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Intercepted decarboxylative allylations of nitroalkanoates

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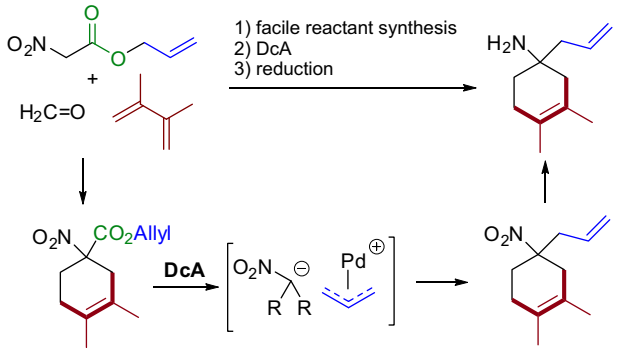
ABSTRACT

Using palladium-catalyzed decarboxylation, several cascade reactions of allyl and prenyl nitroalkanoates that lead to nitro-containing chemical building blocks are described. A nitronate Michael addition/Tsuji–Trost allylation cascade was developed, leading to functionally dense chemical building blocks. Likewise, a Tsuji–Trost/decarboxylative protonation sequence was developed for the synthesis of orthogonally functionalized 2° nitroalkanes. The latter method provides rapid access to the indolizidine core.

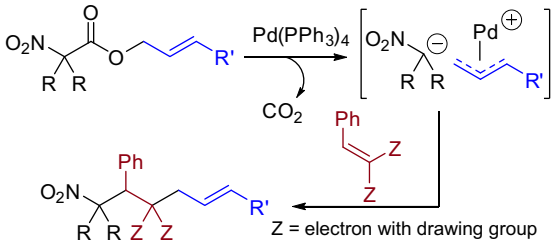
Introduction

Palladium-catalyzed decarboxylative allylation (DcA) is a convenient method to generate functionalized chemical building blocks with only CO_2 as a byproduct.[1,2] Using this chemical reactivity, various methods have been developed for the synthesis of nitrogen-containing chemical building blocks.[3] This is of significance since nitrogen-containing materials often exhibit interesting biological activities. In this regard, we reported the rapid decarboxylative allylation of nitroalkanes (Scheme 1).[4] Nitroalkanes readily allow the incorporation of nitrogen into alkaloids and other biologically active nitrogenous compounds because they have the advantageous chemical properties of a relatively low pK_a (~10 in H_2O)[5] and facile reducibility to amines. As shown in Scheme 1, nitroacetic esters are readily functionalized by α-alkylation.[6,7] Decarboxylative allylation then provides tertiary nitroalkanes that are readily reduced to amines.

One advantage of the DcA of nitroalkanes is that it allows the generation of reactive nucleophiles and electrophiles in situ. We and others have previously demonstrated that these nucleophilic and electrophilic coupling partners can be funneled down alternate reaction pathways such as Michael-addition/Tsuji–Trost allylation cascades (interceptive DcA)[1,8] or capture by protonation.[9] Herein we report that allyl nitroalkanoates can participate in similar cascade reactions. We present a Michael-addition/Tsuji–Trost cascade leading to functionally dense nitro group-containing compounds (Scheme 2) as well as a Tsuji–Trost/decarboxylative protonation cascade strategy to access functional allylated 2° nitroalkanes (Scheme 3).



Scheme 1. DcA of allyl nitroalkanoates.



Scheme 2. Cascade Michael addition/Tsuji–Trost allylation initiated by decarboxylation of allyl nitroalkanoates.

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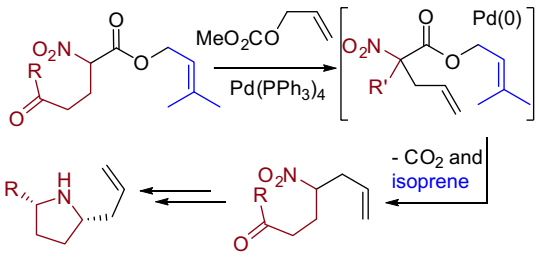
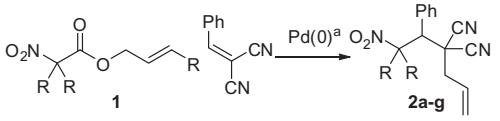
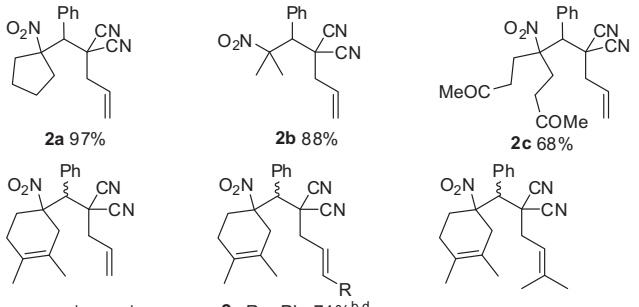


Scheme 3. Cascade Tsuji–Trost/decarboxylative protonation of allyl nitroalkanoates.

Table 1
Interceptive decarboxylative allylation of allyl nitroalkanoates with benzylidenemalononitrile



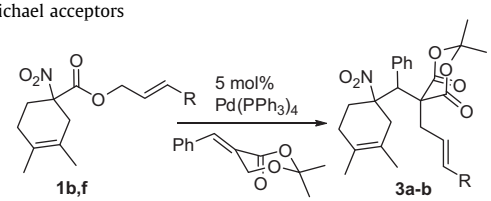


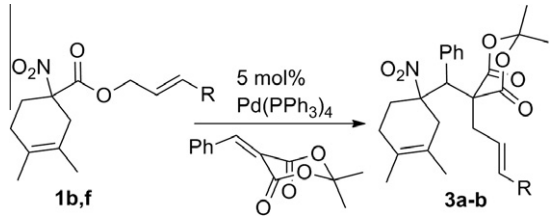
[a] Reaction conditions: 1:1 **1**: benzylidenemalononitrile, 5 mol % $Pd(PPh_3)_4$, DCM, rt, 12 h.
[b] 1:1 d.r.
[c] Toluene in lieu of DCM, rt, 12 h.
[d] >20:1 linear: branched.

Michael addition/Tsuji–Trost allylation cascades

To begin, we treated allyl nitroalkanoates under similar conditions to those developed for the successful DcA reaction of allyl nitroalkanoate (5 mol % $Pd(PPh_3)_4$, DCM),[4] however an equivalent of benzylidenemalononitrile was included in the reaction mixture. Gratifyingly, the intermediate allyl electrophile and nitronate nucleophiles were intercepted with the benzylidene malononitrile to form highly functionalized nitroalkanes (Table 1). The intercepted DcA reaction was not nearly as rapid as the standard DcA reaction, requiring 12 h for completion. The uninterrupted decarboxylative allylation reaction of allyl nitroalkanoates required < 5 minutes to achieve completion under the same conditions.[4] The slower rate of interceptive DcA is easily explained by the coordination of benzylidene malononitrile to Pd(0), rendering the catalyst less electron-rich and less prone to undergo oxidative addition with the allylic carboxylate. Nonetheless, various allyl nitroalkanoates were excellent coupling partners (**2a–d**). α,α-Dialkyl nitroalkanes (**2a**,**b**), including Michael (**2c**)[7] and Knoevenagel/Diels–Alder (**2d**) adducts[6] were compatible coupling partners. It was unfortunate, though not surprising, that Diels–Alder adduct **2d** was formed with no diastereoselection; changing the solvent from DCM to toluene did not improve the diastereoselectivity, but the cascade reaction progressed comparably well. Aside from allyl nitroalkanoate (**2a–d**), cinnamyl, hexenyl, and prenyl nitroalkanoates were excellent coupling partners (**2e–g**), giving exclusively the linear product. Although **2e–g** were formed with no diastereoselection, the diastereomers of **2g** could be chromatographically separated. The successful synthesis of prenylated product **2g** was particularly gratifying given that attempted decarboxylative prenylation of **1a** led primarily to the protonation product (Eq. 1). While palladium-π prenyl complexes often undergo β-elimination instead of the desired C–C linkage, prenylation methodologies have been developed for some nucleophiles.[10]

Table 2
Interceptive decarboxylative allylation of allyl nitroalkanoates with Meldrum's acid derived Michael acceptors

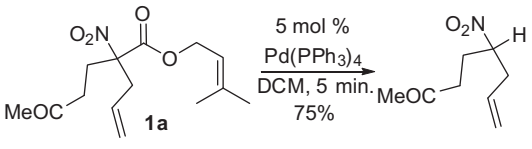




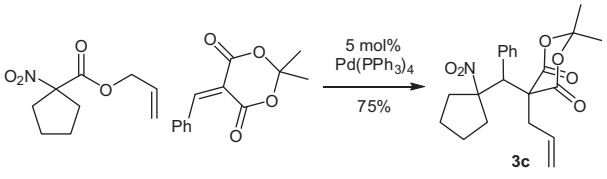
Entry	R	Solvent	Temp.(°C)	Time (h)	% Yield (d.r.)
1	H	DCM	rt	12	trace
2	H	DCM	40	12	trace
3	H	DCE	80	12	trace
4	H	THF	rt	12	74 (7:3)
5	H	Tol	rt	12	70 (7:3)
6	Pr	THF	60	1	55 (7:3)

[a] The relative configuration of the major diastereomer is not known.

Having demonstrated that the Michael addition/Tsuji–Trost cascade process was successful with benzylidenemalononitrile, we wished to extend this methodology to Michael acceptors derived from Meldrum's acid (Table 2). Surprisingly, the reaction failed to produce any of the desired product under the same conditions developed for benzylidenemalononitrile (Table 2, entry 1). Furthermore, heating the reactants at various temperatures in chlorinated solvents failed to give a desirable result (Table 2, entries 2–3). Fortunately, good yields could be achieved in THF (entry 4) or toluene (entry 5). Interestingly, a modest diastereoselectivity was observed, though different solvents did not affect this ratio. Aside from simple unsubstituted allyl esters, the alkyl-substituted hexenyl nitroalkanoate provided a modest yield of the Michael addition/Tsuji–Trost coupling product (entry 6). Simple cyclopentyl allyl nitroalkanoate could also undergo a clean reaction in 75% isolated yield (Eq. 2, **3c**).

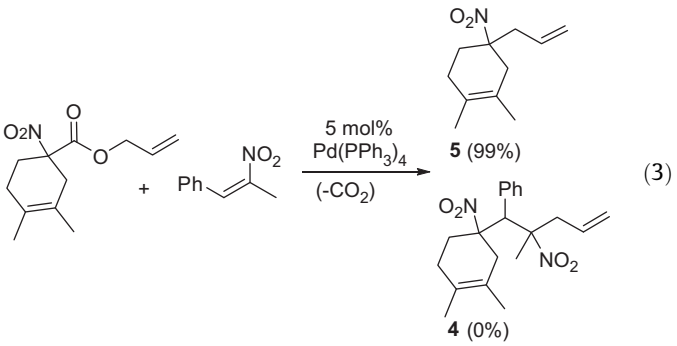


(1)



(2)

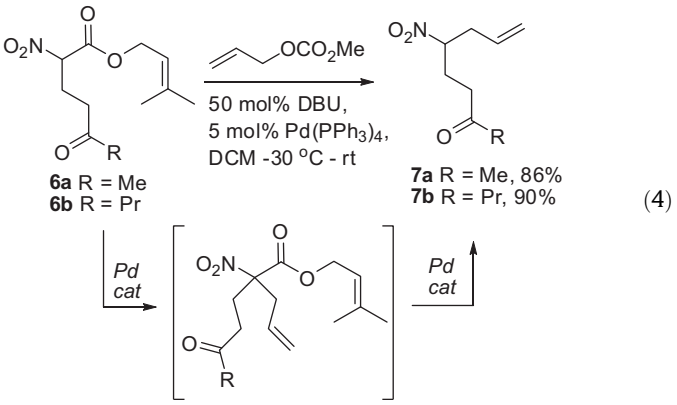
We also attempted to utilize nitrostyrenes as coupling partners for interceptive DcA (Eq. 3). Unfortunately, there appears to be no driving force for the Michael addition to form **4**, and DcA to produce **5** was the only reaction pathway observed (Eq. 3).[4] In the successful examples of interceptive DcA, the anion generated upon Michael addition is always more stable than that of the initial nucleophile. Thus, there is a thermodynamic driving force for reaction progression. Comparison of the relevant pK_a values (in DMSO) further illuminates the driving force for nitronate (pK_a ~17) addition to malononitriles (pK_a ~12) and Meldrum's acid adducts (pK_a ~7.5).[5] Moreover, our results trend with Mayr's observation that Michael acceptors derived from malononitrile and Melrum's acid are more electrophilic than a Pd-π-allyl complex,[11] thus addition of nitronates to benzylidene malononitriles is expected to be kinetically faster than allylation.



(3)

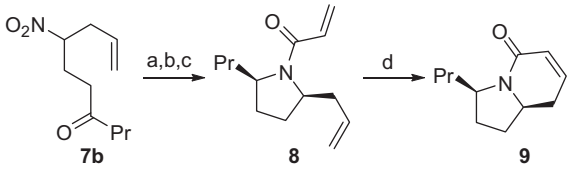
Michael addition/Tsuji–Trost allylation cascades

In addition to the development of the Michael addition/Tsuji–Trost cascades initiated by decarboxylation, we were intrigued by the clean conversion of the prenyl nitroalkanoate into the protonated 2° nitroalkane product (Eq. 1). Historically, allylated 2° nitroalkanes can be challenging to access due to competing over alkylation. Thus, the nitroalkane nucleophile is commonly used in excess to selectively give the 2° nitroalkane.[12] Clearly, this is an unattractive solution if one wishes to utilize precious nitroalkane reactants. Since nitroalkanoates are excellent Tsuji–Trost substrates,[13] we proposed that a single pot Tsuji–Trost allylation/decarboxylative protonation strategy could quickly lead to synthetically useful 2° nitroalkanes (Scheme 3). Moreover, with appropriate substitution, functional groups can be paired to quickly access *cis*-1,5-dialkyl pyrrolidines and the indolizidine core.[14,15]



(4)

We began by synthesizing substrates **6** from prenyl nitroalkanoate using Yb(OTf)$_3$-catalyzed Michael additions (Eq. 4).[7b] Once the nitroalkanoates were alkylated with the vinyl ketone, substrates **6** were allowed to react with allyl carbonate in the presence of catalytic amounts of DBU (50 mol %) and Pd(PPh$_3$)$_4$ (5 mol %) at -30 °C. The palladium catalyst first effects the Tsuji–Trost allylation of the nitroalkanoate. Upon warming, this reaction is followed by decarboxylative protonation to yield secondary nitroalkanes **7a** and **7b** in good yields. Moreover, synthetically useful quantities (>1 g) of **7b** were prepared for further chemical manipulation.



(a) 20 Equiv.Zn Dust, 10 Equiv. HCl, *i*PrOH (b) DIBALH, DCM -78°C-rt
(c) 1.1 equiv. acryloyl chloride, 1.2 equiv. pyridine, DCM 0 °C - rt
(3-steps 65% yield) (d) 5 mol% Grubbs' II, tol, 60 °C 2 h, 88% yield.

Scheme 4. Synthesis of the indolizidine core.

To demonstrate the utility of this process, compound **7b** was then converted to the indolizidine core in 4 steps (Scheme 4). Upon reduction of the nitro group,[6] spontaneous condensation to the imine occurred.[11] This imine was immediately reduced to *cis*-1, 5-pyrrolidine as a single diastereomer.[15] As purification of this secondary amine was deemed too challenging, it was not purified until after acylation with acryloyl chloride. This 3-step process progressed in 65% overall yield. Interestingly, this amide exists as a 1:1.2 mixture of rotamers about the amide-bond. Fortunately, heating with Grubbs' second generation catalyst (5 mol %), the diastereomers underwent convergent metathesis leading to a single ring-closed product **9** in 88% yield.

In conclusion, we have shown that nitronates and Pd-π-allyl complexes derived from allyl nitroalkanoates can be diverted from decarboxylative allylation (DcA) through reaction pathways including Michael addition/Tsuji–Trost cascades and Tsuji–Trost/decarboxylative protonation reactions.

Acknowledgment

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Supplementary data

Supplementary data (detailed experimental analysis and spectral analysis including ^{1}H, ^{13}C, and HRMS or GC–MS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.138.

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