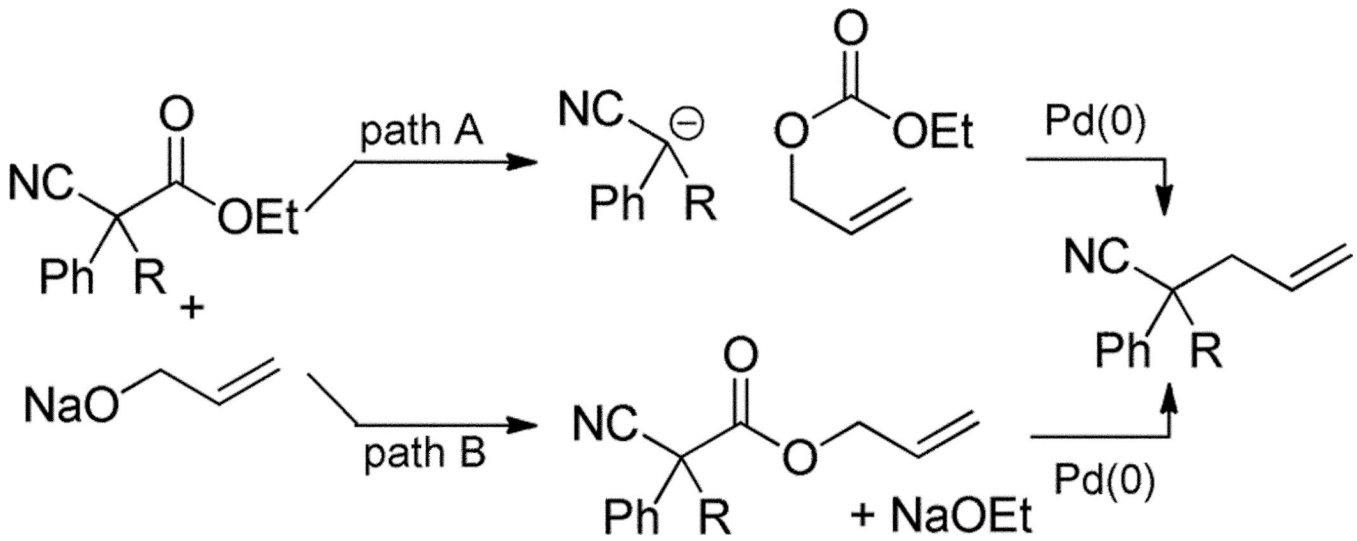


(a) LiH, Ac-Imidazole, DMSO, rt, 94% (b) 4 equiv. K_2CO_3 and 2-iodopropane, 5h, DMSO, 71% Yield (c) 2.5 mol % $Pd(PPh_3)_4$, 1 equiv. allyl alcohol, 2 equiv. NaH, THF

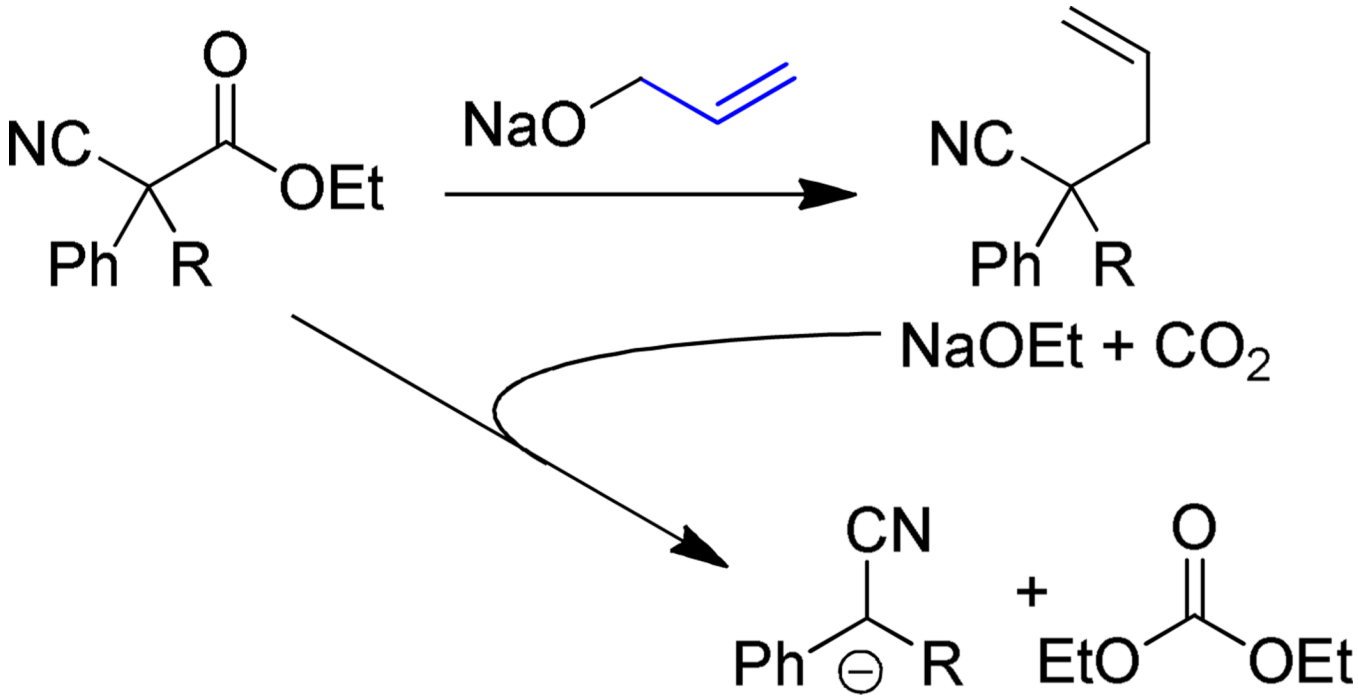
Scheme 6.
Synthesis of a Verapamil Precursor from Homoveratronitrile



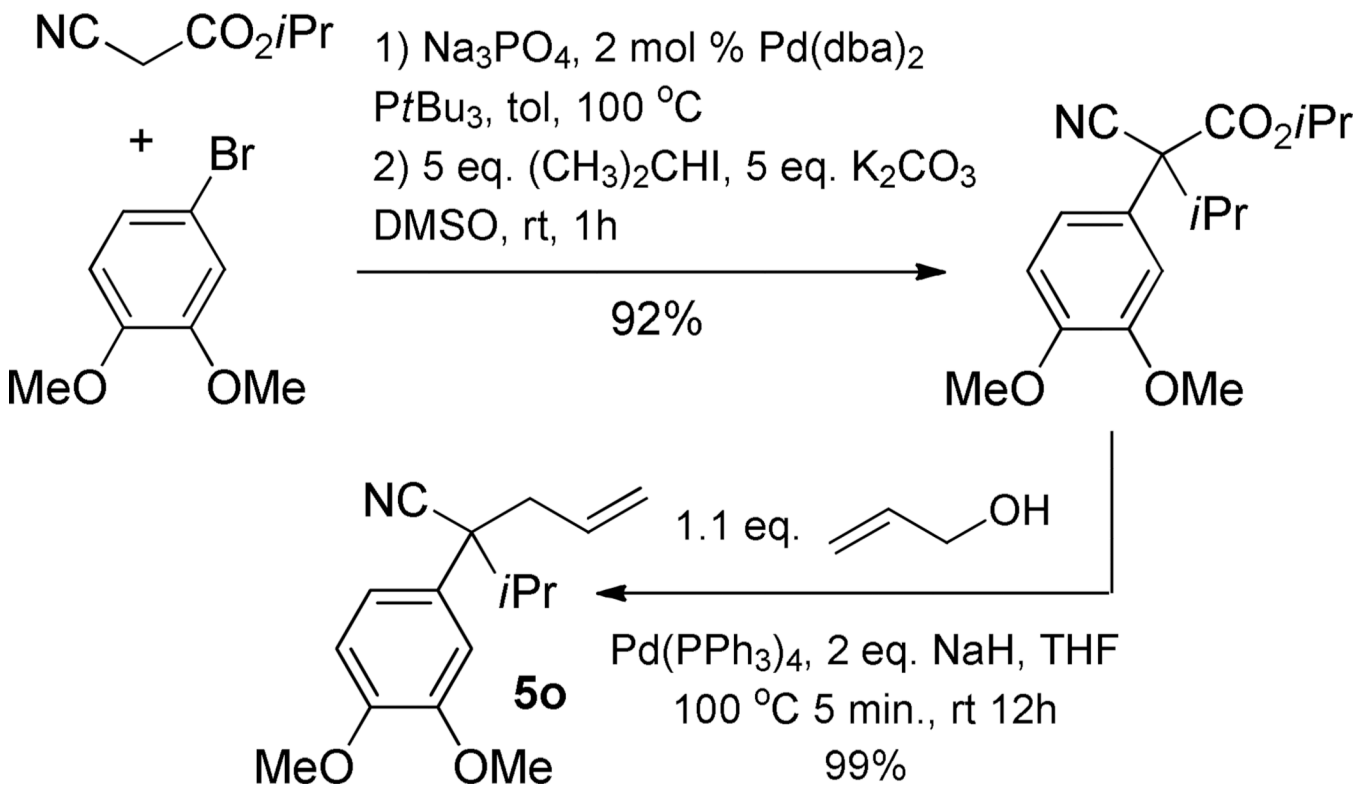
Scheme 7.
DaA of cyanoacetic ester



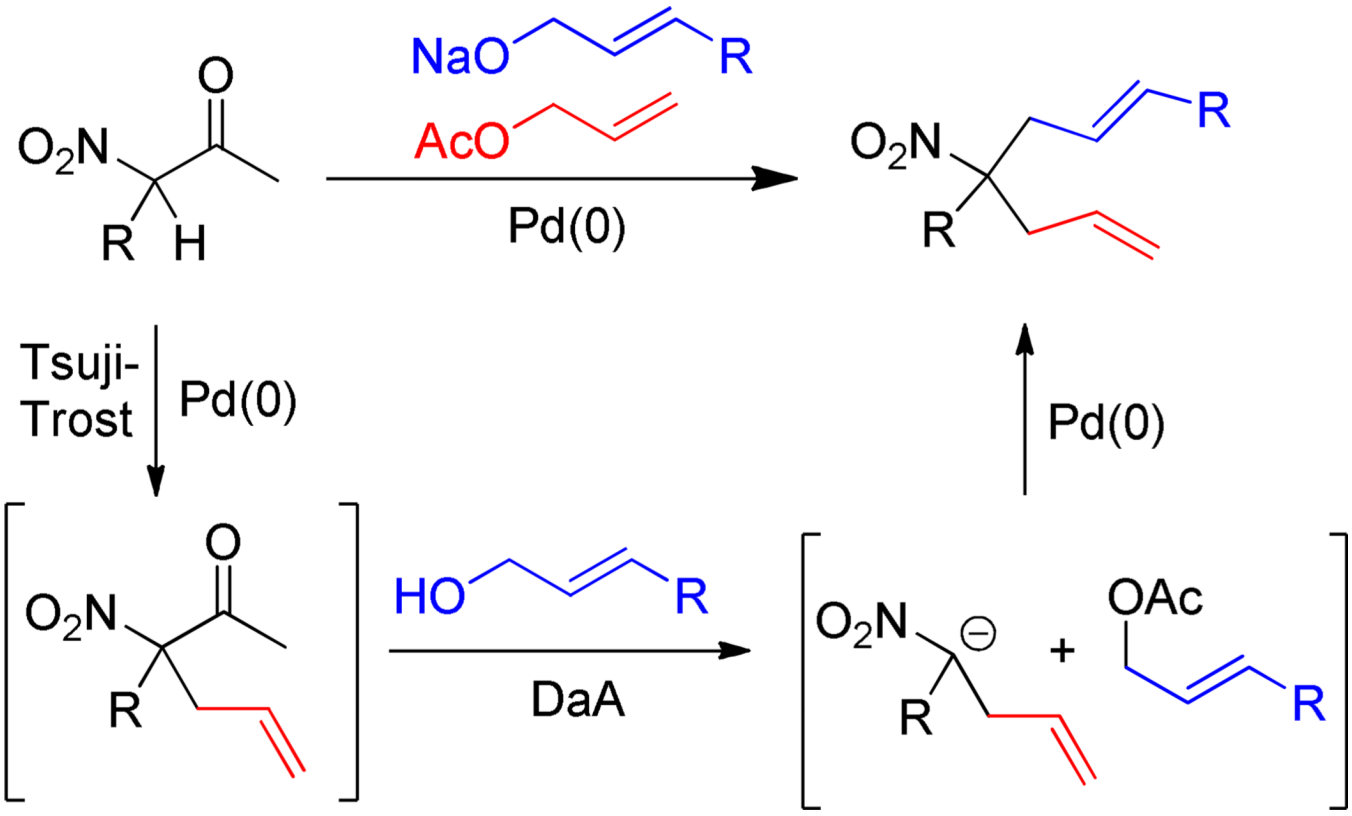
Scheme 8.
Mechanisms of allylation



Scheme 9.
Inhibition by ethoxide



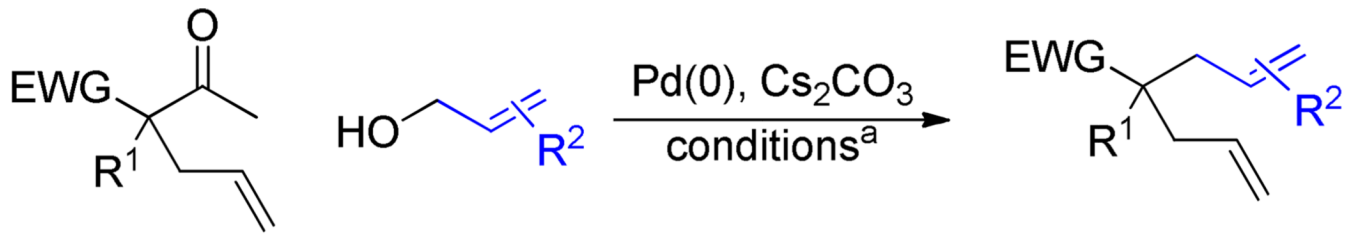
Scheme 10.
Synthesis of a Verapamil Precursor from Isopropyl Cyanoaceate

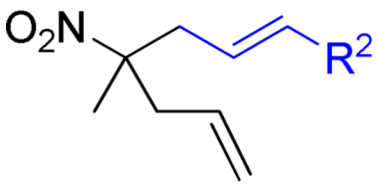


Scheme 11.
New Approaches to the Synthesis of 1,6-heptadienes

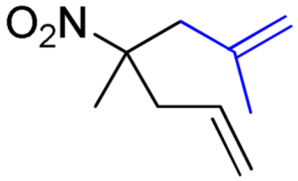
Table 1

Deacylative Allylation of Nitroketones and Derivatives

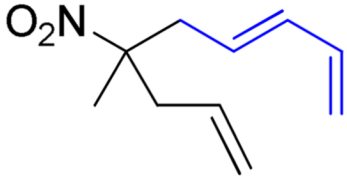




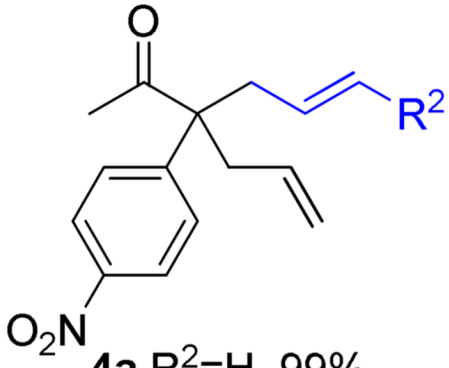
3a R^2=H 87%
3b R^2=Ph, 89%[b,c]
3c R^2=Me[d]
3d R^2=*n*-Pr, 79%[b]



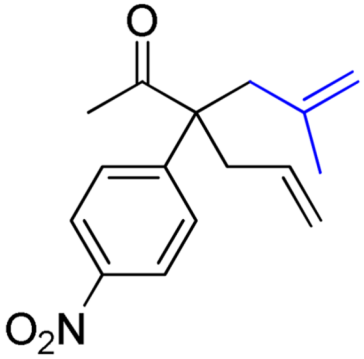
3e 92%



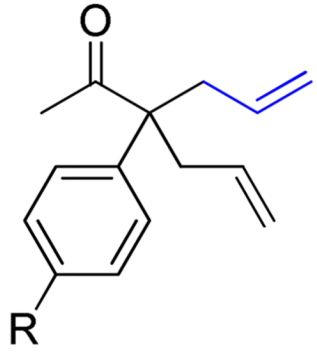
3f 78%[b,e]



4a R^2=H, 99%
4b R^2=Ph, 73%[b]
4c R^2=*n*-Pr, 91%[b]



4d 78%



4e R = COMe, 84%
4f R = H, 13%

[a] 2.5 mol % $Pd(PPh_3)_4$, 1.2 equiv. allyl alcohol, 1 equiv. Cs_2CO_3 80 °C, overnight, DCM:DCE (1:1) for nitro compounds, THF for acetylacetone derivatives

[b] >20:1 l:b.

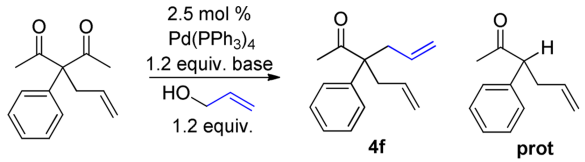
[c] 10 mol % $Pd(PPh_3)_4$

[d] 5.6 1: *E*:*Z*, 3.8:1, *l*:*b*

[e] DCE, 7h

Table 2

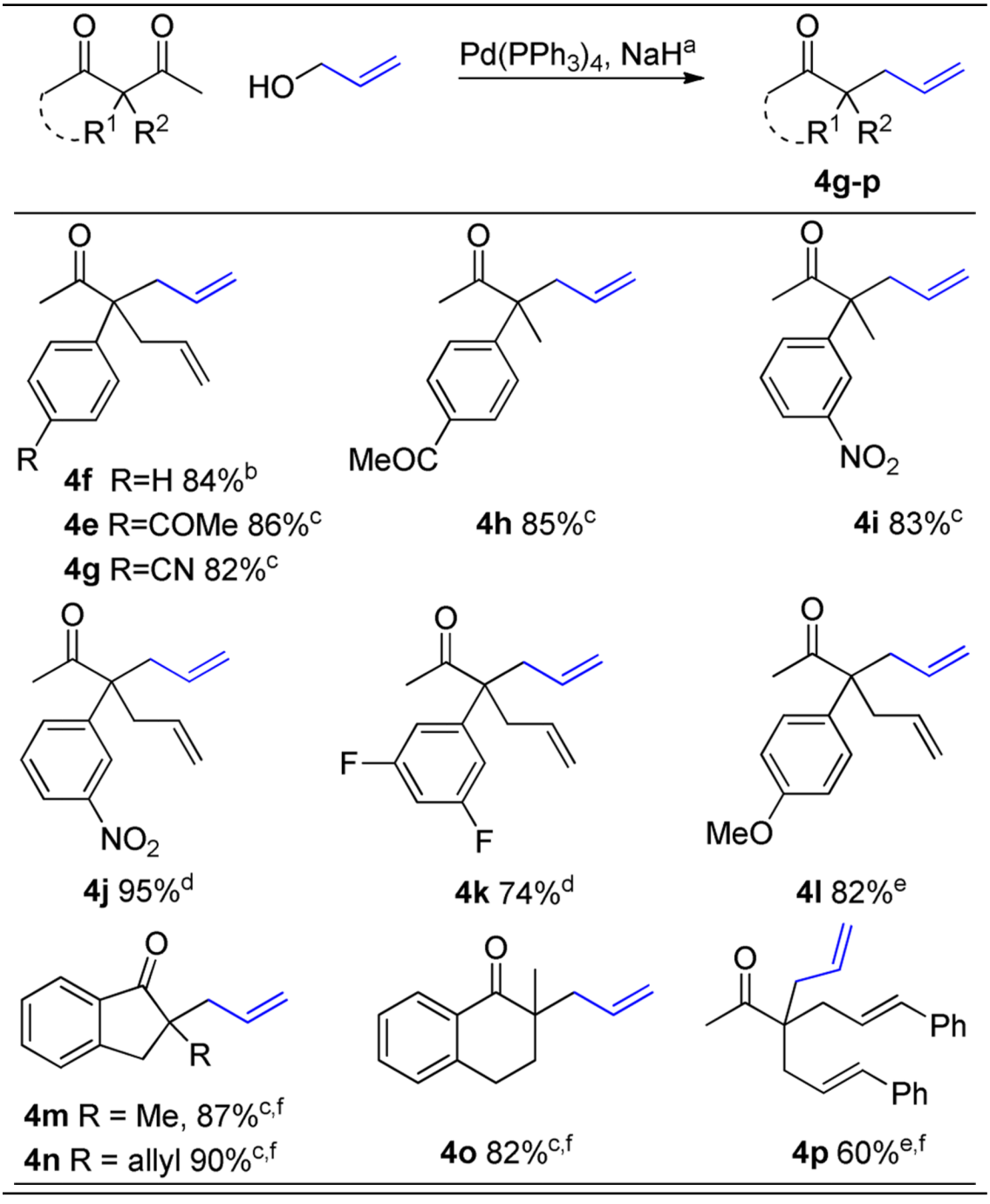
Optimization of Deacylative Allylation



entry	solvent	base	time (h)	temp (°C)	conv. (4f:prot)
1	Tol	Cs_2CO_3	15	80	25% (0:100)
2	DCE	Cs_2CO_3	15	80	0%
3	THF	Cs_2CO_3	15	80	100% (20:80)
4	CH_3CN	Cs_2CO_3	15	80	100% (70:30)
5	DMF	Cs_2CO_3	15	80	100% (75:25)
6	DMSO	Cs_2CO_3	15	80	100% (67:33)
7	NMP	Cs_2CO_3	15	80	100% (87:13)
8	NMP	tBuOK	3	80	100% (82:18)
9	DMSO	NaH	3	60	100% (85:15)
10	THF	NaH	1	60	100% (89:11)

Table 3

DaA of 1,3-diketones with allyl alcohols



[a] 1.0:1.05 ketone:allyl alcohol, 1.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$ 60 °C

[b] DMSO, 3h

[c] THF, 60 min.

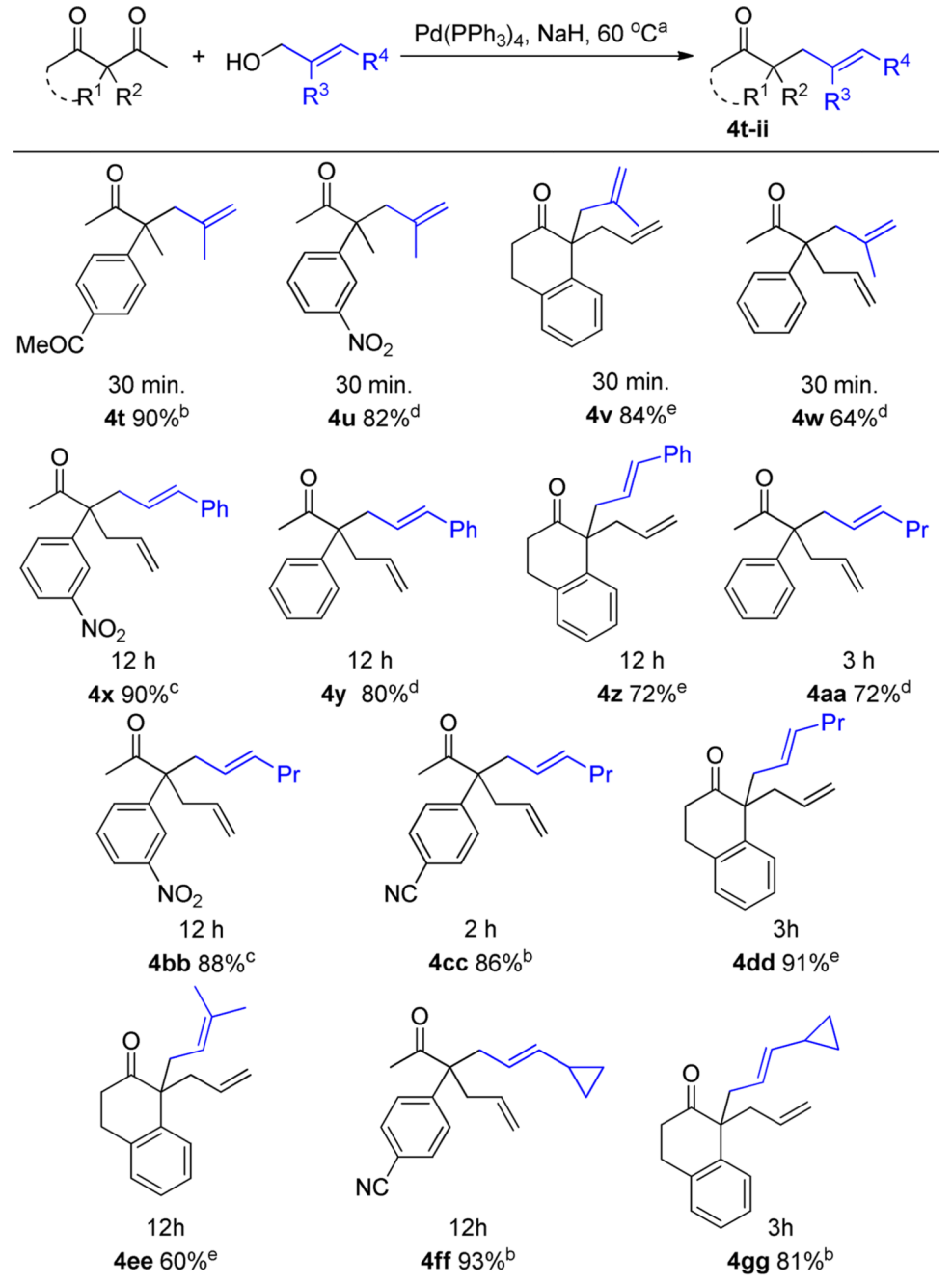
[d] NMP, Cs_2CO_3 80 °C, 12h

[e] THF, 12h

[f] 2.1 equiv. NaH

Table 4

Deacylative Allylation of Acetylacetone Derivatives



[a] 1.0:1.05 ketone:allyl alcohol, 1.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$,

[b] THF,

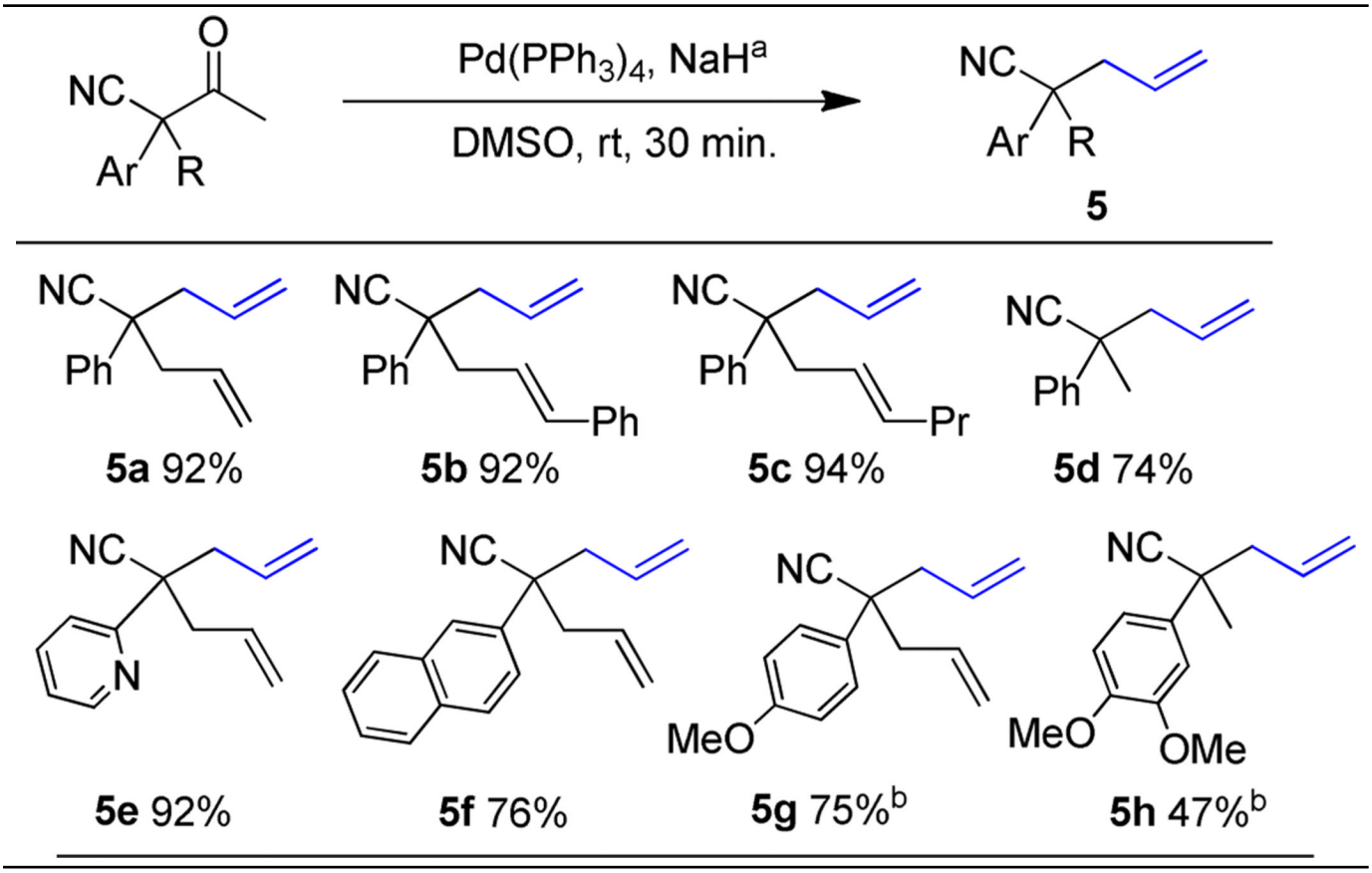
[c] NMP, Cs_2CO_3, 80 °C,

[d] DMSO,

[e] MeCN

Table 5

Deacylative Allylation of Cyanoacetone Derivatives

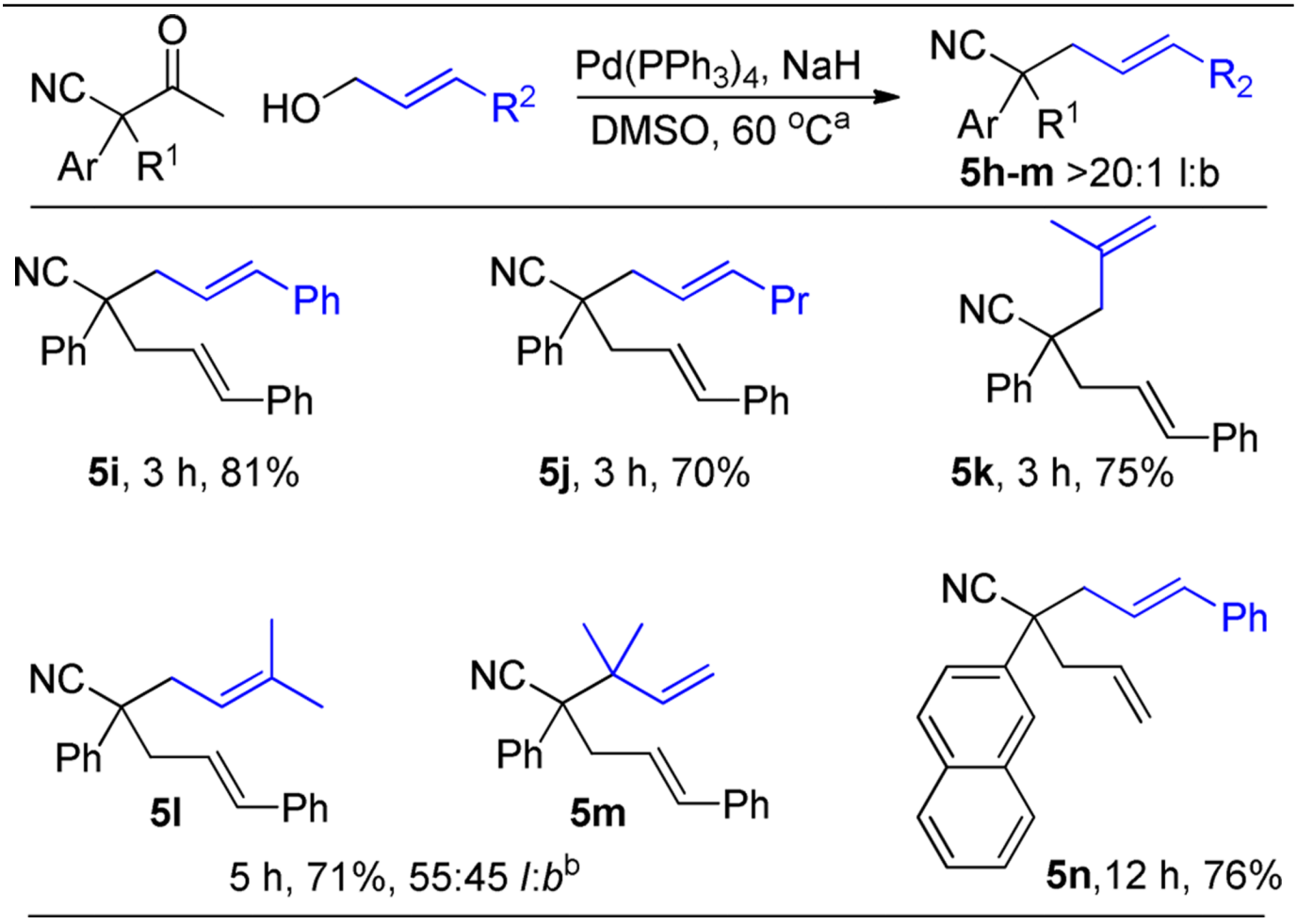


[a] 1:1.05 cyanoacetone : allylic alcohol, 1.1 equiv. NaH

[b] 60 °C, 12h

Table 6

DaA of α-Arylcyanoacetones with Allylic Alcohols

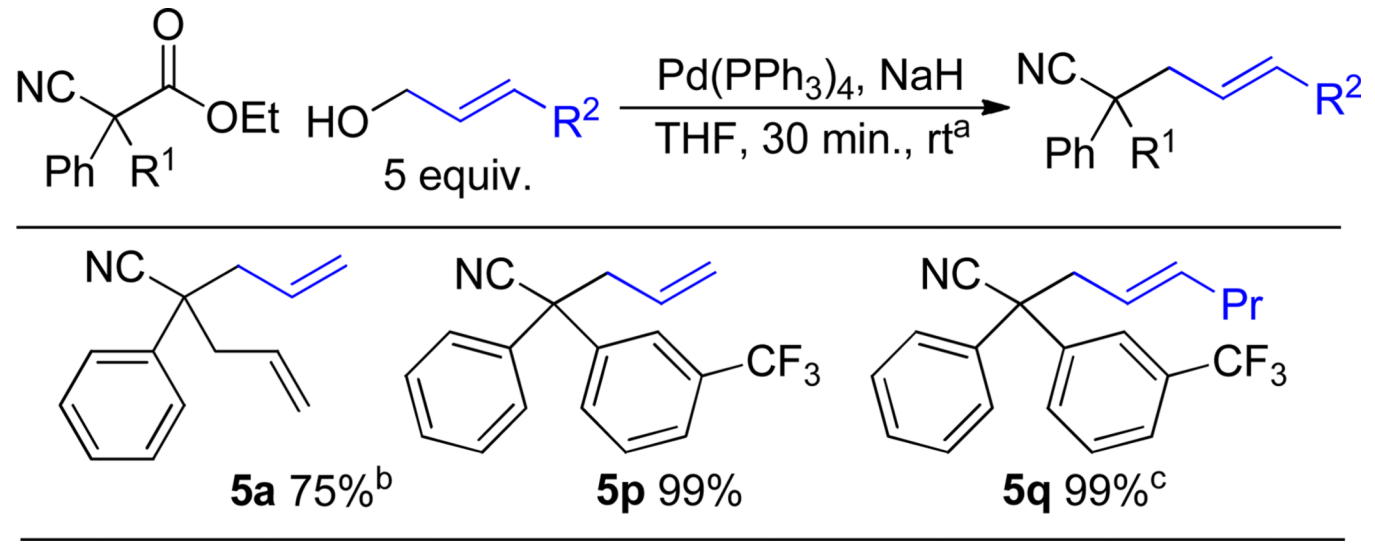


[a] 1:1.05 cyanoacetone:allylic alcohol, 1.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$

[b] inseparable mixture

Table 7

Deacylative Allylation of Ethyl Cyanoactate Derivatives



[a] 1:5 ethyl cyanoacetone:allylic alcohol, 1.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$

[b] DMSO

[c] >20:1 *l:b*

Table 8

Deacylative Allylation of Isopropyl Cyanoacetate Derivatives

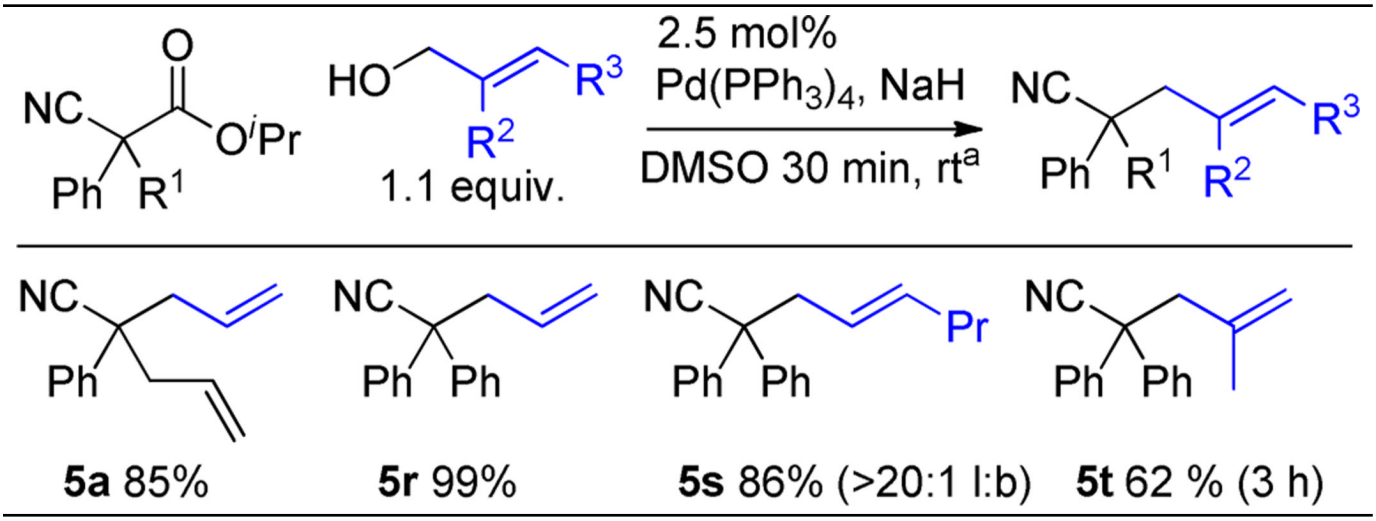
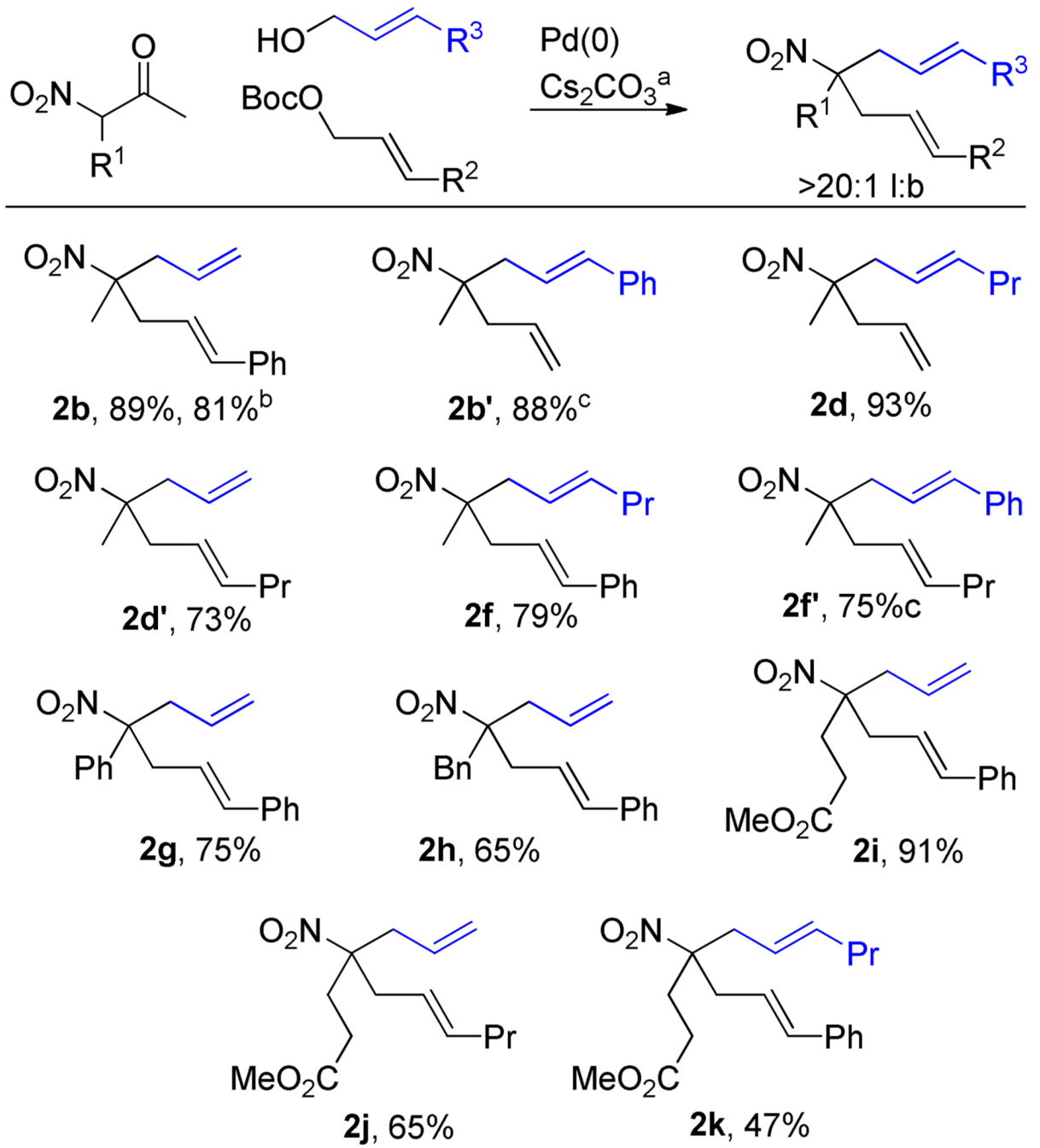


Table 9

3-Component Bisallylation of Nitroacetone Derivatives



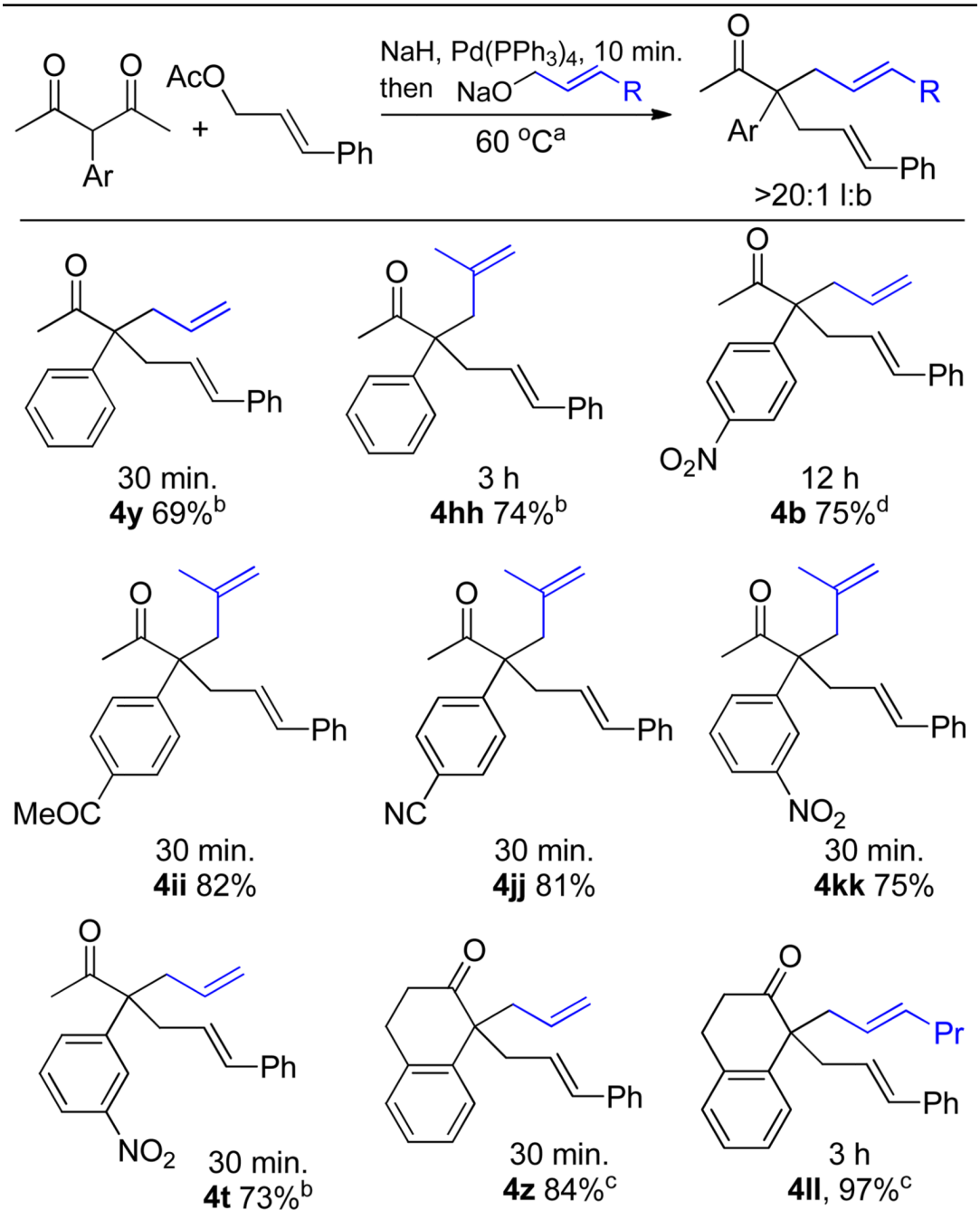
(a) 1:1:1.2 Nitroacetone:allyl carbonate:allyl alcohol, 2.5 mol % $Pd(PPh_3)_4$, 1 equiv. of Cs_2CO_3, DCM:DCE (1:1), 80 °C, 12h.

(b) 81% yield using 2 equiv. of Cs_2CO_3 and cinnamyl acetate.

(c) 10 mol % $Pd(PPh_3)_4$

Table 10

3-Component Bisallylation of Acetylacetones



[(a)] 1:1:1.1 ketond, cinnamly acetate, allylic alcohol, 2.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$, 60 °C THF

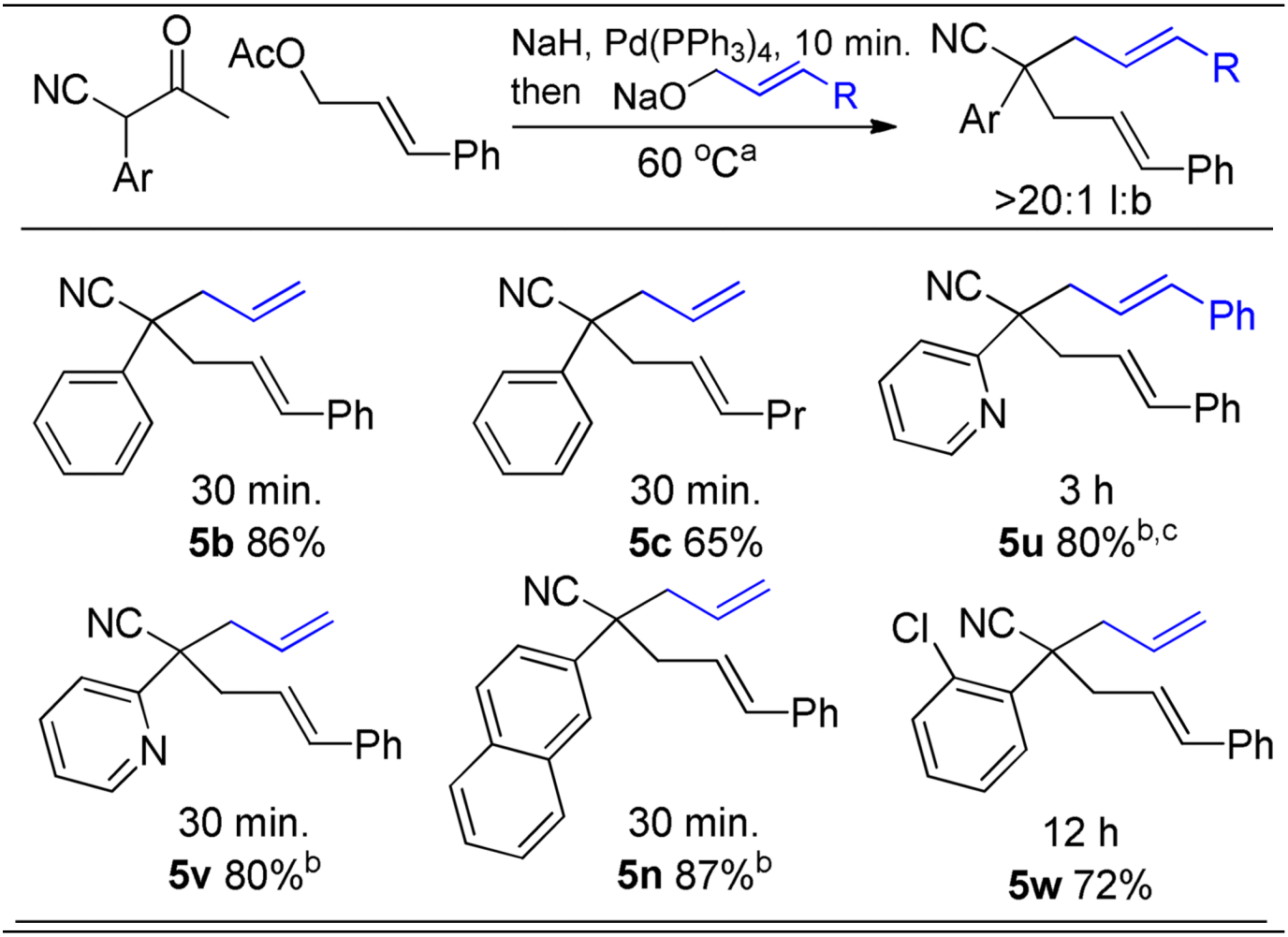
[(b)] DMSO

[(c)] MeCN

(d) Cs_2CO_3

Table 11

3-Component Bisallylation of Cyanoacetone Derivatives



[(a)] 1:1:1.1 cyanoacetone : allylic acetate : allylic alcohol, 2.1 equiv. NaH, 2.5 mol % $Pd(PPh_3)_4$, DMSO, 60 °C

[(b)] THF

[(c)] 10:1 *l:b* in DaA