Deacylative allylation of nitroalkanes: unsymmetric bisallylation via 3-component coupling

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Catalytic Tsuji-Trost allylation has become a ubiquitous method for allylation of active methylene compounds.[1] While monoallylation products are typically formed, bisallylation of malonates and related ketone enolates leads to 1,6-dienes.[2] Given the utility of these 1,6-heptadienes in metal-catalyzed cycloisomerization reactions,[3] it would be beneficial if one could perform controlled bisallylation of less stabilized carbon nucleophiles. Unfortunately, the one-pot bisallylation of other carbon nucleophiles is not well documented and usually requires harsh reaction conditions.[4] Moreover, the addition of two different allyl electrophiles to form unsymmetric 1,6-dienes in a one-pot operation is exceedingly rare.[5] Herein, we describe the development of an unsymmetric bisallylation of carbon nucleophiles and introduce catalytic deacylative allylation as a new strategy for tandem in situ generation and coupling of nucleophiles with allyl electrophiles (eq. 1).[1]

We initiated our pursuit of a 3-component catalytic bisallylation reaction with the investigation of the deacylative allylation of nitroalkanes. Palladium-catalyzed allylation of nitroalkanes is a well-known, albeit non-trivial, process.[6,7] For example, monoallylation of nitromethane and primary nitroalkanes is complicated by competing bisallylation, so excess nitroalkane is often required to achieve monoallylation.[6] To begin, it was expected that we could take advantage of the ease of Tsuji-Trost allylation of highly stabilized nitroacetone nucleophiles to form allylated nitroketones (eq. 2).[8] Ballini and others have shown that simple nitroalkanes can be generated by deacylation of related nitroacetone derivatives.[9,10] Indeed performing Tsuji-Trost reactions in the presence of methanol and base proceeded with deacylation to selectively afford the monoallylated nitroalkanes (eq. 2). Similar

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.
See supporting information for full experimental procedures, $^1$H NMR, $^{13}$C NMR, and GC/MS data for starting materials, compounds 1a-d, 2a-n, and 4a-d.
treatment of the cyclic nitroketones likewise provided clean monoallylated products containing a pendant ester (eq. 3). Thus, clean one-pot monoallylation of nitroalkanes is possible using a deacylative Tsuji-Trost reaction.¹⁸,¹¹

Like most other deacylative (retro-Claisen) reactions,¹² our monoallylation reactions simply use the acyl group as an activating group that can be readily removed. However, we hypothesized that an allyl alcohol could deacylate the intermediate α-nitroketone to generate a nitronate anion and simultaneously generate an allyl acetate electrophile (eq. 1). Such a process would allow selective 3-component bisallylation using nitroacetones, an allyl acetate or carbonate, and an allylic alcohol (Scheme 1). Because allyl alcohols are relatively nonreactive toward palladium catalysts, the nitroacetone is expected to undergo rapid, selective Tsuji-Trost allylation with the allylic acetate. The resulting product nitroketone can undergo further allylation only via a deacylative allylation protocol. Ultimately, it was anticipated that these kinetically distinct steps could be combined to afford a 3-component unsymmetric bisallylation reaction.

The proposed coupling hinged on the hypothesis that an allyl alcohol could decacylate an α-nitroketone to generate an allyl acetate and a nitronate anion in situ. To begin, a model allylated nitroacetone was synthesized via Tsuji-Trost allylation and treated under a variety of reaction conditions. We were pleased to find that various primary allyl alcohol derivatives participated in Pd(PPh₃)₄-catalyzed deacylative allylation when 1 equivalent of Cs₂CO₃ base was added (Table 1). The allylation worked well for 2-hexenol as well as for cinnamyl alcohol, providing the linear allylation products 2b and 2c respectively. However, the coupling of cinnamyl alcohol did require a higher palladium catalyst loading of 10 mol % to achieve high yield. The higher catalyst concentration promotes the desired C-allylation of the intermediate nitronate at the expense of problematic vinylogous Hass-Bender oxidation of cinnamyl acetate to cinnamaldehyde.⁷b,¹³ When crotyl alcohol was the coupling partner, a decrease in linear to branched selectivity (3.8:1) was observed (entry 5, Table 1). A similar drop in regioselectivity was noted in the decarboxylative allylation of nitroacetates with crotyl alcohol derivatives.⁷b While the primary alcohol derivatives provided products in good to excellent yields, the deacylative allylation appears to have a steric limitation as a secondary allylic alcohol provided the desired product in poor yield (entry 6, Table 1).

Having demonstrated the requisite deacylative allylation, we turned our attention to the 3-component bisallylation of an α-nitroketone. Indeed treatment of α-methyl nitroacetone with an allyl carbonate (or acetate) and allyl alcohol selectively produced the desired nitroalkyl 1,6-diene 2c in high yield (eq. 4). Importantly, attempts to make the same product directly
from nitroethane gave rise to a complex mixture of allylated products. Thus, deacylative allylation provides a unique avenue to unsymmetrically substituted 1,6-diienes.

Since the allyl carbonate provided a higher yield than the allyl acetate (eq 5), subsequent exploration of the reaction scope focused on coupling of allyl carbonate derivatives (Table 2). A comparison of 2c (derived from allyl alcohol) and 2c' (derived from cinnamyl alcohol) suggests that the allyl carbonate and alcohol partners can be reversed with little or no change in yield. With regard to the nitroketone substrate, α-phenyl and alkyl ketones were viable coupling partners (e.g. 2g and 2h, Table 2). Notably, an α-substituent with a base sensitive methyl ester moiety survived the reaction conditions leading to the functionalized products 2i–k. Importantly, the fact that the methyl ester remains intact shows that acyl substitution of nitroacetones by allyl alcohols is more facile than acyl substitution of esters. Lastly, a cyclic α-nitroketone provides the ring-opened nitroalkane with a pendant carboxylic acid (eq. 5). The carboxylic acid could be obtained in good yield, however it was necessary to convert it to the methyl ester to effect complete purification.

While the bisallylation reactions described above utilize secondary nitroketones, trisallylation of a primary nitroketone is possible using 2 equivalents of an allyl carbonate and 1.3 equivalents of allyl alcohol (eq. 6). Thus, deacylative allylation allows the selective synthesis of 2m from 4 reactant molecules via the formation of 3 new C–C bonds in 81% yield.

In addition to the deacylative allylations of nitroketones, preliminary studies suggest that deacylative allylation will also allow intermolecular allylations of activated ketones (Table 3). We and others have previously developed decarboxylative allylations of ketones which proceed via formation of ketone enolates via C–C cleavage. While these reactions have significant utility, their use is somewhat hampered by the need to incorporate the electrophile and nucleophile in the same molecular entity prior to decarboxylative coupling.
The allylations in Table 3 suggest that deacylative allylation may allow similar reactions to take place in an intermolecular fashion. Finally, ketone substrates that participate in deacylative allylation also allow selective 3-component coupling to form unsymmetric heptadienes (eq. 7).

In closing, we have developed deacylative allylation as a synthetic strategy for directly utilizing inexpensive, readily available allyl alcohols in electrophilic allylation reactions. Not only does deacylative allylation allow selective monoallylation of nitronates, but it also can be used in tandem with Tsuji-Trost allylation of stabilized nitronates to allow controlled synthesis of unsymmetric 1,6-dienes via 3-component coupling. Precise control of the kinetics of the couplings obviates many possible side reactions (e.g. homoallylation, allylation of alkoxide intermediates), leading to a highly selective bisallylation. Similar strategies are expected to allow the selective multi-component allylations of a wide variety of acyl pronucleophiles using allyl alcohols.

Experimental Section

Representative procedure for the deacylative allylation of nitroacetones

In a glove box under an argon atmosphere, a flame dried pressure vial equipped with a septum was charged with \( \text{Pd(PPh}_3)_4 \) (14 mg, 0.0125 mmol) and \( \text{Cs}_2\text{CO}_3 \) (165 mg, 0.5 mmol). Anhydrous DCE (1 mL) was added and the vial sealed. After removing the vial from the glove box, a solution of \( \alpha \)-allyl, \( \alpha \)-methyl nitroacetone (47 mg, 0.3 mmol) and allyl alcohol (22 mg, 0.36 mmol) in dry DCM (500 \( \mu \)L) was added via syringe and the transfer vessel was washed with 2 \( \times \) 250 \( \mu \)L portions of DCM to ensure complete transfer of the substrates to the reaction mixture. The pressure vial was then submerged in an oil bath at 80 °C and left to stir overnight. After the allotted reaction time, the vessel was cooled to room temperature and the resulting solution was diluted with 15% \( \text{Et}_2\text{O/pentane} \) (~5 mL) and eluted through a silica plug with excess 15% \( \text{Et}_2\text{O/pentane} \) (~50–75 mL). After removal of the volatiles via rotary evaporation, the crude oil was subjected to column chromatography (gradient column: 2% to 4% \( \text{Et}_2\text{O/pentane} \)) yielding the pure product 2a as a colorless oil (40 mg, 87% Yield). Spectral data for 2a: \( ^1\text{H NMR} \) (500 MHz, CDCl3) \( \delta = 5.61 \) (m, 2H), 5.12 (d, \( J = 8.9 \) Hz, 2H), 5.09 (d, \( J = 16.3 \) Hz, 2H), 2.67 (dd, \( J = 14.2, 7.3 \) Hz, 2H), 2.48 (dd, \( J = 14.2, 7.3 \) Hz, 2H), 1.47 (s, 3H). \( ^{13}\text{C NMR} \) (126 MHz, CDCl3) \( \delta = 128.7, 118.4, 88.3, 41.2, 19.6 \). MS e/z: found 109.2 (M-NO\(_2\)), 46.0 (NO\(_2^+\)).

Representative procedure for the 3-component Tsuji-Trost/deacylative allylation of nitroacetone

In a glove box under an argon atmosphere, a flame dried pressure vial equipped with a septum was charged with \( \text{Pd(PPh}_3)_4 \) (14 mg, 0.0125 mmol) and \( \text{Cs}_2\text{CO}_3 \) (165 mg, 0.5 mmol). Anhydrous DCE (1 mL) was added and the vial sealed. After removing the vial from the glove box, a solution of \( \alpha \)-methyl nitroacetone (47 mg, 0.3 mmol) and tert-butyl cinnamyl carbonate (124 mg, 0.5 mmol) in dry DCM (500 \( \mu \)L) was added via syringe and the transfer vessel was washed with 2 \( \times \) 250 \( \mu \)L portions of DCM to ensure complete...
transfer of the substrates to the reaction mixture. Next, allyl alcohol (36 mg, 0.6 mmol) was injected via syringe and the resulting pressure vial was submerged in an oil bath at 80 °C and left to stir overnight. After the allotted reaction time, the vessel was cooled to room temperature and the resulting solution was diluted with 15% EtOAc/hexanes (~5 mL) and eluted through a silica plug with excess 15% EtOAc/hexanes (~50–75 mL). After removal of the volatiles via rotary evaporation, the crude oil was subjected to column chromatography (gradient column: 2% EtOAc/Hexanes) yielding the pure product 2c as a colorless oil (103 mg, 89% Yield).

Spectral data for 2c: 1H NMR (500 MHz, CDCl3) δ = 7.25 (m, 4H), 7.17 (m, 2H), 6.41 (d, J = 15.7 Hz, 1H), 5.96 (dt, J = 15.3, 7.5 Hz, 1H), 5.63 (m, 1H), 5.14 (d, J = 9.2 Hz, 1H), 5.11 (d, J = 16.4 Hz, 1H), 2.83 (ddd, J = 14.2, 7.3, 1.3, 1H), 2.72 (dd, J = 14.2, 7.3, 1H), 2.63 (ddd, J = 14.2, 7.7, 1.3 Hz, 1H), 2.52 (dd, J = 14.2, 7.7 Hz, 1H), 1.51 (s, 3H). 13C NMR (126 MHz, CDCl3) δ = 136.6, 135.4, 130.8, 128.6, 127.8, 126.3, 122.1, 120.7, 90.9, 43.5, 42.6, 22.1. MS e/z: found 231.2(M+), 185.2 (M-NO2), 46.0 (NO2+).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


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Scheme 1.
Proposed bisallylation via deacylative allylation.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl alcohol</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>HO-</td>
<td>2a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>HO-</td>
<td>2b</td>
<td>79(^b)</td>
</tr>
<tr>
<td>3</td>
<td>HO-</td>
<td>2c</td>
<td>89(^{b,c})</td>
</tr>
<tr>
<td>4</td>
<td>HO-</td>
<td>2d</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>HO-</td>
<td>2e</td>
<td>79(^d)</td>
</tr>
<tr>
<td>6</td>
<td>HO-</td>
<td>2b</td>
<td>25(^b)</td>
</tr>
</tbody>
</table>

\(^a\) 2.5 mol % Pd(PPh\(_3\))\(_4\), 1.2 equiv. allyl alcohol, 1 equiv. Cs\(_2\)CO\(_3\), DCM:DCM (1:1), 80 °C, 12 h.

\(^b\) l:b >19:1

\(^c\) 10 mol % Pd(PPh\(_3\))\(_4\)

\(^d\) 5.6:1 E:Z, 3.8:1 l:b
### Table 2

**3-component unsymmetric bisallylation**

- **2c** 89%
- **2c'** 88%[^b]
- **2b** 93%
- **2b'** 73%
- **2f** 75%[^b]
- **2f'** 79%
- **2g** 75%
- **2h** 65%
- **2i** 65%
- **2j** 91%
- **2k** 47%

[^a]: 2.5 mol % Pd(PPh₃)₄, 1 equiv. allyl carbonate, 1.2 equiv. allyl alcohol, 1 equiv. Cs₂CO₃, DCM:DCE (1:1) 80 °C, overnight.

[^b]: 10 mol % Pd(PPh₃)₄
Table 3

Deacylative allylation of nitrophenyl acac.

<table>
<thead>
<tr>
<th>Acetyl Group</th>
<th>Product</th>
<th>Reaction Conditions</th>
</tr>
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<tbody>
<tr>
<td>CH₂(COOCH₃)₅</td>
<td>4a</td>
<td>2.5 mol % Pd(PPh₃)₄, 1 equiv. Cs₂CO₃, THF, 80 °C, 12 h</td>
</tr>
<tr>
<td>CH₂(COOCH₃)₅</td>
<td>4b</td>
<td>2.5 mol % Pd(PPh₃)₄, 1 equiv. Cs₂CO₃, THF, 80 °C, 12 h</td>
</tr>
<tr>
<td>CH₂(COOCH₃)₅</td>
<td>4c</td>
<td>2.5 mol % Pd(PPh₃)₄, 1 equiv. Cs₂CO₃, THF, 80 °C, 12 h</td>
</tr>
<tr>
<td>CH₂(COOCH₃)₅</td>
<td>4d</td>
<td>2.5 mol % Pd(PPh₃)₄, 1 equiv. Cs₂CO₃, THF, 80 °C, 12 h</td>
</tr>
</tbody>
</table>

Yield: 4a 97%, 4b 91%, 4c 73%, 4d 78%