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COMMUNICATIONS

Published on Web 01/11/2007

Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ethers

Étienne Bélanger, Katy Cantin, Olivier Messe, Mélanie Tremblay, and Jean-François Paquin*

Canada Research Chair in Organic and Medicinal Chemistry, Département de chimie, Université Laval, Québec, QC, Canada G1K 7P4

Received October 19, 2006; E-mail: jean-francois.paquin@chm.ulaval.ca

The presence of a fluorine atom can often modify the activity of a bioactive molecule by changing its solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, or chemical reactivity.[1] Thus, the number of drugs or agrochemicals with at least one fluorine atom has increased dramatically over the past years.[2] However, a structural evaluation of fluorinated drugs reveals that only a small number possess a stereogenic (sp^3-hybridized) carbon atom bearing fluorine.[3] The limited number of methods allowing the asymmetric synthesis of fluorinated compounds is likely to be a reason for this lack of diversity,[4] and the development of novel methodologies is therefore highly desirable.[5] α-Fluorocarbonyl compounds, in particular tertiary α-fluorinated ketones (**2**, Figure 1), is a class of fluorinated compounds that has received much attention recently.[5] Two main strategies for the enantioselective preparation of tertiary α-fluorinated ketones (**2**) have been investigated so far (Figure 1).[4]

The best results obtained thus far using these strategies necessitate the use of *β*-ketoester derivatives as starting substrate. In the first case (**1** → **2**), Togni,[6] Sodeoka,[7] and others[4,8] have shown that **2** could be produced from **1** (R = carbonyl) by using chiral metal complexes (Ti, Pd, Cu, etc.) along with an achiral electrophilic source of fluorine. While promising results have been obtained with this strategy, the requisite use of 1,3-dicarbonyls or *β*-ketophosphonates limits its general applicability.[9] More recently, Nakamura and Stoltz independently showed that **2** could be obtained from **3** (R = allyl ester) via a catalytic, enantioselective decarboxylation of racemic α-fluoro-*β*-keto esters.[10]

In the course of our study on the development of novel synthetic approaches to organofluorine compounds, we became interested in the chemistry of fluorinated silyl enol ethers.[11] We envisioned that their use as nucleophiles in the palladium-catalyzed allylic alkylation reaction[12,13] could provide facile access to compounds such as **2**. We envisaged that this reaction would offer the promise of a general solution to the synthesis of fluorinated stereogenic centers with the significant advantages over previously documented procedures since it will not be limited to substrates containing dicarbonyl compounds. We therefore describe herein the application of this new approach to the development of the first enantioselective Pd-catalyzed allylation reaction of fluorinated silyl enol ethers.[14,15]

Initial studies were performed using the fluorinated silyl enol ether derived from α-tetralone (**4**)[16] as substrate along with allyl ethyl carbonate (1.1 equiv) as the allyl source, 35 mol % of tetrabutylammonium triphenyldifluorosilicate (TBAT) to activate the silyl enol ether in situ,[17] and $[Pd(C_3H_5)Cl]_2$ as the Pd catalyst.

Different ligands were then examined using a 4 h reaction period using THF as the solvent (Table 1). No product was isolated using either the Trost ligand or Josiphos while BINAP furnished **5**[18] in 33% yield but with a disappointing 10% ee. The use of *t*-Bu-PHOX[19] dramatically improved the enantiomeric excess resulting in the isolation of the desired product in 91% ee. A solvent

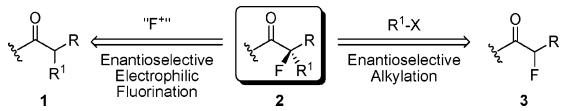
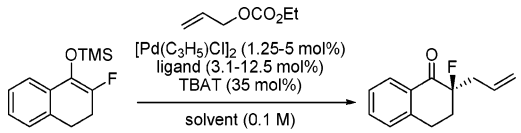


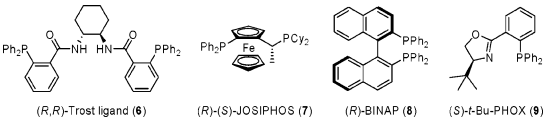
Figure 1. Enantioselective access to tertiary α-fluorinated ketones.

Table 1. Reaction Optimization for the Allylation of **4**[a]



entry[a]	Pd catalyst (mol %)	ligand	solvent	*T* (°C)	yield (%)[b]	ee (%)[c]
1	5	**6**	THF	20	traces	n.d.
2	5	**7**	THF	20	0	
3	5	**8**	THF	20	33	10
4	5	**9**	THF	20	37	91
5	5	**9**	CH_2Cl_2	20	50	26
6	5	**9**	Et_2O	20	62	93
7	5	**9**	benzene	20	76	92
8	5	**9**	toluene	20	73	93
9	2.5	**9**	toluene	20	53	93
10	1.25	**9**	toluene	20	47	93
11[d]	1.25	**9**	toluene	20	65	93
12[d]	1.25	**9**	toluene	40	85	92

[a] Reaction time = 4 h. [b] Isolated yield. [c] Determined by chiral HPLC (see Supporting Information for details); n.d. = not determined. [d] Reaction time = 17 h.

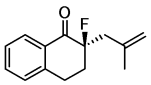
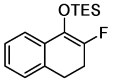
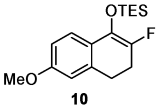
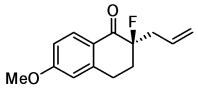
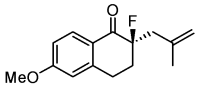
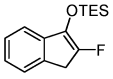
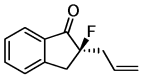
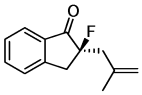
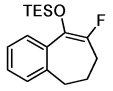
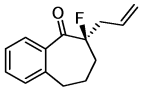
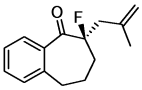
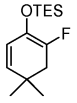
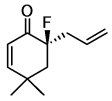
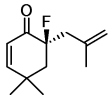


screening was then performed using the PHOX ligand. While the use of CH_2Cl_2 resulted in a marked decrease in enantiomeric excess (26% ee), the use of Et_2O resulted in an improved yield (62%) while maintaining the enantiomeric excess (93% ee). Finally, both benzene and toluene afforded the desired product in good yield and excellent ee, and toluene was chosen for further optimization.[20] The effect of catalyst loading was next examined, and reducing the amount of catalyst from 5 to 1.25 mol % for a reaction time of 4 h caused a significant drop in yield (73% to 47%), however without any influence on the enantiomeric excess (entries 8−10). Finally, a longer reaction time (17 h) and gentle heating at 40 °C allowed the desired product to be isolated in excellent yield with 92% ee (entry 12).

With the optimal conditions in hand, a variety of substrates were examined (Table 2).[18] A variety of allyl sources could be used, ethyl allyl carbonate (entries 1, 4, 5, 7, 9, and 11) could be

10.1021/ja067501q CCC: $37.00

Table 2. Reaction of Various Cyclic Fluorinated Silyl Enol Ethers[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]
1	**4**	**5**	85	92
2[d]	**4**	**5**	75	92
3	**4**		81	95
4		**5**	91	91
5[e]	 **10**		83	90
6[e]	**10**		70	91
7[e]	 **11**		93	83
8[e]	**11**		93	90
9	 **12**		65	85
10	**12**		62	89
11	 **13**		52[f]	90
12[e]	**13**		62[f]	87

[a] Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (1.25 mol %), (*S*)-*t*-Bu-PHOX (3.1 mol %), allyl ethyl carbonate or ethyl 2-methylallyl carbonate (1.1 equiv), TBAT (35 mol %), toluene (0.1 M), 40 °C, 14−18 h. [b] Isolated yields. [c] Determined by chiral HPLC (see Supporting Information for details). [d] Diallylcarbonate was used instead of allyl ethyl carbonate. [e] The reaction was performed using $[Pd(C_3H_5)Cl]_2$ (2.5 mol %) and (*S*)-*t*-Bu-PHOX (6.25 mol %). [f] The lower yields are due to product loss because of its low boiling point.

substituted by diallyl carbonate (entry 2) with similar results while the use of ethyl 2-methylallyl carbonate resulted in the desired 2-methylallylated products in good yield and excellent ee (entries 3, 6, 8, 10, and 12). Interestingly, the more stable TES silyl enol ether was equally effective in this transformation (entry 4). This reaction was examined in a range of five-, six-, and seven-membered ketones, and in all cases, good to excellent yields of the α-fluoroketones were obtained with excellent enantioselectivities. While this reaction can also be applied to acyclic fluorinated silyl enol ethers, the selectivity obtained is so far moderate.[10b,21]

In summary, we have developed the first enantioselective Pd-catalyzed allylation reaction of fluorinated silyl enol ethers. This reactions allows the efficient and stereoselective synthesis of allylated tertiary α-fluoroketones from achiral fluorinated precursors. Extension of this methodology to other classes of substrates is currently underway and will be reported in due course.

Acknowledgment. We gratefully acknowledge the Université Laval for financial support of this work. J.-F.P. thanks the Canada Research Chair Program for a Tier 2 CRC in Organic and Medicinal Chemistry. OmegaChem Inc. is thanked for a generous gift of L-*tert*-leucine.

Supporting Information Available: Experimental procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Silyl enol ether **4** was easily prepared in two steps from α-tetralone. See Supporting Information for details.
(17) While using less TBAT reduced the yield, an increased amount had no significant effect. Another fluoride source such as CsF was ineffective.
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(21) For example, the reaction of the (*Z*)-triethylsilyl enol ether of 2-fluoropropiophenone furnished the desired product with ca. 40% ee.

JA067501Q