Allylation

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Knoevenagel Adducts as Trimethylenemethane Dipole Surrogates

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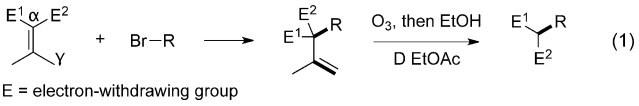
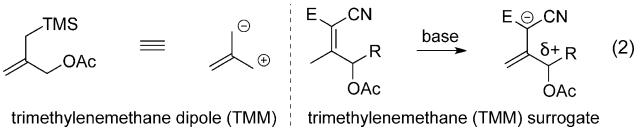
Abstract: *Knoevenagel adducts derived from readily available acetoxyacetone and malonic acid derivatives served as trimethylenemethane surrogates for formal 1,3-difunctionalization through a sequence of selective γ-deprotonation/α-alkylation and palladium(0)-catalyzed allylic alkylation. Herein, we report the discovery and development of a three-component 1,3-difunctionalization of Knoevenagel adducts as well as a unique palladium(0)-catalyzed branch-selective allylic alkylation.*

Knoevenagel adducts are attractive chemical building blocks owing to their environmentally friendly construction through condensation[1,2] and their ability to undergo selective chemical transformation.[3,4] For example, the γ-C–H deprotonation/α-alkylation of Knoevenagel adducts results in a C–C bond as well as an alkene functional group for further manipulation.[3] Grossman and Varner demonstrated that ketone-derived Knoevenagel adducts can undergo alkylation and then an ozonolysis/retro-Claisen condensation sequence to yield monosubstituted malonic acid derivatives [Eq. (1)].[3b,c]

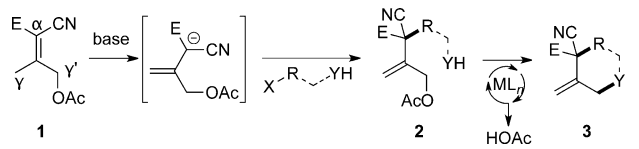


(1)

Rather than cleavage of the alkene functional group, we reasoned that formal 1,3-difunctionalization of the acetoxyacetone-derived Knoevenagel adduct **1** was possible (Scheme 1). Selective γ- versus γ′-deprotonation results in an allyl anion that can undergo α-alkylation to introduce a new C–C bond[3] as well as an allyl acetate functional group, which is a productive electrophile for functionalization (Tsuji–Trost reaction).[5] Thus, substrate **2** can directly participate in a second functionalization reaction with nucleophiles to yield 1,3-difunctionalized building blocks **3** with high efficiency. Moreover, we envisioned intra- and intermolecular variants of this formal 1,3-difunctionalization (Scheme 1). Although there are numerous methods for either α- or γ-functionalization,[3,4] general strategies for the difunctionalization of Knoevenagel adducts are scarce. Instead, 1,3-difunctionalization is commonly achieved with reagents that are used to generate trimethylenemethane (TMM), which has been used extensively in [3+2] cycloaddition reactions [Eq. (2); TMS = trimethylsilyl].[6] Herein we report our first studies on Knoevenagel adducts as TMM surrogates.



(2)



Scheme 1. Proposed 1,3-difunctionalization of Knoevenagel adducts. E = electron-withdrawing group, R = alkyl group, X = leaving group, Y–H = pronucleophile.

The first challenge was the development of a γ- versus γ′-selective deprotonation/α-alkylation sequence (Scheme 1, **1**→**2**)). Though it is understood that allyl anions derived from Knoevenagel adducts react exclusively at the α position with alkyl halides and palladium–π-allyl electrophiles,[3] regioselective deprotonation (γ vs. γ′) has yet to be examined. The desired chemical events for our strategy are γ-deprotonation and α-alkylation to give allyl acetates **2**, whereas γ′-deprotonation/α-alkylation yields a vinyl acetate. The selectivity challenge was made greater by the suspicion that the γ′-C–H atoms in **1** are several orders of magnitude more acidic than the γ-C–H atoms.[7]

The second challenge was that allylic acetates with a quaternary carbon atom at the 2-position are underexplored in Tsuji–Trost allylation chemistry.[8] Moreover, it was reported that the palladium-catalyzed allylic substitution of a 2-*tert*-butyl allyl acetate/carbonate derivative was sluggish and low yielding, probably owing to the bulky 2-substituent.[8]

To begin our investigation, we synthesized a variety of acyloxyacetone-derived Knoevenagel adducts **1a–d** with different ester (E) groups and acyloxy groups in two steps from hydroxyacetone through acylation then Knoevenagel condensation.[9] Notably, the Knoevenagel condensation resulted in starting materials **1a–d** as *E*/*Z* isomeric mixtures.[9] Also, we chose bulky oxygen activating groups (pivaloyl and *tert*-butoxycarbonyl, Boc) with the hope of sterically biasing the deprotonation event.

With Knoevenagel adducts **1a–d** in hand, we began investigating conditions for kinetically selective deprotona-

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tion (γ vs. γ′). Unfortunately, standard deprotonation conditions for kinetic selectivity (bulky bases at cryogenic temperatures) failed to give the desired product cleanly.[10] However, we were pleased to discover a simple protocol for γ-deprotonation/α-allylation with kinetic selectivity when allyl *tert*-butyl carbonate was utilized as the electrophile in the presence of a catalytic amount of [Pd(PPh$_3$)$_4$]. Knoevenagel adducts **1a–d** were allylated in good yield to give **2a–d** on a gram to multigram scale in all cases under operationally simple conditions (0 °C→RT). Next, under standard Tsuji–Trost conditions ([Pd(PPh$_3$)$_4$] (1 mol %), Cs_2CO_3, THF or toluene) with *para*-methoxyphenol as the nucleophile, the second allylic alkylation occurred without incident for substrates **2a–d**. We thus confirmed our hypothesis that Knoevenagel adducts can undergo 1,3-difunctionalization through the discovery of an iterative allylic alkylation sequence.

We next examined other types of nucleophiles that can react with allylic acetates. With little change from the conditions in Scheme 2, an electron-rich phenol and 2-naphthol underwent successful alkylation to give **3e** and **3f**, respectively, in good yield (Scheme 3). Similarly, the use of a malonate nucleophile yielded **3h** in reasonable yield. Diminished reactivity and decomposition were observed with electron-deficient phenols (e.g. 4-chlorophenol) and sterically demanding diethyl allylmalonate. Considering a possible mechanism involving outer-sphere palladium–π-allyl substitution, we reasoned that the low yield could be due to decreased nucleophilicity (electronically and/or sterically) and a challenging C–Nu bond-forming trajectory at the palladium–π-allyl intermediate because of the adjacent quaternary center (Figure 1).[5]

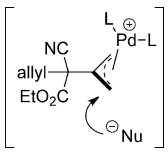
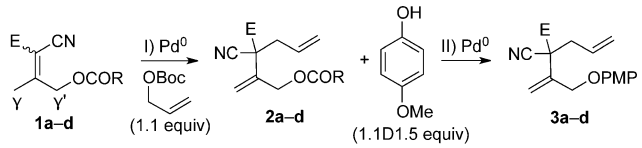


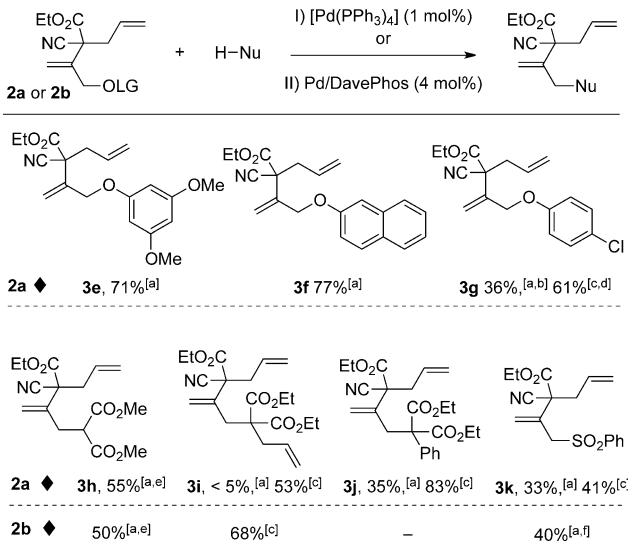
Figure 1. Mechanistic challenge of 2-quaternary palladium–π-allyl substitution.

For these more electronically and/or sterically challenging nucleophiles, it was discovered that a combination of palladium and the ligand 2-dicyclohexylphosphanyl-2′-(N,N-dimethylamino)biphenyl (Davephos) was particularly effective for allylic alkylation of the allylic electrophile with a quaternary center. With the Pd/Davephos combination, **3i** was prepared in 68 % yield, as compared to < 5 % with [Pd(PPh$_3$)$_4$].



1a E = CO_2Et, R = *t*Bu	**2a**, 78%	**3a**, 72%[a]
1b E = CO_2Et, R = O*t*Bu	**2b**, 81%	**3b**, 93%[a]
1c E = CO_2Bn, R = *t*Bu	**2c**, 56%	**3c**, 69%[b]
1d E = CO_2*t*Bu, R = *t*Bu	**2d**, 68%	**3d**, 64%[b]

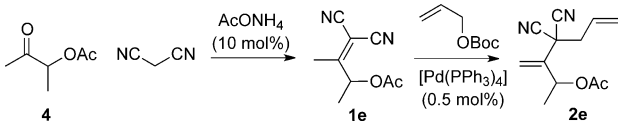
Scheme 2. Sequence development. Reaction conditions: I) [Pd(PPh$_3$)$_4$] (1 mol %), THF, 0 °C→RT, 10 min (1–5 g scale); II) Cs_2CO_3 or NaH, [Pd(PPh$_3$)$_4$] (1 mol %), CH_2Cl_2, room temperature, 1.5 h (0.5–1 g scale). [a] The reaction was carried out with Cs_2CO_3. [b] The reaction was carried out with NaH. Bn = benzyl, PMP = *para*-methoxyphenyl.



Scheme 3. Scope of the reaction with respect to the nucleophile. Reaction conditions: I) NaH (1 equiv), pronucleophile (1.5 equiv), [Pd(PPh$_3$)$_4$] (1 mol %), toluene, room temperature, 1.5 h, 100 mg scale; II) NaH (1 equiv), pronucleophile (1.5 equiv), [Pd$_2$dba$_3$] (2 mol %), DavePhos (8 mol %), toluene, 50 °C, 2–18 h. [a] Yield for the reaction under conditions I. [b] The reaction was carried out in *N*,*N*-dimethylformamide instead of toluene. [c] Yield for the reaction under conditions II. [d] The catalyst was formed from [Pd(Cp)(allyl)] (10 mol %) and DavePhos (10 mol %). [e] Cs_2CO_3 was used instead of NaH. [f] The reaction was carried out in diethyl ether instead of toluene. dba = dibenzylideneacetone, LG = leaving group.

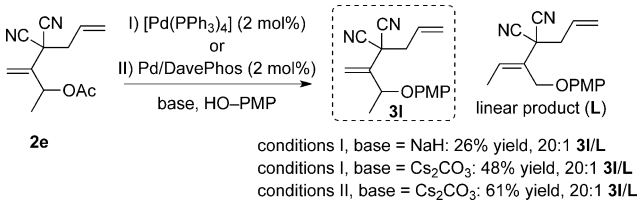
Increased yields were also observed for the synthesis of **3g** and **3j** under these conditions.

We next explored the viability of the commercially available acyloin derivative **4** as a starting material. Knoevenagel condensation and initial allylic alkylation occurred without incident to yield **2e** on a gram scale (Scheme 4).[9]



Scheme 4. Synthesis and transformation of an acyloin-derived Knoevenagel adduct.

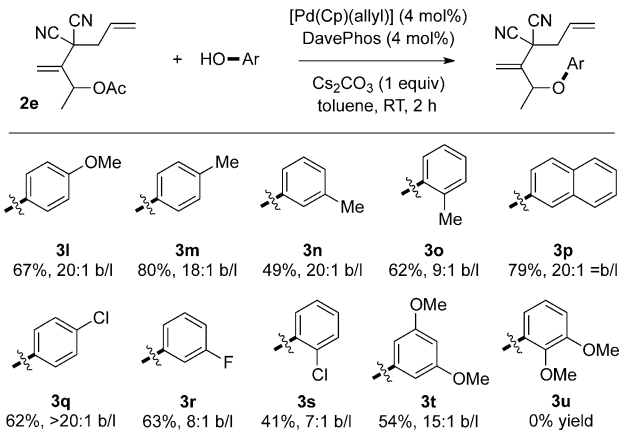
Compound **2e** underwent successful allylic substitution with *para*-methoxyphenol in the presence of [Pd(PPh$_3$)$_4$] or Pd/Davephos, whereby the Pd/Davephos combination was most effective and promoted the formation of **3l** in 61 % yield (Scheme 5).[11] Interestingly, the substitution occurred with selectivity for the branched product with both palladium catalysts (10–> 20:1 branched (**3l**)/linear (**L**)), which is unusual for palladium catalysis.[12] For these few known cases,[12] it is thought that the ligand on Pd dictates the regiochemical outcome.[13] In our case, various Pd/ligand combinations resulted in good selectivity for the branched product, thus suggesting that the reaction is controlled primarily by the substrate. In comparison, palladium–π-allyl



Scheme 5. Palladium-catalyzed branched-selective allylic alkylation. Reaction conditions: I) NaH or Cs_2CO_3, $[Pd(PPh_3)_4]$ (2 mol%), toluene, room temperature, 2 h; II) Cs_2CO_3, [Pd(Cp)(allyl)] (2 mol%), DavePhos (2 mol%), toluene, room temperature, 2 h.

intermediates generated from allylic *gem*-diacetates (or related compounds) undergo substrate-controlled branched-selective allylic alkylation owing to the electronic impact of the terminal oxygen atom on the palladium–π-allyl intermediate.[14] Generally speaking, common methods for branched-selective allylic alkylation utilize iridium-based catalysts.[15]

Regarding the scope of the reaction (Scheme 6), palladium(0)-catalyzed branched-selective allylic alkylation of **2e** was observed with a variety of sterically and electronically differentiated phenols. With *para*- or *meta*-substituted phenols, both good yields and good selectivity for the branched product were observed. For example, all *para*-substituted reagents tested reacted with 18–20:1 branched/linear selectivity (products **3l**, **3m**, **3q**). *meta*-Tolyl and 3,5-dimethoxy aromatic rings were incorporated in good yield and with 20:1 and 15:1 branched/linear selectivity, respectively. Although a good yield (63%) was observed for the incorporation of a 3-fluorophenyl moiety, the reaction occurred with only 8:1 selectivity for the branched product. A 2-naphthyl moiety was incorporated in good yield with excellent selectivity for the branched product. Yields were reasonable for the introduction of *ortho*-substituted aromatic rings to give products **3o** (2-methyl, 62%) and **3s** (2-chloro, 41%), but the selectivity for the branched product decreased below 10:1 in both cases. Surprisingly, 2,3-dimethoxyphenol was not a competent nucleophile; only decomposition was observed, and the desired product **3u** was not detected. Thus, we found this branched-selective allylic alkylation to be most efficient with phenol derivatives without a steric bias as nucleophiles.



Scheme 6. Studies of the reaction scope.

Mechanistically, we suggest that the selectivity for the branched product is due to an unusual geometry imparted by the quaternary center in the palladium–π-allyl intermediate (Figure 2). When the palladium–π-allyl intermediate bears a H atom at the 2-position and an aliphatic or aromatic group at the 1-position (Figure 2), it is well-understood that the palladium–π-allyl intermediate adopts a geometry in which the 2-H and 1-R group are *syn*, and allylic alkylation occurs by a sterically driven attack at the least-substituted position.[5] In our case, the 2-quaternary center and the methyl group could potentially adopt an *anti* arrangement, and we suggest that the unusual selectivity results from this geometric orientation.[13]

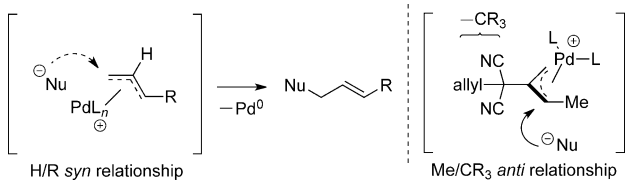
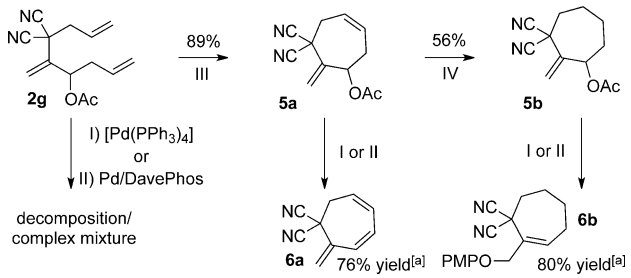


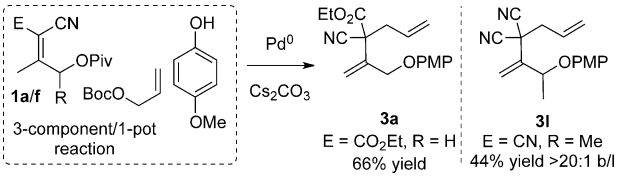
Figure 2. Mechanistic hypothesis for the unexpected selectivity for branched products.

To probe our hypothesis (Figure 2), we prepared cyclic analogues **5a** and **5b**, as these substrates are locked in a *syn* arrangement (Scheme 7) and should therefore undergo linear-selective allylic alkylation (Figure 2). With $[Pd(PPh_3)_4]$ or Pd/Davephos catalyst systems, **5a** underwent clean β-hydrogen elimination to the cycloheptyl triene, thus providing no insight into the origins of our branched selectivity. Fortunately, upon selective hydrogenation of the endocyclic double bond, the hypothesized selectivity was observed when $[Pd(PPh_3)_4]$ was utilized as a catalyst. The Pd/DavePhos combination was also effective, although the reaction was less clean and lower yielding.



Scheme 7. Mechanistic probe and the synthesis of cycloheptenes. Reaction conditions: I) Cs_2CO_3 (1.5 equiv), HOPMP (1.5 equiv), $[Pd(PPh_3)_4]$ (1 mol%); II) Cs_2CO_3 (1.5 equiv), HOPMP (1.5 equiv), [Pd(Cp)(allyl)] (4 mol%); III) Grubbs II catalyst (0.5 mol%), CH_2Cl_2; IV) Pd/C, H_2. [a] Yield for the reaction under conditions I.

As both steps of the two-step iterative allylic alkylation described above are catalyzed by Pd^0, we reasoned that a one-pot 1,3-difunctionalization should be possible (Scheme 8). Without any change in the reaction conditions, the Knoevenagel adducts **1a** and **1f** underwent one-pot palladium-catalyzed iterative allylic alkylation with allyl carbonate and *para*-methoxyphenol in comparable yields to those observed for the two-step sequence.



Scheme 8. One-pot 1,3-difunctionalization of Knoevenagel adducts. Piv = pivaloyl.

In conclusion, we have introduced a strategy for the 1,3-difunctionalization of Knoevenagel adducts as TMM surrogates. We also uncovered a palladium(0)-catalyzed branched-selective allylic alkylation, which may result from an *anti* arrangement of the palladium–π-allyl intermediate. Currently, our major limitation is that the initial γ-deprotonation/α-alkylation can only be performed with an allyl carbonate as the electrophile. Future studies are aimed at intramolecular variants for efficient carbocycle formation, as well as the application of this method in the synthesis of complex molecules.

Acknowledgements

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Keywords: 1,3-difunctionalization · allylation · Knoevenagel condensation · palladium catalysis · trimethylenemethane

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