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Decarboxylative allylations of ester enolate equivalents†

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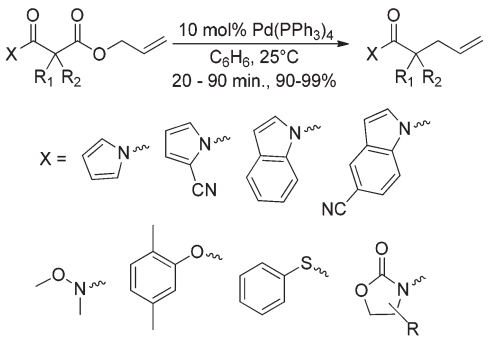
A variety of ester enolate equivalents are generated *in situ* and undergo α-allylation in high yields *via* palladium-catalyzed decarboxylative allylation. The transformations are complete within very short reaction times under ambient conditions. Synthesis of α-allylated acyl derivatives provides access to other carboxylic acid and alcohol derivatives *via* acyl group substitution or reduction.

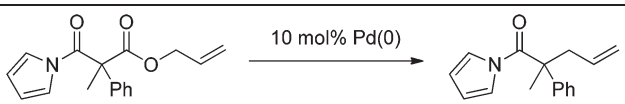
Allylation of nucleophiles *via* palladium-catalyzed decarboxylative allylation is a chemically mild and environmentally benign approach to produce allylic amines, ketones, nitriles and nitroalkanes.[1] While the α-allylation of ketone enolates has received significant attention, preparation of α-allylic esters *via* decarboxylative allylation is comparatively difficult and demands harsher conditions.[1b,2] In 2007, Ohta and coworkers reported a palladium-catalyzed decarboxylative allylation of diallyl malonates under milder conditions.[2a] However, the reported method is restricted to malonates with an α-aryl group; no reaction with diallyl 2,2-dialkylmalonates was observed.[2a] More recently, Miller showed that allyl 2,2,2-trifluoroethyl malonates allow the α-allylation of esters, however the reported chemistry was limited to α-unsubstituted malonates.[2c,3] To allow the allylation of α-monosubstituted ester enolate equivalents, Trost has also utilized 2-imidazolo-substituted enol carbonate reactants.[2d] However, the imidazole leaving group must be activated by alkylation prior to substitution.[4] Herein, we report the decarboxylative allylation of ester enolate equivalents utilizing synthetically flexible β-dicarbonyl reactants that undergo substitution without prior activation (Scheme 1).

Our initial studies were focused on allylation of acyl pyrroles. To our delight **1** underwent decarboxylative allylation quickly and cleanly with 10 mol% of $Pd(PPh_3)_4$ within 25 minutes (Table 1, entry 1). Furthermore, it was found that the reaction could be carried out in THF solvent or with other palladium sources such as Pd_2dba_3 and CpPd(allyl) in the presence of dppf ligand (Table 1, entries 3 and 4).



Scheme 1

Table 1 Screening of catalysts



1 **2**

Entry	Catalyst, ligand	Solvent	Yield[a] (%)
1	$Pd(PPh_3)_4$	C_6H_6	97
2	$Pd(PPh_3)_4$	THF	90
3	Pd_2dba_3, dppf	C_6H_6	97
4	CpPd(allyl), dppf	C_6H_6	90

[a] Isolated yield.

As expected, the acylpyrrole products are excellent precursors for further derivatization.[5] Evans,[5a,b] Fu[5c] and Arai[5d] have shown that *N*-acyl pyrroles undergo acyl substitution with water, alcohols and amines to produce acids, esters and amides. Our acylpyrrole derivative behaves similarly, allowing transformation to a tertiary alcohol, primary alcohol and carboxylic acid in high yields (Scheme 2).

Having established a successful method for decarboxylative α-allylation of an acyl pyrrole, we chose to investigate the

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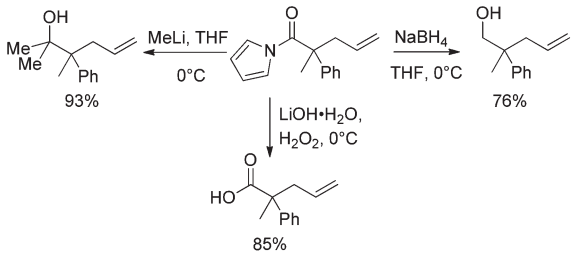
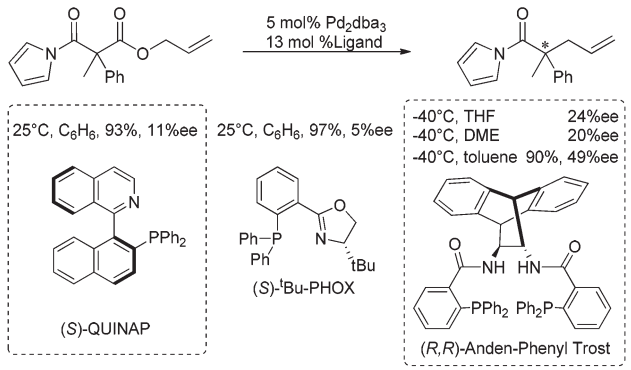
† Electronic supplementary information (ESI) available: Full characterization of all new compounds, spectra of all new compounds, crystal structure file (CIF) of **1c**. CCDC 1019501. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01752h



Scheme 2



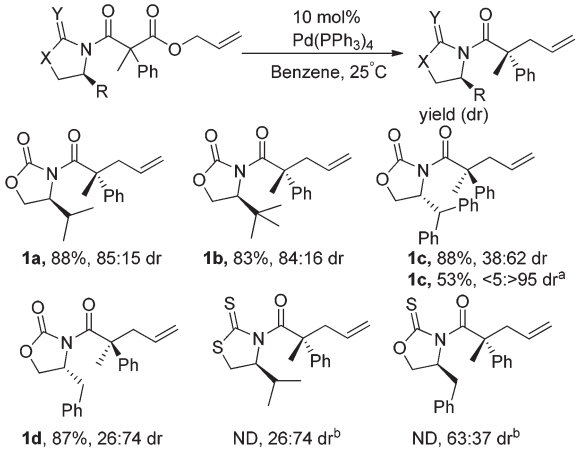
Scheme 3

enantioselectivity of the reaction with Pd_2dba_3 using various chiral non-racemic ligands such as (*S*)-QUINAP, (*R*)-BINAP, (*S*)-^{t}Bu-PHOX, and TROST ligands. Even though the conversions are excellent with these ligands, the observed enantiomeric excesses were low. The maximum enantiomeric excess (49% ee) was observed using the (*R*,*R*)-anden-phenyl Trost ligand at −40 °C in toluene (Scheme 3). Since it is known that enolates with a defined geometry undergo highly enantioselective allylation,[2d,6,7] our relatively low ee is most easily explained by a low *E*/*Z* selectivity in generation of the enolate.

Having investigated catalyst control of the product stereochemistry, we turned our attention to investigation of substrate control of the stereoselectivity. Several acyl oxazolidinone reactants were synthesized and subjected to conditions for decarboxylative allylation. Gratifyingly, all of them underwent decarboxylative allylation within 30 minutes, giving good yields of product (Table 2). While the yields are good, the use of chiral auxiliaries only led to modest improvement in stereocontrol, with the maximum diastereoselectivity being 85 : 15. Nonetheless, this is the highest stereoselectivity achieved for the decarboxylative allylation of acyclic β-oxo esters. In one case, the major diastereomer of **1c** could be obtained diastereopure in 53% yield by recrystallization and X-ray crystallographic analysis proved the stereochemical outcome of the reaction (Fig. 1). The observed stereochemistry is most easily explained based on an inner-sphere allylation[8] based on Evans chiral auxiliary model (Fig. 1).[9,10]

Having shown that acyl pyrroles and acyl oxazolidinones undergo efficient decarboxylative allylation, we became curious

Table 2 Diastereoselective DcA



[a] After recrystallization. [b] drs based on ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.

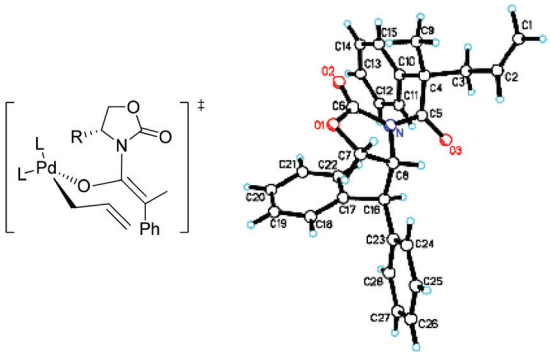
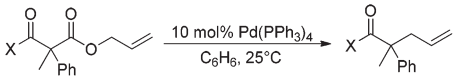


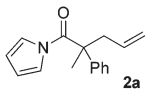
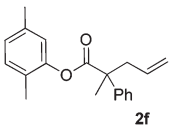
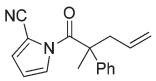
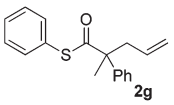
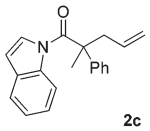
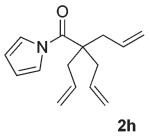
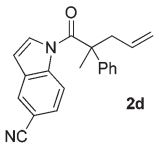
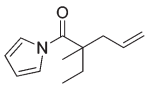
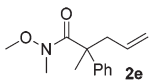
Fig. 1 Stereochemical rationale.

whether other ester/amide enolate equivalents would participate in decarboxylative allylation. Indeed, other amide enolates such as pyrrole-2-carbonitrile, indole, and indole-5-carbonitrile undergo high-yielding allylation in just 10–15 minutes at room temperature (Table 3, entries 2–4) while somewhat less reactive, a Weinreb amide enolate underwent allylation with Pd_2dba_3 in the presence of dppf ligand at 80 °C in high yield (Table 3, entry 5). A phenyl ester enolate also underwent decarboxylative allylation in high yield (entry 6), while an aryl thioester enolate provided product in only moderate yield (57%, entry 7). Lastly, it was found that the methodology could be successfully applied toward the allylation of α,α-dialkyl substrates (entries 8 and 9). Interestingly, while the α,α-diallyl acyl pyrrole (entry 8) underwent decarboxylative coupling in THF solvent under ambient conditions, significantly harsher conditions were required for the allylation of α-methyl, α-ethyl acyl pyrrole amide enolate (**2i**). Nonetheless, each product was isolated in high yield.

Next the substrate scope of decarboxylative allylation of phenyl ester enolates was examined using easily substituted dimethylphenyl esters (Table 4). Among α-monosubstituted

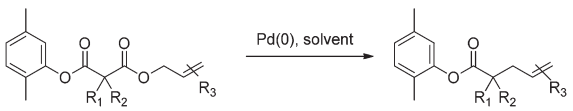
Table 3 DcA of ester enolate equivalents

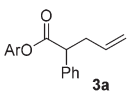
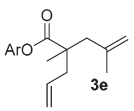
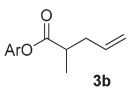
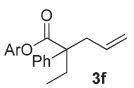
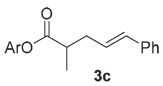
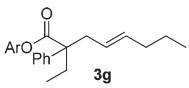
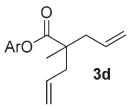
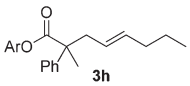


Entry	Product	Time (min)	Yield[a,e] (%)	Entry	Product	Time (min)	Yield[a,e] (%)
1	 **2a**	25	97	6	 **2f**	60	99
2	 **2b**	15	81	7	 **2g**	30	57
3	 **2c**	10	99	8	 **2h**	30	99[c]
4	 **2d**	10	96	9	 **2i**	180	98[d]
5	 **2e**	90	89[b]				

[a] $Pd(PPh_3)_4$ 10 mol%, C6H6, rt, 0.03 M. [b] Pd_2dba_3 10 mol%, dppf 10 mol%, C_6H_6, 80 °C, 0.03 M. [c] $Pd(PPh_3)_4$ 10 mol%, THF, rt, 0.03 M. [d] Pd_2dba_3 5 mol%, dppf 10 mol%, toluene, 110 °C, 0.03 M. [e] Isolated yield.

Table 4 DcA of ester enolate equivalents



Entry	Product	Time (min)	Yield[a,c] (%)	Entry	Product	Time (min)	Yield[a,c] (%)
1	 **3a**	15	95[b]	5	 **3e**	60	93
2	 **3b**	120	97	6	 **3f**	15	99[b]
3	 **3c**	300	92	7	 **3g**	60	99[b]
4	 **3d**	180	95	8	 **3h**	360	82[b]

[a] Pd_2dba_3 5 mol%, dppf 10 mol%, toluene, 110 °C, 0.03 M. [b] $Pd(PPh_3)_4$ 10 mol%, C_6H_6, rt, 0.03 M. [c] Isolated yield.

phenolic ester substrates, an α-phenyl aryl ester (entry 1) underwent allylation smoothly with $Pd(PPh_3)_4$ in 15 minutes under ambient conditions, while α-methyl substituted aryl esters (entries 2 and 3) required elevated temperatures and longer reaction times for reaction completion. In addition, α,α-dialkyl aryl esters gave good yields under the reported reaction conditions (entries 4 and 5). Lastly, various allyl functionalities including cinnamyl (**3c**), β-methallyl (**3e**) and hexenyl (**3g**, **h**) are well tolerated under the reaction conditions.

Conclusions

In conclusion, we have developed a rapid, high yielding method for the synthesis of α-allylated ester equivalents. A wide range of different ester enolates and ester enolate equivalents undergo catalytic allylation under conditions that are conducive to decarboxylative enolate formation. Importantly, the method allows the construction of quaternary carbon centers, although there remains significant room for improvement of the stereoselectivity.

Notes and references

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