Organofluorine Compounds

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Synthesis of Chiral α-Fluoroketones through Catalytic Enantioselective Decarboxylation**

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A number of biologically active compounds bear secondary stereogenic centers next to a carbonyl group as a key structural feature, which are often susceptible to racemization during manipulation, storage, synthesis, or under physiological conditions under which they are expected to exhibit useful functions. Optically active α-fluoroketones could serve as nonracemizable surrogates of these compounds and have received much attention in medicinal chemistry.[1,2] Interest in their synthesis therefore resulted in several recent reports on the enantioselective synthesis of α-fluorinated carbonyl compounds from the corresponding α-protio precursors,[3] but the scope of the known fluorination methods is still limited.[4] We report herein a new alternative synthetic strategy in which racemic α-fluoroketones are converted into optically active ketones through enantioselective C–C bond reorganization.

A racemic α-fluoro-β-ketoester **1** was converted into the corresponding optically active α-fluoroketone **2** by palladium-catalyzed extrusion of carbon dioxide (Table 1). On the basis of the original Tsuji reaction mechanism, we surmised that the reaction possibly proceeds first through the formation of a palladium enolate, through which the new chirality is introduced under the influence of a chiral ligand.[5] This palladium enolate, which is tetrasubstituted and bears a fluorine substituent *cis* to the carbonyl oxygen atom,[5b] is probably related to that generated by palladium-catalyzed decarboxylation of the corresponding enol allyl carbonate reported recently by the groups of Stoltz and Trost.[6]

Investigation of the reaction conditions by using [Pd_2-$(dba)_3$] as a catalyst precursor and a variety of chiral ligands

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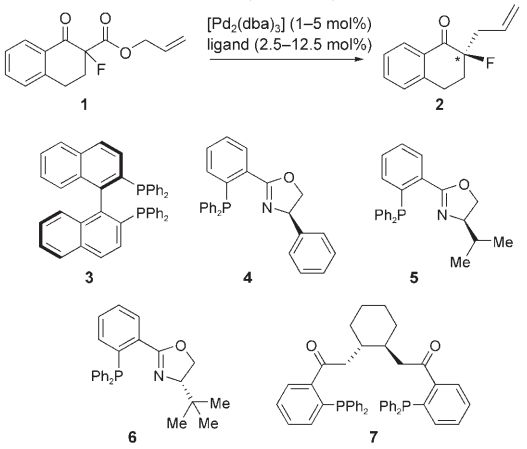
(1.25 equiv relative to Pd) gave us some insight into the nature of the catalytic process. A comparison of entry 1 of Table 1 with the remaining entries shows that the reaction is vastly accelerated by the phosphine ligands **3**–**7**. After screening of a variety of ligands[7] including binap (**3**),[8] which gave low selectivity (Table 1, entry 2), we found that chiral phosphinooxazolines **4**–**6**[9] were suitable for the reaction. The enantioselectivity is very sensitive to the substituent on the oxazoline ring: phenyl-substituted ligand **4** led to only 11% *ee*, whereas the selectivities improved greatly with the isopropyl- **5** (83% *ee*) and the *tert*-butyl-substituted **6** analogues (96% *ee*) (Table 1, entries 3–5). The catalyst loading can be decreased to 1 mol% at the expense of reaction rate, but without erosion of yield and selectivity (Table 1, entries 5–7). The choice of solvent is very important, as seen in the significant decrease in the selectivity when the reaction was carried out in dichloromethane (25% *ee*; Table 1, entry 9) instead of in THF or diethyl ether (96% *ee*; Table 1, entry 8). A decrease in the reaction temperature from 25 to 0°C did not change the performance of the reaction (Table 1, entry 10). The chiral bisphosphine ligand **7**, which gave good results in the related decarboxylative allylation reaction of allyl enol carbonates,[6b] was ineffective in the present reaction (Table 1, entry 11).

Table 1: Enantioselective decarboxylative allylation of tetralone **1**.[a]



Entry	Ligand	*t* [h]	Solvent	$[Pd_2(dba)_3]$[b] [mol%]	Yield [%][c]	*ee* [%][d]
1	none	24	THF	5	0	–
2	**3**	5	THF	5	83	11
3	**4**	3	THF	5	91	11
4	**5**	3	THF	5	94	83
5	**6**	3	THF	5	95	96
6	**6**	4	THF	2.5	95	96
7	**6**	10	THF	1	93	94[e]
8	**6**	4	Et_2O	5	93	96
9	**6**	5	CH_2Cl_2	5	89	25
10	**6**	4	THF	2.5	94	96[f]
11	**7**	10	THF	5	9	n.d.[g]

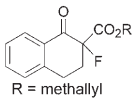
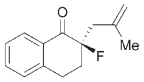
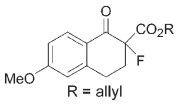
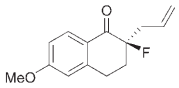
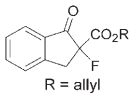
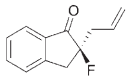
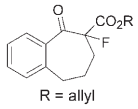
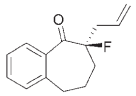
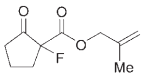
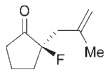
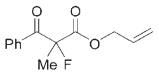
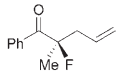
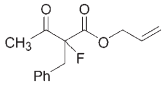
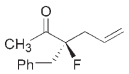
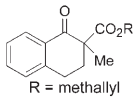
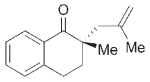
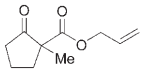
[a] All reactions were performed on a 0.5-mmol scale at a 0.05 M substrate concentration at ambient temperature (22–25°C), unless otherwise noted. [b] dba = dibenzylideneacetone. [c] Yields of isolated product. [d] The enantiomeric excess was determined by chiral HPLC analysis on a Daicel Chiralcel OJ-H column. The antipode of **2** is the major product in entries 2, 3, and 4. [e] The reaction was conducted on a 1-mmol scale. [f] The reaction was performed at 0°C. [g] The *ee* value was not determined, and the yield is based on the ratio of areas of the uncalibrated GC peaks for **1** and **2**.

The scope of the reaction was examined and representative results are shown in Table 2. The α-fluorinated ketoester starting materials were readily obtained from the corresponding α-protio compounds in quantitative yields through standard methods.[11] Results obtained with α-alkyl- and α-alkenyl-β-ketoesters instead of α-fluoro compounds are also included (Table 2, entries 10–12).

The decarboxylation reaction of a methallyl tetralone compound (Table 2, entry 3) gave almost the same level of selectivity as the allyl analogue. The selectivity improved to 99% *ee* when the catalyst loading was doubled (Table 2, entries 2 and 3), which suggests that there are ligand-independent racemic pathways operating along with the desired enantioselective catalytic process. Methoxy substitution on the aromatic ring of tetralone that may exert certain conjugation electronic effects on the reaction did not affect the selectivity (Table 2, entry 4). Modification of the saturated ring of the tetralone structure affects the enantioselectivity (Table 2, entries 5 and 6), which suggests that the steric environment has larger impact on the selectivity. The aromatic moiety of the tetralone is not required for high enantioselectivity, as can be seen in the example of the cyclopentane analogue (Table 2, entry 7). However, the selectivity was slightly lower. This example shows that the decarboxylative mechanism dictates the regioselective formation of the more-substituted α-fluoro ketone. The reaction can also be applied to acyclic ketones but the selectivity is moderate (Table 2, entries 8 and 9). This seems reasonable because an *E*/*Z* mixture of the palladium enolate may form in situ and lead to lower selectivity. This issue is related to the reaction mechanism and needs further studies.

The reaction could be a viable method for the creation of nonracemic all-carbon quaternary centers (Table 2, entries 10 and 11).[12] This reaction seems to be related to that reported recently by the Trost and Stoltz groups,[6] but is different in practice as the method creates a quaternary carbon center from synthetically more-readily accessible β-ketoesters rather than from allyl enol carbonates. A few characteristics are noteworthy: The new chirality is also generated at a palladium enolate. The putative tetrasubstituted enolate intermediate bears three alkyl groups and one oxygen atom rather than a fluorine substituent, but the enantioselectivity was still found to be high (Table 2, entry 10). However, the selectivity decreases when the ketone is part of a five-membered ring (Table 2, entry 11) and when the substrate bears an α-alkenyl group (Table 2, entry 12).[13] The intermediate in this case is a conjugated dienolate of palladium instead of a simple palladium enolate. The undesirable effect of the conjugation is apparent, in contrast to the slightly positive effect of the highly electron withdrawing fluorine atom (Table 2, entries 3 and 10). Interestingly, the reaction still results in C–C bond formation at the α-carbon atom

Table 2: Enantioselective synthesis of chiral α,α-disubstituted ketones from racemic substrates.[a]

Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	**1**	**2**	95	96
2[d]			96	99
3	R = methallyl		95	97
4	 R = allyl		92	96
5	 R = allyl		94	91
6	 R = allyl		94	93
7			82[e]	85
8			89	51
9			91	55
10	 R = methallyl		94	95
11			87[e]	84
12			89	39

[a] All reactions were performed on a 1.0-mmol scale with a 0.05 M substrate concentration in THF for 4–10 h at 22–25 °C in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) and ligand **6** (6.25 mol%), unless otherwise noted. [b] Yields of isolated product. [c] The enantiomeric excess was determined by chiral HPLC analysis, except in entries 7 and 11 for which it was determined by GC analysis (see Supporting Information). The absolute configuration of the major enantiomers was inferred from the sign of their circular dichroism spectra identical to those observed for the compounds in entries 10 and 11,[10] whose stereochemistry was determined by comparison of their optical rotation with that of the known compounds.[6] [d] The reaction was carried out with $[Pd_2(dba)_3]$ (5 mol%) and **6** (12.5 mol%). [e] The yield suffered from evaporative loss owing to the low boiling point of the product.

rather than at the distal carbon atom (which would produce a more-stable α,β-unsaturated ketone product).

In summary, we have developed a new class of enantioselective C–C bond-forming reactions that is useful for regio- and enantioselective synthesis of α-allyl-α-fluoro ketones as well as ketones that bear an α-quaternary center. The reaction is mechanistically different to the recently reported enantioselective synthesis of α-fluoro carbonyl compounds and appears to involve intriguing mechanistic details that are as yet to be explored by theory and experiments.

Experimental Section

A 50-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar was flame dried in vacuo, cooled to room temperature, and charged with $[Pd_2(dba)_3]$ (22.9 mg, 0.025 mmol, 0.025 equiv) and ligand **6** (24.2 mg, 0.0625 mmol, 0.0625 equiv) under argon. The system was evacuated slowly and flushed with argon three times. THF (20 mL) was added. The mixture was stirred for 30 min, and ketoester **1** (248 mg, 1.0 mmol, 1.0 equiv) was added dropwise through a syringe to the reaction mixture. The resulting solution was stirred for 4 h at 25 °C (full conversion checked by TLC and GC), and the solvent was then evaporated in vacuo. Purification by column chromatography on silica gel (eluent: Et_2O/hexane 5:95) gave the fluoroketone **2** (193.9 mg, 95% yield) as a colorless oil.

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