Catalytic Asymmetric Synthesis of Cyclic α-Allylated α-Fluoroketones

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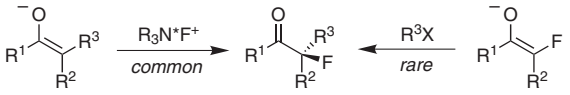
Received 12 June 2006

Abstract: This manuscript details the development of an asymmetric, palladium-catalyzed, decarboxylative coupling of fluoro-enolates with allyl electrophiles.

Key words: fluorine, enolate, decarboxylation, palladium

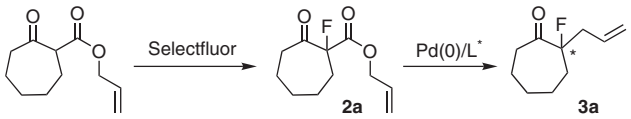
The synthesis of organofluorine compounds is an area of widespread interest due to the utility of fluoro-organic compounds in pharmaceuticals, material science, and agricultural chemistry.[1] The development of relatively non-hazardous, commercially available, and easily handled electrophilic fluorinating reagents such as Selectfluor has made a significant impact in the preparation of fluoro-organic compounds.[2,3] Recently, particular attention has been directed toward development of catalysts for the asymmetric electrophilic fluorination of enolates to produce enantioenriched α-fluoro carbonyl compounds (Scheme 1). While chiral, non-racemic zinc,[4a] nickel,[4b] copper,[4c] and palladium[4d] catalysts have been successfully developed for the enantioselective fluorination of easily enolizable β-keto esters, catalytic methods for the enantioselective synthesis of simple α-fluoro ketones are not well developed. Procedures employing Selectfluor with catalytic amounts of various proline derivatives have only recently been disclosed for the enantioselective fluorination of aldehydes[5a] and ketones,[5b] however, the enantioselectivities obtained are moderate.[6] Until recently, published methods for the asymmetric fluorination of ketone enolates relied on the stoichiometric addition of enantioenriched *N*-fluorosultams or cinchona alkaloids to enolates,[7,8] or diastereoselective fluorination of enantioenriched ketones.[9]



Scheme 1

Asymmetric alkylation of fluorinated enolates is an alternative approach toward the synthesis of enantioenriched α-fluoro ketones that remains relatively unexplored (Scheme 1).[10] Perhaps this is because the generation of fluorinated ketone enolates is unexpectedly difficult. For instance, aldol reactions of fluoro ketones using typical kinetic bases often fail, and the generation of boron enolates results in enolization at the non-fluorinated carbon.[11] A noteworthy exception was reported by Shimizu in which palladium-catalyzed decarboxylation is used to access fluorinated ketone enolates under mild conditions.[12]

During the course of our studies[13] on the asymmetric palladium-catalyzed decarboxylative allylation of allyl β-keto carboxylates,[14,15] we became interested in developing a catalytic system capable of inducing high levels of enantioenrichment at the stereogenic α-carbon formed in the γ,δ-unsaturated ketone product. More specifically, we envisioned a route which would take advantage of the ease with which β-keto esters can be fluorinated, followed by the Pd-catalyzed decarboxylative allylation reaction to yield products of high enantiopurity at the fluorinated carbon center (Scheme 2).



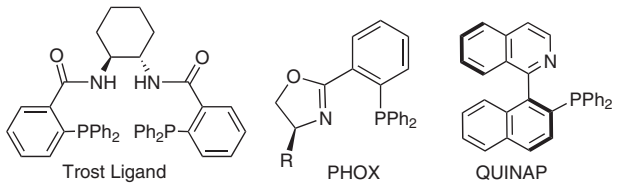
Scheme 2

Encouraged by reports on the asymmetric alkylation of allyl enol carbonates,[15b,c] an extensive survey of various chiral ligands was conducted for the transformation of fluorinated β-keto ester **2a** to ketone **3a** (Table 1). It was found that chiral P,N ligands provided the highest levels of reactivity as well as selectivity. In contrast, the use of bidentate nitrogenous ligands led to a catalytically inactive species. More surprisingly, the Trost ligand-modified palladium complex, which is known to be effective for the rearrangement of allyl-β-keto esters and enol carbonates,[13a,15c] failed to catalyze the reaction. In the course of these studies Nakamura reported the use of PHOX ligands for the asymmetric allylation of fluoro-enolates,[15a] thus QUINAP was selected for further studies.

With the optimized reaction conditions in hand, the scope of the reaction was briefly examined. Various fluorinated, cyclic enolates were allylated with good enantioselectivity and good to excellent yields (Table 2). In all cases the enolate was regiospecifically generated and byproducts resulting from equilibration of enolate regioisomers were not observed. For several saturated monocyclic β-keto esters that were not previously investigated, we have compared the enantioselectivities of the reaction utilizing the *tert*-butyl PHOX ligand (Table 2 in parentheses) with

SYNLETT 2006, No. 17, pp 2824–2826
Advanced online publication: 09.10.2006
DOI: 10.1055/s-2006-950265; Art ID: S12806ST

Table 1 Ligand Screen for Conversion of **2a** to **3a**[a]

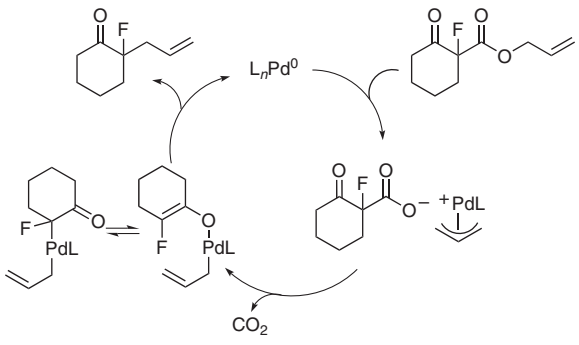


Ligand	% ee	Ligand	% ee
(*S*)-QUINAP	85.5 (*S*)	(*R*)-*i*-PrPHOX	76 (*S*)
(*S*)-*t*-BuPHOX P	88 (*R*)	(1*S*,2*S*)-Trost ligand	NR
(*R*,*M*)-PINAP	38 (*S*)	(*R*,*R*)-MeDuPhos	13 (*S*)
(*S*)-PhanPhos	8 (*R*)	(*R*,*S*)-JosiPhos	2 (*S*)
(*R*)-MOP	30 (*S*)	(*R*)-MonoPhos	7 (*S*)

[a] Reactions were ran with $Pd_2(dba)_3$ (2.5 mol%) and ligand (5.5 mol%) at 40 °C in C_6D_6.

those obtained using the QUINAP ligand. While the PHOX ligand performed somewhat better for substrates **2a**–**c**, QUINAP was much more effective for substrate **2g**. Furthermonre, the (*S*)-*t*-BuPHOX ligand provided the *R* fluoro ketone while (*S*)-QUNIAP affored the *S* product. We are currently working on models that will help explain the origin of the enantioselectivity.

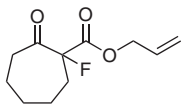
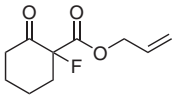
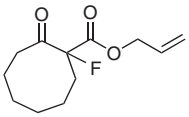
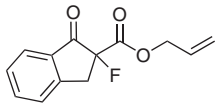
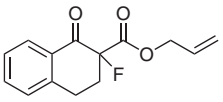
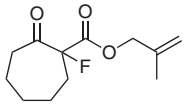
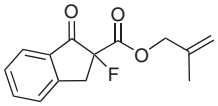
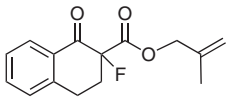
The mechanism of the decarboxylative allylation reaction has been investigated and is commonly thought to begin with the oxidative additon of substrates to Pd(0),[13–15] producing cationic π-allyl palladium intermediates (Scheme 3). Decarboxylation of the resulting β-keto carboxylates leads to the in situ generation of non-stabilized, fluorinated palladium enolates. To maintain the preferred 16-electron configuration for palladium, this requires either dissociation of one of the arms of the bidentate ligand or formation of a σ-allyl complex. Reductive elimination from the allyl(enolato)palladium complex would result in product formation and regenerate the Pd(0) catalyst.



Scheme 3

In conclusion, decarboxylative coupling of allyl β-keto esters is an atom economical approach to the synthesis of chiral non-racemic α-fluoro and α-alkyl ketones. These reactions take advantage of the ease with which β-keto esters are derivatized, which is a distinct advantage over related decarboxylative couplings of enol carbonates.[13]

Table 2 Yields and Enantioselectivities for Decarboxylative Allylation of Fluoroenolates with the QUINAP Ligand

Substrate	Time (h)	Yield (%)[a]	er[a]
 **2a**	8	92 (91)	82:18 (94:6)
 **2b**	3.5	84 (73)	84:16 (91:9)
 **2c**	8	83 (94)	88:12 (90:10)
 **2d**	5	97	86:14
 **2e**	3	83	89:11
 **2g**	12	82 (64)	94:6 (73:27)
 **2h**	5	87	88:12
 **2i**	6	58	94:6

[a] Results for *t*-Bu-PHOX ligand are shown in the parentheses.

Catalytic Decarboxylative Allylation Reactions

In a Schlenk tube under Ar, $Pd_2(dba)_3$ (2.5 mol%) and QUINAP (5.5 mol%) were dissolved in anhyd benzene (2 mL) and stirred for 1–2 min at 40 °C. The solution of catalyst was then cannula-transferred to a Schenk tube containing the allyl-β-keto ester (4 mmol) in benzene (2 mL). The reaction was stirred in a 40 °C oil bath for the reported time (Table 2). Following solvent evaporation, the crude product was purified by flash chromatography (SiO_2, 3% Et_2O–hex). Enantiomeric excesses were determined by GC utilizing a chiral stationary phase (Chiraldex B-TA).

2-Allyl-2-fluorocycloheptanone (3a)
GC: Chiraldex B-TA: Hold 50 °C for 5 min, ramp 1 °C/min to 95 °C; t_R = 43.4, 44.8 min.

IR (CD_2Cl_2): 1712, 1606, 1433 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.64 (ddt, *J* = 7, 10, 18 Hz, 1 H, C*H*=CH_2), 5.01 [d, *J* = 10 Hz, 1 H, CH=CH(H)$_{cis}$], 5.00 [d, *J* = 18 Hz, 1 H, CH=CH(H)$_{trans}$], 2.53 (m, 2 H), 2.33 (m, 2 H), 1.91 (m, 1 H), 1.73 (m, 2 H), 1.55 (m, 3 H), 1.44 (m, 1 H), 1.16 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.82 (d, *J* = 24.0 Hz, C=O), 130.85 (=CH), 119.40 (=CH_2), 101.70 (d, *J* = 185.22 Hz, CF), 41.11 (d, *J* = 22.6 Hz, allylic CH_2), 39.94 (CH_2), 35.18 (d, *J* = 23.9 Hz, CH_2), 27.80 (CH_2), 24.29 (d, *J* = 2.5 Hz, CH_2), 24.02 (d, *J* = 2.5 Hz, CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –161.66 (m).

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_{15}OF$: 171.1185; found: 171.1184.

2-Allyl-2-fluorocyclohexanone (3b)
GC: Chiraldex B-TA: Hold 50 °C for 5 min, ramp 1 °C/min to 95 °C; t_R = 37.9, 43.6 min.

IR (CD_2Cl_2): 1728, 1604, 1413 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.73 (ddt, *J* = 7, 10, 18 Hz, 1 H, CH=CH_2), 5.09 [d, *J* = 10 Hz, 1 H, CH=CH(H)$_{cis}$], 5.08 [d, *J* = 18 Hz, 1 H, CH=CH(H)$_{trans}$], 2.60 (m, 2 H), 2.43 (m, 1 H), 2.30 (m, 1 H), 2.03 (m, 1 H), 1.82 (overlapping m, 4 H), 1.62 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.28 (d, *J* = 20.2 Hz, C=O), 130.77 (=CH), 119.26 (=CH_2), 97.71 (d, *J* = 183.78 Hz, CF), 39.36 (allylic CH_2), 38.76 (d, *J* = 2.5 Hz, CH_2), 37.19 (d, *J* = 2.5 Hz, CH_2), 27.18 (CH_2), 21.42 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –156.44 (m).

HRMS: *m*/*z* [M + H] calcd for $C_9H_{13}OF$: 157.1029; found: 157.1034.

2-Allyl-2-fluorocyclooctanone (3c)
GC: Chiraldex B-TA: Hold 50 °C for 5 min, ramp 1 °C/min to 100 °C; t_R = 52.5, 53.1 min.

IR (CD_2Cl_2): 1712, 1606, 1465 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.67 (ddt, *J* = 7, 10, 17 Hz, 1 H, C*H*=CH_2), 5.05 [d, *J* = 10, 1 H, CH=CH(H)$_{cis}$], 5.03 [d, *J* = 17 Hz, 1 H, CH=CH(H)$_{trans}$], 2.63 (m, 1 H), 2.55 (ddd, *J* = 7, 14, 20 Hz, 1 H), 2.37 (ddd, *J* = 7, 14, 19 Hz, 1 H), 2.23 (m, 1 H), 2.10 (m, 1 H), 1.98 (m, 1 H), 1.87 (m, 1 H), 1.71 (m, 1 H), 1.55 (m, 5 H), 1.17 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.97 (d, *J* = 25.0 Hz, C=O), 131.10 (=CH), 119.49 (=CH_2), 101.93 (d, *J* = 188.1 Hz, CF), 42.12 (d, *J* = 22.6 Hz, allylic CH_2), 39.70 (CH_2), 37.68 (d, *J* = 22.6 Hz, CH_2), 27.41 (CH_2), 26.00 (CH_2), 24.85 (CH_2), 21.37 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –167.59 (m).

HRMS: *m*/*z* [M + H] calcd for $C_{11}H_{17}OF$: 185.1342; found: 185.1353.

Acknowledgment

We thank the Petroleum Research Fund (44453-AC) and the National Science Foundation (CHE-0548081) for financial support. ECB thanks the Madison and Lila Self foundation for support.

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