Allylation

DOI: 10.1002/anie.200600721

A Versatile Hexadiene Synthesis by Decarboxylative sp^3–sp^3 Coupling/Cope Rearrangement

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The sp^3–sp^3 coupling of two allyl fragments is a potentially powerful way of generating 1,5-dienes, which are found in a host of biologically active natural products.[1] However, there are surprisingly few catalytic transformations that couple two different allyl groups with high selectivity.[2–4] Seminal studies by Schwartz showed that electrophilic π-allyl palladium complexes, which are conveniently accessed by oxidative addition of allylic acetates, underwent stoichiometric coupling with nucleophilic magnesium allyl reagents.[4] Presumably this reaction proceeds by transmetalation from Mg to give bis(allyl) palladium complexes which reductively eliminate the hexadiene.[5] Transmetalation from tin was also possible, and allowed the catalytic Stille-type coupling of allylic bromides with allyl stannanes.[4] However, this method is clearly nonideal because it suffers from poor yields and requires the synthesis and use of stoichiometric quantities of toxic allyl stannanes.

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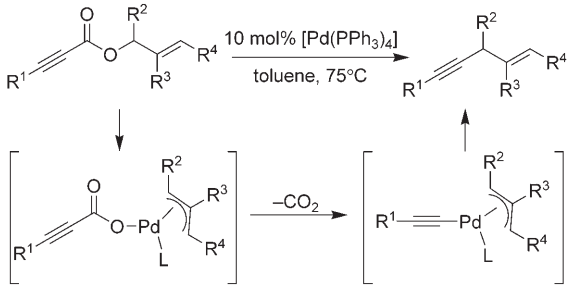
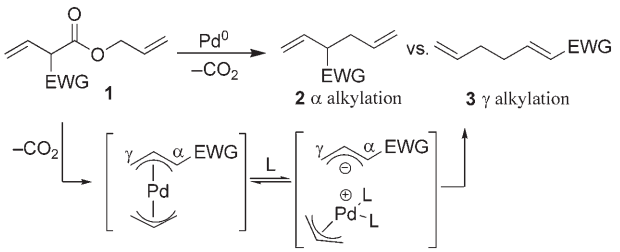
Recently, our group developed an sp^3–sp coupling of allyl electrophiles with acetylide nucleophiles (Scheme 1).[6] In doing so, it was demonstrated that decarboxylative metalation can be used to access organometallic intermediates, and is



Scheme 1. Decarboxylative sp^3–sp coupling of allyl electrophiles with acetylide nucleophiles.

thus an alternative to transmetalation. Such decarboxylative coupling reactions are advantageous because they allow the use of readily available carboxylic acids or esters (as opposed to organometallic reagents), occur under neutral conditions, and produce CO_2 as the only by-product.[7,8]

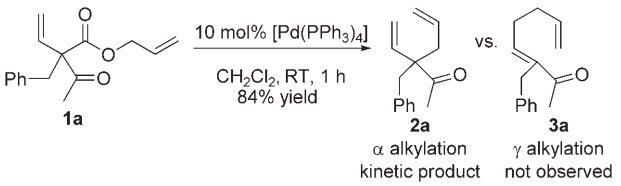
As decarboxylative metalation can potentially be used to circumvent transmetalation, it is desirable to determine what other types of organometallic intermediates can be accessed by decarboxylation. With the goal of developing an alternative to the Stille-type allyl–allyl coupling, we became curious as to whether the loss of CO_2 from 3-butenoates could be used to produce bis(allyl) palladium complexes, thus allowing the coupling of two allyl species (Scheme 2).



Scheme 2. Decarboxylative sp^3–sp^3 coupling. EWG = electron-withdrawing group.

Our research in this area has led us to believe that the rate of decarboxylation correlates with the pK_b of the anion generated following loss of CO_2.[7] Therefore, the development of a decarboxylative sp^3–sp^3 coupling was initiated using substrates **1**, where the allyl anion generated by decarboxylation is potentially stabilized by an electron-withdrawing carbonyl group such as a ketone.[9] Such substrates are readily prepared by the $In(OTf)_3$-catalyzed vinylation (TfO = trifluoromethanesulfonate) of β-keto esters with acetylenes.[10] Decarboxylation of these substrates could lead to two possible unsaturated ketones: one derived from alkylation of the α position of the dienolate generated upon decarboxylation (**2**), and the other generated from γ alkylation of the

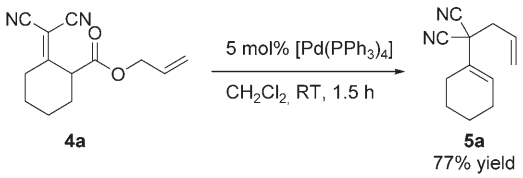
dienolate (**3**, Scheme 2).[11] It was gratifying to find that treatment of **1a** with 10 mol% $[Pd(PPh_3)_4]$ in CH_2Cl_2 resulted in the formation of α-allylated product **2a** in 84% yield of isolated product (Scheme 3).



Scheme 3. Decarboxylative dienolate allylation.

A variety of vinyl-substituted β-keto esters likewise provided the α-alkylation product as the only isolated product. As shown in Table 1, the reaction allows coupling of a variety of substituted allyl fragments with an unsubstituted allyl group. In fact, the chemistry was only limited by the variety of substrates that could be prepared by the vinylation of β-keto esters.[10]

As a consequence of the success of the catalytic decarboxylation of vinylic β-keto esters, our focus shifted to other compounds that incorporate electron-withdrawing groups capable of facilitating decarboxylative metalation. Additionally, we were curious as to whether electron-withdrawing groups could initially be integrated at the olefinic position of the nucleophilic allyl fragment rather than at the position α to the ester group. As nitrile groups are expected to stabilize the incipient charge during decarboxylation and can be further manipulated by reduction or hydrolysis, alkylidene malononitriles **4** were chosen as promising substrates. Moreover, the starting materials are easily prepared by a simple Knoevenagel condensation of malononitrile[12] with readily available allylic β-keto esters.[13] To test the feasibility of the proposed reaction, **4a** was allowed to react with 5 mol% $[Pd(PPh_3)_4]$ in CH_2Cl_2 (Scheme 4). After 1.5 h at ambient temperature, the



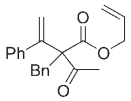
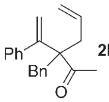
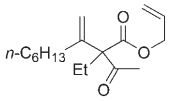
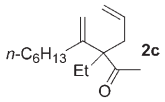
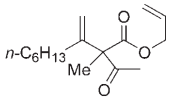
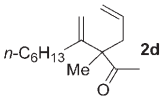
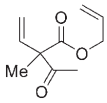
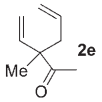
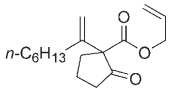
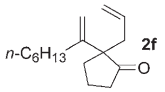
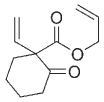
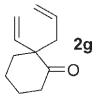
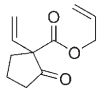
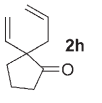
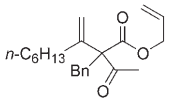
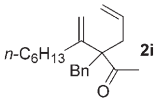
Scheme 4. Decarboxylative dicyanoallyl allylation.

reaction was complete and the product was isolated as a single regioisomer in good yield. Importantly, the analogous control reaction of **4a**, which was run in the absence of catalyst at 150 °C for 30 min, showed no degradation or product formation. Thus, the reaction is palladium-catalyzed, and the predominance of α alkylation indicates that the regioselectivity is the result of kinetic control.

We further examined the reactivity of other alkylidene malononitriles in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ and found that the reaction was tolerant of a variety of electrophilic allyl fragments (Table 2). Primary, substituted, cyclic, and acyclic allylic esters were all used, and the substitution pattern had no substantial effect on yields or reaction rates. Esters of disubstituted allylic alcohols exhibit excellent regioselectivity in favor of α alkylation, while those of terminally unsubstituted allylic alcohols give rise to mixtures of α- and γ-alkylated products.[14] These results suggest that the α position is sterically less hindered and γ alkylation can be avoided if one employs a sufficiently large allylic alcohol fragment. Additionally, as might be expected for a reaction involving π-allyl palladium intermediates, ester **4i** of a monosubstituted allylic alcohol undergoes highly regioselective alkylation at the less substituted allyl terminus. Thus, decarboxylative coupling results in regioselective α coupling at the cyanoallyl fragment and coupling at the electrophilic allyl fragment occurs at the less hindered site.

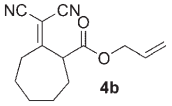
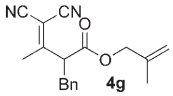
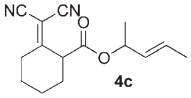
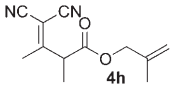
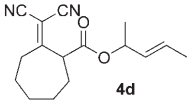
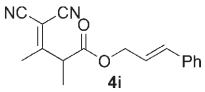
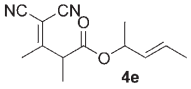
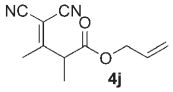
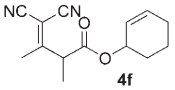
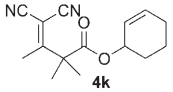
In addition to the regioselectivity of C–C bond formation, the utility of decarboxylative coupling lies in the ability to kinetically and *regiospecifically* generate allyl anion equivalents (Scheme 5). In contrast, generation of the equivalent anions by metalation with a strong base would produce mixtures of regioisomers (Scheme 5).[2a] By utilizing decarboxylative metalation, a variety of cyclic and acyclic dicyanoallyl anion equivalents are generated regiospecifically at the site that carries the carboxy group. One current limitation of this chemistry is that substitution at the α position of the

Table 1: Decarboxylative allyl–dienolate coupling.[a]

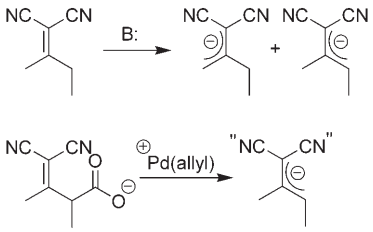
Substrate	Product	Yield [%]
	 **2b**	65
	 **2c**	77
	 **2d**	86
	 **2e**	61
	 **2f**	79
	 **2g**	80
	 **2h**	69
	 **2i**	82

[a] Yields of isolated products for reactions carried out using $[Pd(PPh_3)_4]$ (0.05 mmol) and allyl β-keto esters (0.50 mmol) in CH_2Cl_2 (3.0 mL) at room temperature under N_2 for 0.5–1 h.

Table 2: Decarboxylative coupling of alkylidene malononitriles.[a]

Substrate	α/γ	Yield [%]	Substrate	α/γ	Yield [%]
 **4b**	78:22	80[d]	 **4g**	79:21	58[d]
 **4c**	>97:3	97	 **4h**	62:38	76[d]
 **4d**	93:7	84	 **4i**	86:14	97[d]
 **4e**	>95:5[b]	84	 **4j**	84:16	91[d]
 **4f**	>95:5[c]	92	 **4k**	>95:5	93

[a] Yields of isolated products for reactions carried out using $[Pd(PPh_3)_4]$ (0.05 mmol) and β-alkylidene malononitrile (1.0 mmol) in CH_2Cl_2 (5 mL) at room temperature under N_2 for 1–2 h. [b] $E/Z = 15:1$. [c] $E/Z = 8.3:1$. [d] Combined yield of two isomers.



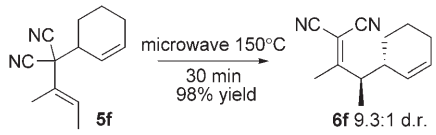
Scheme 5. Regiospecific generation of allyl anion equivalents. B = base.

substrates is necessary to prevent decomposition of the starting materials. However, Table 2 shows that compounds that are α-substituted undergo coupling in good to excellent yields. Furthermore, NOE measurements indicate that the resulting olefinic products are preferentially formed as the *E* isomers.

The α-selective decarboxylative allyl–allyl coupling is an efficient route to 1,5-dienes, whereas the development of an analogous γ-selective transformation would provide a versatile synthetic method for the synthesis of 1,5-hexadienes. In this regard, it was expected that Cope rearrangements could be used to access the thermodynamically favored γ-allylation products directly from the α-allylation products. The resulting α,β-unsaturated nitriles and ketones are expected to be versatile synthetic intermediates as a result of the electronic differentiation of the two olefinic double bonds. With this in mind, the optimal conditions for Cope rearrangement of the α-alkylation products to produce γ-alkylation products were briefly investigated. Specifically, a number of the products were treated to either thermal conditions in a microwave reactor or conditions for Pd^{II} catalysis as described by Overman and Renaldo,[15] to afford the α,β-unsaturated 1,5-dienes.[16]

The Pd^{II}-catalyzed Cope rearrangement occurs under mild conditions with substrates such as **2i**, but the rearrangement is limited to substrates that are substituted at the 2- or 5-position as outlined by Overman and Renaldo.[17] For substrates that do not meet the criteria necessary for Pd^{II}-catalyzed rearrangement (that is, **2a**), the Cope rearrangement was effected in excellent yield by heating at 180 °C in a microwave reactor.[18]

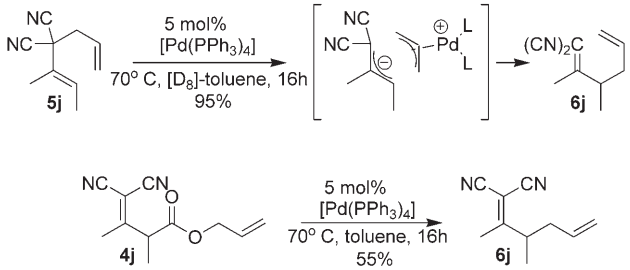
The α-alkylated isomers of alkylidene malononitriles likewise underwent thermal Cope rearrangement to give the γ-alkylated isomers in a microwave reactor at 150 °C in essentially quantitative yields (Scheme 6). Moreover, the Cope rearrangements occurred



Scheme 6. Microwave-assisted Cope rearrangement.

with the expected stereochemical control to provide substrates with contiguous stereocenters in good diastereoselectivity.

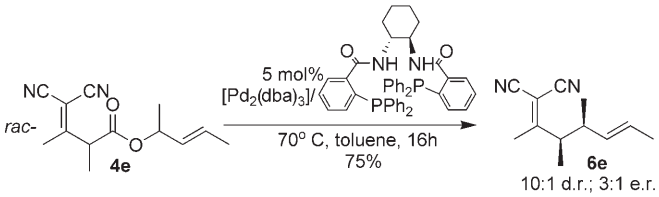
In addition to more standard thermal and Pd^{II}-catalyzed Cope rearrangements, Yamamoto and co-workers have demonstrated that it is possible to catalyze a Cope-like rearrangement of α-alkylation products resembling **5** by using Pd^0.[2a] As our decarboxylative coupling method allows the synthesis of a wide variety of α-allylated products, we are able to subject these substrates to modified conditions for Pd^0-catalyzed Cope rearrangements. For example, the α-allylation product **5j** underwent rearrangement to the γ-allylation product **6j** upon treatment with $[Pd(PPh_3)_4]$ in toluene at 70 °C (Scheme 7).



Scheme 7. Pd^0-catalyzed tandem allylation/Cope rearrangement.

The control reaction without $[Pd(PPh_3)_4]$ resulted in < 5% rearrangement under identical conditions. The fact that the decarboxylative coupling and the Cope-like rearrangement are both Pd^0-catalyzed suggested that a one-pot tandem decarboxylative allylation/Cope rearrangement was feasible. Indeed, reaction of the alkylidene malononitrile **4j** with $[Pd(PPh_3)_4]$ in toluene at 70 °C provided the γ-allylation product **6j** as the exclusive regioisomer (Scheme 7).

Finally, the ability to perform a tandem decarboxylative coupling/Cope rearrangement suggested that an asymmetric rearrangement might be possible through appropriate choice of a chiral ligand. To test the feasibility of this approach, the rearrangement of *rac*-**4e** was performed using Pd^0 modified with the Trost ligand, which led to product formation in good yield with high diastereoselectivity and modest enantioselectivity (Scheme 8). While the enantioselectivity is not optimal,



Scheme 8. Asymmetric tandem allylation/Cope rearrangement. dba = *trans,trans*-dibenzylideneacetone.

this reaction represents the first asymmetric rearrangement of this type. Moreover, the ability to set contiguous stereocenters by Pd^0-catalyzed allylation is rare, and thus tandem allylation/Cope rearrangements will potentially allow extension of allylation strategies to new substrates. Current efforts are directed toward maximizing the enantioselectivity of the allyl–allyl coupling while maintaining high diastereoselectivities.

In summary, we have shown that Pd^0-catalyzed decarboxylation is a simple and convenient way to trigger the formation of nucleophilic allyl species in the presence of electrophilic π-allyl palladium complexes. The resulting sp^3–sp^3 coupling reaction favors kinetic allylation at a position α to electron-withdrawing groups, and the analogous γ-allylation products can be obtained by conversion to the thermodynamic product under conditions of microwave irradiation or Pd^{II} catalysis. With sufficiently stabilized allyl nucleophiles, the Cope rearrangement can be catalyzed by Pd^0, which leads to the development of a tandem allylation/Cope rearrangement. Thus, either α- or γ-coupling products are available in high yield from methylene malononitrile nucleophiles, and the desired regioisomer is obtained simply by controlling the temperature of the reaction mixture.

Experimental Section

General procedure for the palladium-catalyzed decarboxylation of vinylic β-keto esters: A round-bottom side-arm flask (25 mL) containing $[Pd(PPh_3)_4]$ (0.050 mmol, 10.0 mol%) was evacuated and purged with argon gas. An allylic β-keto ester (0.50 mmol) and dichloromethane were added to the system and the reaction mixture was stirred at room temperature for 0.5–1.5 h. Next, the mixture was diluted with dichloromethane and filtered through a short Celite and silica gel pad. The filtrate was concentrated and the residue was purified on a column of silica gel using hexane/dichloromethane (85:15) as eluent to afford the decarboxylative coupling products **2**.

General procedure for the palladium-catalyzed decarboxylation of alkylidene malononitriles: In a dried Schlenk flask under argon, $[Pd(PPh_3)_4]$ (0.025 mmol) was added to substrates **4** (0.5 mmol) dissolved in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 1–2 h, then concentrated and directly purified by flash chromatography (SiO_2, 5% EtOAc/hexane).

Received: February 23, 2006
Revised: April 9, 2006
Published online: July 3, 2006

Keywords: allylation · decarboxylation · hexadienes · palladium · rearrangement

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