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Construction of Trifluoromethyl-Bearing Quaternary Carbon Centers by Intramolecular Decarboxylative Allylation of α-Trifluoromethyl β-Keto Esters

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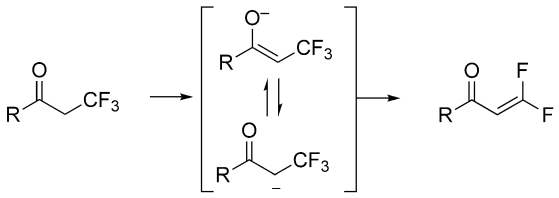
Abstract: A new palladium-catalyzed decarboxylative allylation of allyl α-trifluoromethyl-β-keto esters was developed in the presence of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and 1,2-bis(diphenylphosphino)ethane (dppe) in tetrahydrofuran. α-Trifluoromethyl ketones featuring a quaternary carbon center were produced in good yields and the dreaded α,β-unsaturated-β,β-difluoro ketones resulting from β-elimination of a fluoride ion was not observed.

Keywords: allylation; decarboxylation; intramolecular reactions; palladium; trifluoromethyl group

Introduction

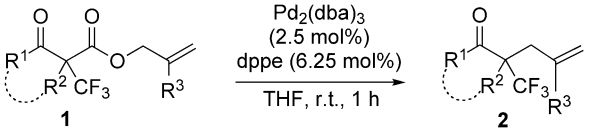
The field of organofluorine chemistry has blossomed dramatically over the past decade to become an extremely rich area of research.[1] The increasing number of approved fluorinated pharmaceutical agents entering the market is fuelled by the rapid development of efficient synthetic methods that include direct fluorination and manipulation of fluorinated building blocks. In this context, the trifluoromethyl motif has stimulated high interest due to its specific physical and biological properties, responsible of its increasing occurrence in a wide range of biologically active compounds but also in materials for optoelectronic devices.[2] Among several effective methods that have been investigated for the synthesis of trifluoromethylated organic molecules,[3] we were interested in the approach based on the α-trifluoromethylated carbanion synthons, which is one of the main challenges.[4] The chemistry of α-trifluoromethylated carbanions and related species has remained unexplored, despite their great mechanistic and synthetic significance in organic chemistry.[4] It is well recognized that carbanions in the α-position of a trifluoromethyl group are thermodynamically stabilized by inductive effects and negative hyperconjugation but strongly destabilized due to a defluorination reaction, in particular under basic conditions. In addition, the carbanion possesses a low nucleophilicity due to the electron-withdrawing effect of the trifluoromethyl group. The defluorination could be encountered in the manipulation of α-trifluoromethyl carbonyl compounds. This is particularly true for lithium enolates that produce α,β-unsaturated-β,β-difluoro ketones[5] as represented in Scheme 1.

The undesired β-elimination reaction could be suppressed through the use of aluminum,[5] boron,[6] or titanium enolates[7] as examined in the aldol reaction of α-trifluoromethyl enolates with various aldehydes. In



Scheme 1. The defluorination could be encountered in the manipulation of α-trifluoromethylated carbanion synthons.

these cases, however, results were only partially satisfactory from the synthetic point of view. On the other hand, in 1999 Kitazume and co-workers succeeded in the generation of stable α-trifluoromethyl carbanions by palladium-catalyzed intermolecular allylation reactions of 3,3,3-trifluoropropionates with allyl carbonates.[8] Despite its potential usefulness in synthetic chemistry, Kitazume's methodology has been given scant attention and only a few reports of related palladium-catalyzed intermolecular allylation reactions have appeared, essentially due to the limitations in substrate preparation.[9,10] We recently developed efficient methods to prepare a broad range of α-trifluoromethyl-β-keto esters containing diverse functionality by direct trifluoromethylation of β-keto esters using either CF_3I,[11] or electrophilic trifluoromethylation reagents[12] in high yields. Taking advantage from a practical preparation of the α-trifluoromethyl-β-keto esters,[11–13] we thought the intramolecular version of Kitazume's approach could provide a unique means for constructing trifluoromethylated products. We herein report our approach toward α-carbonyl trifluoromethyl-bearing quaternary carbon centers based on a palladium-catalyzed intramolecular decarboxylative allylation of allyl α-trifluoromethyl-β-keto carboxylates (Scheme 2). To the best of our knowledge, this is the first example of an intramolecular variant of Kitazume's procedure. A series of previously unknown, cyclic, quaternary α-trifluoromethyl carbonyl compounds having indanone and tetralone frameworks was successfully obtained. These compounds are attractive building blocks for medicinal chemistry and also interesting from a synthetic point of view, because these cyclic compounds are difficult to obtain by intermolecular allylation reactions.[8–10]

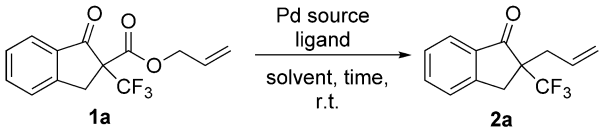


Scheme 2. Palladium-catalyzed intramolecular decarboxylative allylation of allyl α-trifluoromethyl-β-keto carboxylates.

Results and Discussion

Initial studies were performed with the allyl α-trifluoromethyl-β-keto ester derived from indanone as substrate along with tris(dibenzylideneacetone) dipalladium [$Pd(dba)_2$] as a source of soluble Pd(0) and 1,2-bis(diphenylphosphino)ethane (dppe) as a commonly used bidentate ligand in THF at room temperature.[14] Under these conditions, the reaction occurred within 2 h leading to the α-trifluoromethyl-α-allylindanone in 65% yield (Table 1, run 1). Palladium(II) sources could also be used albeit with negative effects on the yield or the reaction time (Table 1, runs 2 and 3). A change in the ligand-to-palladium ratio resulted in an improved yield (80%; Table 1, run 4). Different ligands were examined that include mono- and bidentate phosphines; however, the yield was not improved (Table 1, runs 4–7). A solvent screening revealed that THF is the most appropriate for the reaction. A longer reaction time is required in a chlorinated solvent (CH_2Cl_2), as it is the case in toluene, and the yield was dramatically decreased whereas oxygenated solvents (Et_2O, 1,4-dioxane) gave reasonable yields within a short reaction time (Table 1, runs 8–11). Importantly, β-elimination of a fluoride ion that would have produced α,β-unsaturated-β,β-difluoro ketones was not observed in these crude reaction mix-

Table 1. Optimization of reaction conditions for the decarboxylative allylation.



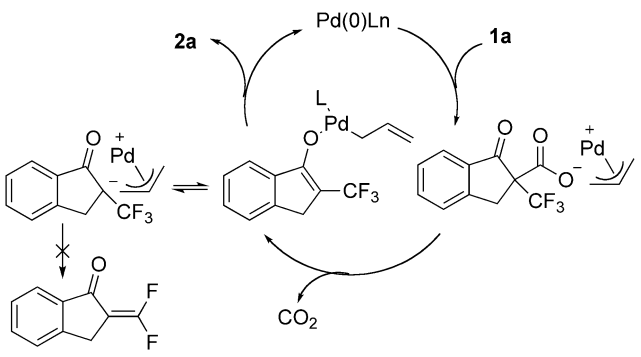
Run	Pd (mol%)	Ligand (mol%)	Solvent	Time [h]	Yield[a] [%]
1	$Pd(dba)_2$ (5.0)	dppe (6.25)	THF	2	65
2	$[PdCl(C_3H_5)]_2$ (2.5)	dppe (6.25)	THF	12	28
3	$Pd(OAc)_2$ (5.0)	dppe (6.25)	THF	3	65
4	$Pd_2(dba)_3$ (2.5)	dppe (6.25)	THF	1	80
5	$Pd_2(dba)_3$ (2.5)	PPh_3 (12.5)	THF	2	69
6	$Pd_2(dba)_3$ (2.5)	dppp (6.25)	THF	5	38
7	$Pd_2(dba)_3$ (2.5)	PCy_3 (12.5)	THF	1	0
8	$Pd_2(dba)_3$ (2.5)	dppe (6.25)	CH_2Cl_2	12	14
9	$Pd_2(dba)_3$ (2.5)	dppe (6.25)	toluene	12	71
10	$Pd_2(dba)_3$ (2.5)	dppe (6.25)	Et_2O	1	69
11	$Pd_2(dba)_3$ (2.5)	dppe (6.25)	1,4-dioxane	1	75

[a] Isolated yield.

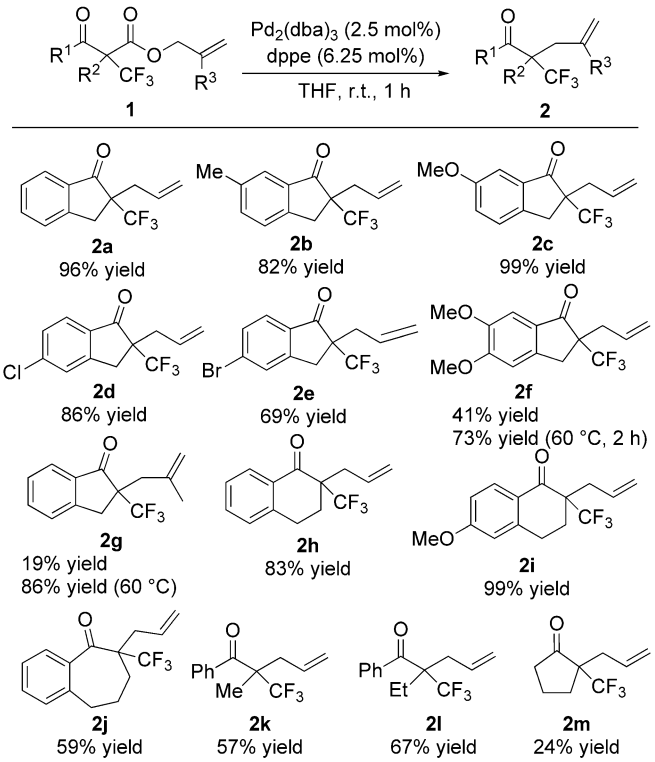
tures. This clearly demonstrates that the allylation proceeds faster than the β-elimination reaction.

The mechanism of the decarboxylative allylation reaction is thought to proceed *via* an oxidative addition of the substrate to Pd(0)-phosphine complex to produce a carboxylate and a cationic π-allyl palladium complex.[14] Decarboxylation of the β-keto carboxylate generates a palladium enolate, which undergoes a reductive elimination leading to the product formation and concomitant regeneration of the Pd(0) catalyst. An intimate relationship between π-allylpalladium complex and α-trifluoromethyl carbanion prevents the β-elimination reaction to unsaturated-β,β-difluoro ketones (Scheme 3).

With adequate conditions in hand, the scope of the decarboxylative allylation was further examined and the results are presented in Scheme 4. A range of allyl α-trifluoromethyl-β-keto esters as substrates for the decarboxylative allylation reaction was easily synthesized by the direct trifluoromethylation of allyl β-keto esters with either our electrophilic trifluoromethylating reagents[12] or radical trifluoromethylation of methyl β-keto esters by means of trifluoromethyl iodide[11] followed by a Ti(O-*i*-Pr)$_4$-mediated transesterification.[15] Indanone derivatives with electron-donor groups or halogen substitution at the aromatic ring gave the desired products in yields ranging from 69 to 99%. In the case of the 5,6-dimethoxyindanone derivative, a moderate yield could be obtained after a longer reaction time. A substrate with a methallyl ester was prepared to evaluate a different transferable group. It appeared that methallyl transfer proceeds equally well as far as the reaction mixture is heated at 60 °C for 1 h instead of room temperature. Good to excellent yields were obtained with larger rings in tetralone and benzosuberone derivatives (59–99%). Acyclic substrates **1k** and **1l** were also evaluated. Both reactions proceeded quite well to provide **2k** and **2l** in 57% and 67%, respectively. The reaction of simple cyclopentanone-derived substrates **1m** was also performed in comparison with indanones under the same reaction conditions. The reaction proceeded smoothly to provide the corresponding allylic trifluoromethyl ketone **2m**, although the yields are low due to the high volatility of the product (Scheme 4).



Scheme 3. Catalytic cycle of palladium-catalyzed intramolecular decarboxylative allylation of allyl α-trifluoromethylindanonecarboxylate.

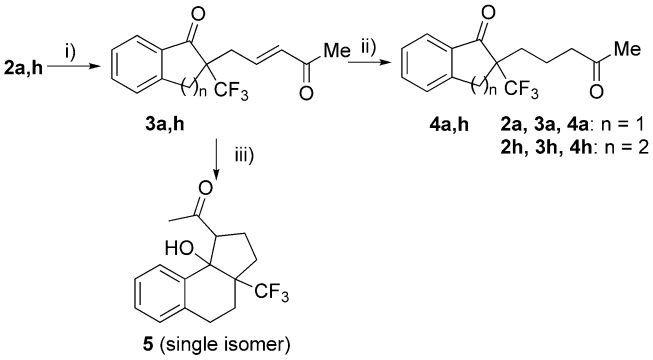


Scheme 4. Variation of substrates for palladium-catalyzed decarboxylative allylation.

The allyl group can be transformed later into a broad range of carbon appendages. One of the examples is shown in Scheme 5. Treatment of **2a**, **h** with methyl vinyl ketone in the presence of Grubbs' 2nd generation catalyst[16b] in CH_2Cl_2 under heating conditions gave the enones **3a**, **h**. Reduction of the enones **3a**, **h** with 10% Pd/C under an atmosphere of hydrogen gas for 12 h afforded 1,6-diketones **4a**, **h** in good yields. The tetralone derived **3h** was also converted into medicinally attractive carbocycle **5** using $[Ph_3PCuH]_6$ in toluene at −40 °C (Scheme 5).[16d]

Towards Asymmetric Reactions

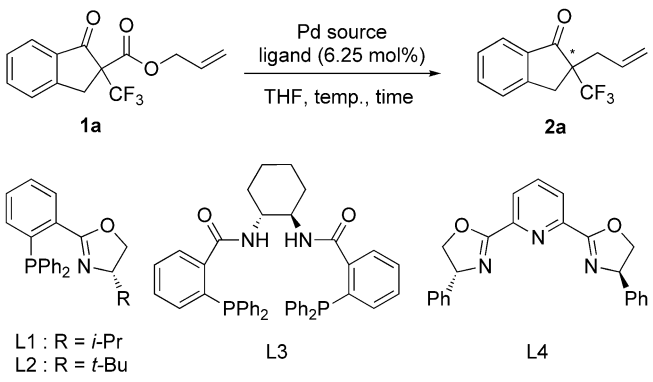
The successes of Stoltz[16] and Trost[17] on asymmetric Tsuji decarboxylative allylations[18] prompted us to attempt the asymmetric version of the intramolecular decarboxylative allylation of α-trifluoromethyl β-keto esters by the use of chiral bisphosphine ligands like the Trost ligand, P,N ligands or the like. A racemic allyl 2-trifluoromethyl-1-indanonecarboxylate (**1a**) was tested to be converted into the corresponding optically active 2-allyl-2-trifluoromethyl-1-indanone (**2a**)



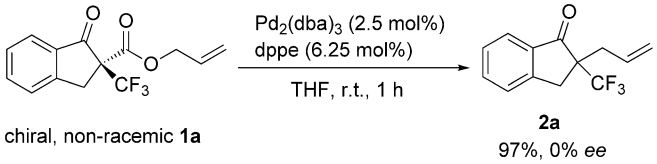
Scheme 5. *Reaction conditions:* i) methyl vinyl ketone (2.5 equiv.), Grubbs' 2nd catalyst (5.0 mol%), CH_2Cl_2, 40 °C, 18 h (**3a**: 40%; **3h**: 47%); ii) 10% Pd-C/H_2 (1 atm), EtOAc, room temperature, 12 h (**4a**: 40% from **2a**; **4h**: 34% from **2h**); iii) $[Ph_3PCuH]_6$ (0.5 equiv.), toluene, −40 °C, 4 h (**5**: 12%).

by palladium-catalyzed extrusion of carbon dioxide (Scheme 6). First, the treatment of **1a** with $[Pd(dba)_2]$ (5 mol%) as a catalyst precursor and a chiral ligand, *i*-Pr-Phox (6.25 mol%) in THF at room temperature gave the desired **2a** in 95% yield; however, no asymmetric induction was detected. We further examined the transformation of **1a** to **2a** using a variety of chiral ligands (6.25 mol%) and $[Pd(dba)_2]$ (5 mol%) or $Pd_2(dba)_3$ (2.5 mol%) at different temperatures, but the produced allyl trifluoromethyl indanone **2a** was racemic (See Table S1 in the Supporting Information for details).[21]

We next attempted the stereospecific, palladium-catalyzed decarboxylative allylation of chiral, non-racemic **1a** under achiral catalyst conditions. Recently, Tunge and co-workers reported that chiral allyl sulfonylacetic esters undergo highly stereospecific, palladium-catalyzed decarboxylative allylation to furnish tertiary homoallylic sulfones in high yields without major loss of the enantiopurity of the starting allyl



Scheme 6. Decarboxylative allylation of **1a** in the presence of chiral ligands.



Scheme 7. Decarboxylative allylation of chiral, non-racemic **1a** in the presence of achiral catalyst.

sulfonylacetic esters.[19] In our case, however, it was disappointing to find that the decarboxylative allylation of enantioenriched **1a** (prepared by enantioselective trifluoromethylation of 2-allyl 1-indanone 2-carboxylate[20,21]) proceeded in a non-stereospecific manner to provide **2a** in 97% yield as a racemate (Scheme 7).

Conclusions

In summary, we have demonstrated that palladium enolates generated by a catalyzed decarboxylation of allyl α-trifluoromethyl-β-keto esters are suitable intermediates for subsequent intramolecular allylation without β-elimination of fluoride ion. This work offers a new entry to cyclic α-trifluoromethyl-α-quaternary ketones that are not easily accessible *via* enolate alkylation and provides valuable information for further breakthroughs in the chemistry of α-trifluoromethyl carbanions. The stereocontrol of the newly formed quaternary stereogenic carbon center is the challenging object of current development and will be reported in due course.

Experimental Section[21]

General Conditions

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen or argon. Solvents were transferred *via* syringe and were introduced into the reaction vessels though a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or $KMnO_4$ in water/heat. Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 63–210 μm.

Typical Procedures for Intramolecular Decarboxylative Allylation of α-Trifluoromethyl-β-keto Esters

2-Allyl-2-trifluoromethyl-1-indanone (2a): To a solution of $Pd_2(dba)_3$ (2.4 mg, 0.00264 mmol, 2.5 mol%) and dppe (2.6 mg, 0.00663 mmol, 6.25 mol%) in THF (2.1 mL, 0.05 M) were added at room temperature under argon, and the mixture was stirred for 30 min. β-keto ester **1a** (30.0 mg,

0.106 mmol, 1.0 equiv.) was added dropwise through a syringe to the room temperature. The resulting solution was stirred at room temperature for 1 h (full conversion checked by TLC), and the solvent was then evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate = 9/1 to give **2a** as a colorless oil; yield: 24.5 mg (0.102 mmol, 96%).

2-Allyl-6-methoxy-2-trifluoromethyl-1-indanone (2c): A solution of $Pd_2(dba)_3$ (1.5 mg, 0.00167 mmol, 2.5 mol%) and dppe (1.7 mg, 0.00418 mmol, 6.25 mol%) in THF (1.3 mL, 0.05 M) was prepared at room temperature under argon, and the mixture was stirred for 30 min. β-Keto ester **1c** (21.0 mg, 0.0668 mmol, 1.0 equiv.) was added dropwise through a syringe at room temperature. The resulting solution was stirred at room temperature for 1 h (full conversion checked by TLC), and the solvent was then evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate = 9/1 to give **2c** as a colorless oil; yield: 17.9 mg (0.0663 mmol, 99%).

2-(2-Methylallyl)-2-trifluoromethyl-1-indanone (2g): A solution of $Pd_2(dba)_3$ (2.3 mg, 0.00250 mmol, 2.5 mol%) and dppe (2.5 mg, 0.00625 mmol, 6.25 mol%) in THF (2.0 mL, 0.05 M) was prepared at room temperature under argon, and the mixture was stirred for 30 min. β-Keto ester **1g** (29.8 mg, 0.100 mmol, 1.0 equiv.) was added dropwise through a syringe at room temperature. The resulting solution was stirred at 60 °C for 1 h (full conversion checked by TLC), and the solvent was then evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate = 9/1 to give **2g** as a colorless oil; yield: 21.9 mg (0.0861 mmol, 86%).

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[21] See Supporting Information for details.

