

Palladium-Catalyzed Decarboxylative Rearrangements of Allyl 2,2,2-Trifluoroethyl Malonates: Direct Access to Homoallylic Esters

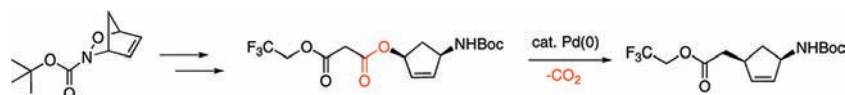
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ABSTRACT



Homoallylic esters are obtained in a single transformation from allyl 2,2,2-trifluoroethyl malonates by using a Pd(0) catalyst. Facile decarboxylation of allyl 2,2,2-trifluoroethyl malonates is attributed to a decrease in pK_a compared to allyl methyl malonates. Subsequent reduction of the homoallylic 2,2,2-trifluoroethyl ester provides a (hydroxyethyl)cyclopentenyl derivative that represents a key intermediate in the synthesis of carbocyclic nucleosides. A select allyl 2,2,2-trifluoroethyl malonate undergoes a decarboxylative Claisen rearrangement to provide a regioisomeric homoallylic ester.

Homoallylic esters are embedded in the core structures of several classes of natural products including macrolide polyketides,¹ α -linolenic acid metabolites and derivatives,² and cyclopentenone prostaglandins.³ Although homoallylic esters may be synthesized in several steps by functional group manipulation,^{2a} direct access to homoallylic esters has been achieved by Krapcho decarboxylation of malonates,⁴ addition of vinyl radicals to α,β -unsaturated esters,⁵ and 1,4-addition of alkenylcopper reagents.⁶

We considered metal-catalyzed decarboxylative allylations as an alternative method to directly prepare homoallylic esters

under mild conditions.⁷ Although α -cyano, α -nitro, α -keto,⁸ and α -sulfonyl⁹ allyl esters readily undergo Pd(0)-catalyzed decarboxylative rearrangements to afford the corresponding homoallylic derivatives, allyl methyl malonates are much less reactive. Their diminished reactivity is attributed to the less stable methoxyethenolate that forms upon decarboxylation. α,α -Dialkyl allyl methyl malonates require harsh conditions (i.e., 120 °C in DMF) to effect Pd(0)-decarboxylative rearrangements.⁸ Diallyl malonates undergo decarboxylative allylation at room temperature but must possess an aryl group at the α -position.¹⁰ To our knowledge, Pd(0)-decarboxylative rearrangements of α,α -unsubstituted allyl alkyl malonates have not been reported. To achieve decarboxylation, we envisioned replacement of the allyl methyl malonate with an allyl 2,2,2-trifluoroethyl malonate. The strong electron-withdrawing ability of the trifluoroethyl group would improve

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the stability of the transient alkoxyethenolate and promote decarboxylation. Herein, we disclose that α,α -unsubstituted allyl 2,2,2-trifluoroethyl malonates are suitable substrates for Pd(0)-catalyzed decarboxylative allylations and provide desired homoallylic 2,2,2-trifluoroethyl esters in high yields.

Our group has previously reported Pd(0)-catalyzed allylic alkylations with cycloadduct **3**¹¹ and related substrates as key steps en route to targeted carbocyclic nucleosides.¹² To access carbonucleoside targets 5'-homocarbovir **1b**¹³ and 5'-homoaristeromycin **2b**,¹⁴ we required a reliable method to install the requisite 4'-hydroxyethyl side chain. We envisioned a Pd(0) decarboxylative rearrangement to afford an α -allyl ester and subsequent reduction to the (hydroxyethyl)-cyclopentyl core structure. Further elaboration would furnish **1b** and **2b** (Figure 1).

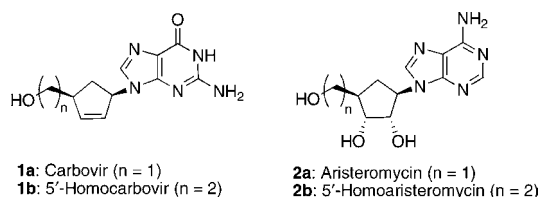
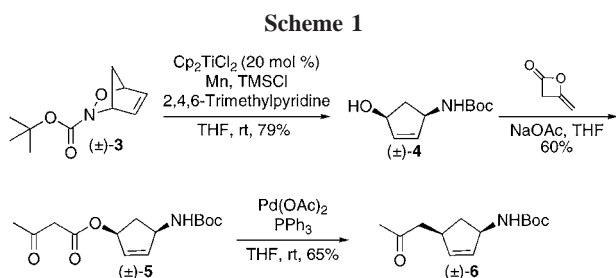


Figure 1. Carbonucleoside target molecules.

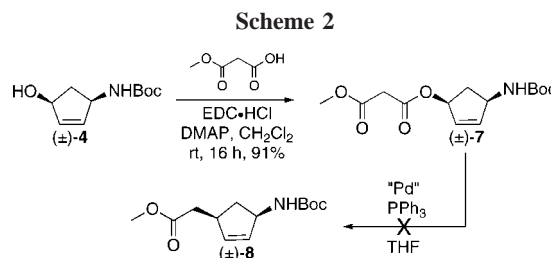
As a model system to explore palladium-catalyzed decarboxylative allylation of 1,4-*syn* disubstituted cyclopentenones, allyl β -keto ester **5** was synthesized in two steps from cycloadduct **3** (Scheme 1).^{15,16} Allyl β -keto esters are reliable substrates



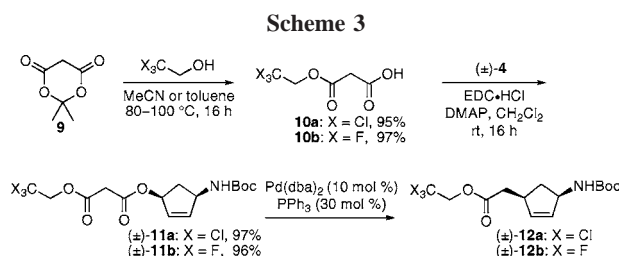
that undergo Pd(0)-catalyzed decarboxylative rearrangements under mild conditions.^{8,17} The mechanism proceeds through oxidative addition to give a metal β -keto carboxylate/ π -allyl system. Upon decarboxylation, nucleophilic attack by the

resulting enolate affords ketone products. When allyl β -keto ester **5** was treated with Pd(0), ketone **6** was isolated in 65% yield as the exclusive product with complete diastereo- and regiocontrol. This initial result demonstrated that appropriately functionalized cyclopentenones derived from **4** are suitable substrates for decarboxylative allylations.

Replacement of the allyl β -keto ester group with an allyl methyl malonate system would provide access to a versatile homoallylic ester side chain. The ester could be converted to an alcohol or aldehyde and give access to key intermediates in the synthesis of carbonucleosides. Cyclopentenol **4** was coupled to methyl malonate to give allyl methyl malonate **7** in 91% yield. Exposure of **7** to various palladium sources (Pd(OAc)₂, Pd(dba)₂, Pd₂(dba)₃·CHCl₃) and temperatures resulted in no reaction and recovery of starting material (Scheme 2).¹⁸



In an attempt to increase stabilization of the anionic intermediate that is formed upon decarboxylation, acids **10a** and **10b** were coupled with cyclopentenol **4** to form allyl 2,2,2-trichloroethyl malonate **11a** and allyl 2,2,2-trifluoroethyl malonate **11b** in high yields, respectively (Scheme 3).



entry	substrate	solvent	temp	time	isolated yield
1	11a	THF	75 °C	8 h	0% ^a
2	11b	THF	50 °C	8 h	37%
3	11b	DMF	100 °C	5 h	53%

^a Starting material was recovered.

Although trichloroethyl derivative **11a** did not undergo decarboxylative rearrangement in the presence of Pd(dba)₂ and PPh₃, trifluoroethyl substrate **11b** provided homoallylic

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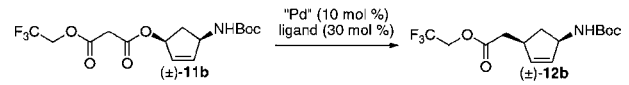
(16) Diketene reaction conditions adapted from a procedure found in: Collado, I.; Mazón, A.; Espinosa, J. F.; Blanco-Urgoiti, J.; Schoepp, D. D.; Wright, R. A.; Johnson, B. G.; Kingston, A. E. *J. Med. Chem.* **2002**, *45*, 3619.

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ester **12b** under similar reaction conditions with complete diastereo- and regiocontrol. The electron-withdrawing effect of the trifluoroethyl group plays a significant role in accelerating the decarboxylative rearrangement.

Next, we turned our attention to optimizing the reaction conditions for formation of α -allyl ester **12b** (Table 1).

Table 1. Selected Reaction Conditions for Optimization Studies



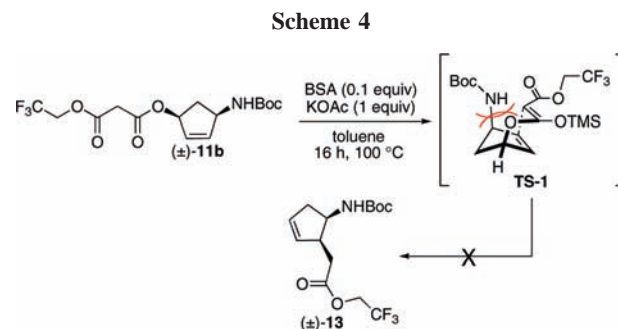
entry	Pd/ligand	solv.	temp	time	isolated yield
1	Pd(OAc) ₂ /PPh ₃	DMF	100 °C	5 h	40%
2	Pd ₂ (dba) ₃ /CHCl ₃ /PPh ₃	DMF	100 °C	5 h	40%
3	Pd(dba) ₃ /P(OPh) ₃	DMF	100 °C	8 h	0% ^a
4	Pd(dba) ₃ / <i>rac</i> -BINAP	DMF	100 °C	4 h	51%
5	Pd(dba) ₃ /PS-PPh ₃	DMF	100 °C	4 h	56%
6	Pd(dba) ₃ /dppe	DMF	100 °C	4 h	60%
7	Pd(dba) ₃ /dppe ^b	THF	75 °C	6 h ^c	82%
8	no palladium/no ligand	DMF	145 °C	16 h	0% ^a

^a Starting material was recovered. ^b Reaction conducted with 5 mol % Pd(dba)₃ and 15 mol % dppe resulted in 50% conversion to product (by ¹H NMR integration) after 6 h. ^c Longer reactions time (16 h) resulted in lower yield (53%).

Accordingly, a series of palladium sources and ligands were investigated with DMF as solvent. The combination of Pd(dba)₃ and 1,2-bis(diphenylphosphino)ethane (dppe) emerged as the optimal source of Pd(0). However, heating the reaction mixture at 100 °C in DMF was undesirable, and removal of DMF complicated the purification and isolation process. Several solvents were explored at lower temperatures. Ultimately, THF proved to be optimal (Table 1, entry 7), and a yield of 82% was obtained.^{19,20} A control reaction (Table 1, entry 8) in the absence of Pd(0) and ligand was also performed to confirm that the process was not thermally driven. Decomposition of malonate **11b** was not observed after stirring at 145 °C in DMF for 16 h. The retention of the 1,4-*syn* stereochemistry of **12b** was expected due to the double inversion via the palladium π -allyl system. The 1,4-*syn* stereochemistry of ester **12b** was confirmed by ¹H NMR. A characteristic coupling pattern ($J = 6.5, 6.5, 13.5$ Hz and $J = 7.8, 7.8, 13.5$ Hz) was observed for the diastereotopic methylene protons in the cyclopentene core.²¹

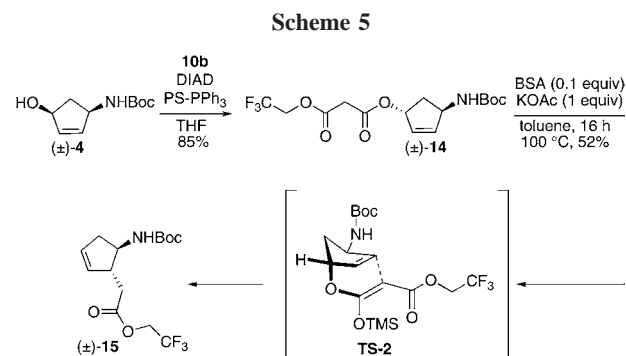
With a reliable method to 1,4-*syn* cyclopentene derivative **12b** established, we turned our attention to the synthesis of

1,2-*syn* cyclopentene derivative **13** by employing a decarboxylative Claisen rearrangement. The base-catalyzed [3,3]-sigmatropic rearrangement–decarboxylation of tosylmalonic mono(allylic) esters has recently been reported.²² While substrate **11b** does not have the additional electron-withdrawing Ts group at the α -position, it was envisioned that the increased electron-withdrawing effects of the trifluoroester would allow for the rearrangement to occur. Malonate **11b** was subjected to *N,O*-bis(trimethylsilyl)acetamide (BSA) and KOAc in anhydrous toluene at 100 °C (Scheme 4).²³ Unfortunately, partial decomposition occurred,



and product **13** was not detected. This result was not unexpected considering the steric bulk imparted by the Boc-protected amine in the pseudoboat transition state **TS-1**.

To avoid a sterically hindered transition state, we synthesized 1,4-*trans* diastereomer **14** as a substrate for the decarboxylative Claisen rearrangement. Alcohol **4** was subjected to Mitsunobu conditions in the presence of acid **10b** to afford 1,4-*trans* malonate **14** (Scheme 5). Malonate **14**



was exposed to the decarboxylative Claisen rearrangement conditions, and ester **15** was obtained in 52% yield. The unfavorable boat-like six-membered transition state **TS-2** could have contributed to the relatively low yield. Malonate

(18) For a detailed table of reaction conditions, see Supporting Information.

(19) The reaction is performed under anhydrous conditions in a sealed tube. High yields (76%) were observed on a 1.5 mmol scale. Decreased yields (61%) were observed on a 6 mmol scale.

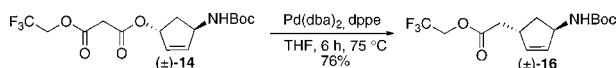
(20) Crude reaction mixture was analyzed by ¹H NMR and showed complete consumption of the allyl 2,2,2-trifluoroethyl malonate and the formation of a single product with complete diastereo- and regiocontrol.

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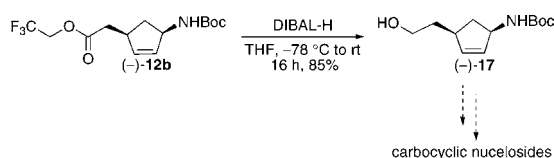
Scheme 6



14 also underwent efficient Pd(0)-catalyzed decarboxylative rearrangement to 1,4-*trans* cyclopentene **16** (Scheme 6).²⁰ The stereochemistry of **15** and **16** was confirmed by analyses of the COSY and/or ROESY NMR spectra.

Finally, allyl 2,2,2-trifluoroethyl malonate (–)-**11b** was synthesized from the readily available aminocyclopentenol (–)-**4**²⁴ and converted to ester (–)-**12b**. Treatment with diisobutylaluminum hydride provided alcohol (–)-**17** in 85% yield (Scheme 7). Alcohol (–)-**17** represents a key interme-

Scheme 7



diolate toward the synthesis of (–)-5′-homocarbovir **1b** and (–)-5′-homoaristeromycin **2b**.

In summary, allyl 2,2,2-trifluoroethyl malonates undergo efficient Pd-catalyzed decarboxylative allylation. Installation of the trifluoroethyl group resulted in improved stabilization of the reactive carbanion intermediate. Simple esters and trichloroethyl ester groups were not effective. We have also identified substrate **14** as a new system for the decarboxylative Claisen rearrangement. Alcohol (–)-**17** is currently being used as a key intermediate to synthesize carbocyclic nucleosides. Those investigations will be reported in due course.

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Supporting Information Available: General methods, experimental details, and ¹H and ¹³C NMR spectra for **5–7**, **10a,b**, **11a,b**, **12b**, and **14–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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