Homogeneous Catalysis

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Palladium-Catalyzed C(sp^2)–H Alkylation of Aldehyde-Derived Hydrazones with Functionalized Difluoromethyl Bromides

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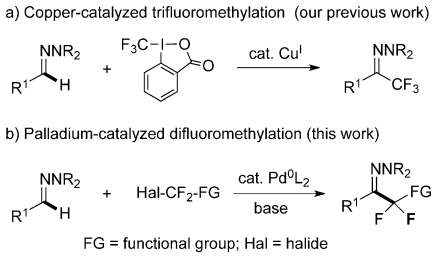
Abstract: *A palladium-catalyzed C(sp^2)–H difluoromethylation of aldehyde-derived hydrazones using bromodifluoromethylated compounds to afford the corresponding functionalized difluoromethylketone hydrazones has been established. It is proposed that a radical/SET mechanism proceeding via a difluoroalkyl radical may be involved in the catalytic cycle. Applications of the methodology to the synthesis of α,α-difluoro-β-ketoesters and α,α-difluoroketones ($RCOCF_2H$) have been illustrated.*

Aldehyde-derived hydrazones are important, readily available reagents in synthetic organic chemistry and involved in a plethora of applications.[1] They are notably attractive as umpolung carbonyl reagents because of the presence of the electron-releasing amino component which activates the azomethine (CH=N) carbon atom position towards electrophilic substitution.[2] Given the unique properties that fluorine substitution can impart on molecules,[3] we recently became interested in the development of methods for C(sp^2)–H electrophilic fluoroalkylation of aldehyde-derived hydrazones, thus anticipating that this would expand their application to potentially useful organofluorine molecules for biological investigations.[4] In 2013, we reported a very mild protocol for introducing a trifluoromethyl (CF_3) group onto the azomethine position of N,N-disubstituted aldehyde-derived hydrazones. The process relies on the use of a hypervalent iodine CF_3-transfer reagent which supposedly acts as a trifluoromethyl radical source in the presence of a copper salt by a single-electron transfer (SET) mechanism (Scheme 1 a).[5] Our current efforts are now focusing on the discovery of efficient protocols for the direct introduction of functionalized difluoromethylene (CF_2) groups. The CF_2 moiety has attracted significant attention in recent years with applications arising in various areas, including medicinal chemistry. For instance, the difluoromethylene moiety (CF_2R, CF_2H) has been recognized as a potential bioisostere of hydroxy or thiol groups, as well as a carbonyl group. The benefits include increased acidity of proximate functional groups and conformational changes.[6] Compared to trifluoromethylation, C(sp^2)–CF_2 bond-forming reactions have been much less explored and new methods are therefore highly desirable. For this purpose, it is of interest to note that while there is still a lack of readily available, broadly useful electrophilic hypervalent(III) iodine CF_2-transfer reagents,[7] various functionalized halodifluoromethylated compounds [Hal–CF_2–FG with FG = CO_2Et, $CONR_2$, $PO(OEt)_2$, SO_2Ph] have been recently shown to be convenient reagents to access difluoromethylated compounds by transition metal catalyzed (or mediated) coupling reactions, and notably those involving palladium.[8–17] Only a limited number of palladium-catalyzed difluoromethylation processes with functionalized difluoromethyl halides have been reported so far. Reports in the late 80's by the groups of Chen[10] and Burton[11] established the palladium(0)-induced addition of fluoroalkyl iodides to alkenes as a SET-initiated radical process[12] involving a difluoromethyl radical, thus leading to the corresponding iododifluoromethylated adducts. More recently in 2014, Wang and co-workers[13] described a palladium-catalyzed aryldifluoromethylation process which affords difluoromethylated oxindole derivatives from N-arylacrylamides and ICF_2SO_2Ph. A difluoromethyl radical triggered by palladium(0) supposedly initiates the reaction. In 2012, the group of Reutrakul[14] reported the Heck-type coupling of $BrCF_2SO_2Ph$ with either styrenes or vinyl ethers and the mechanism is proposed to follow the well-known Heck catalytic cycle. In the same paper, the authors also described the C–H difluoromethylation of various heteroaromatic compounds.[15] Efficient Heck-type protocols applicable to a wide range of fluoroalkyl bromides, including $BrCF_2CO_2Et$ and acetamide derivatives, were proposed by Zhang and co-workers in 2015, with some evidence for a radical/SET mechanism which proceeds by free fluoroalkyl radicals.[16] Previously, the palladium-catalyzed difluoromethylation of aryl boronic acids with $BrCF_2PO(OEt)_2$ had been investigated by the same group.[17a] A SET-initiated radical oxidative addition of the C–Br bond was suggested to be involved in the palladium catalytic cycle. Subsequently, difluoroallylation,[17b] difluoropropargylation,[17c] and hetero-



Scheme 1. Transition metal catalyzed C–H fluoroalkylation of hydrazones.

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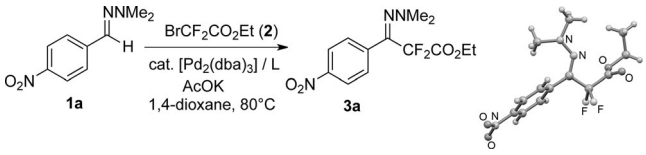
aryldifluoromethylation[17d] of organoborons were reported by this group.

In this context, we reasoned that since oxidative addition of bromodifluoromethyl reagents to palladium is feasible, then electrophilic palladation of aldehyde-derived hydrazones with the resulting FG–$CF_2Pd^{II}Br$ complex might represent a possible alternative strategy to the desired difluoromethylated aldehyde-derived hydrazones (Scheme 1b). To the best of our knowledge, there is only one precedent for the palladium-catalyzed C(sp^2)–H functionalization of hydrazones and it was reported by Hartwig and coworkers[18] in 2006. The report concerned the coupling of aryl bromides with N-*tert*-butylhydrazones to afford the corresponding aryl ketones upon hydrolysis. The reaction is believed to occur by a catalytic mechanism similar to that proposed for the arylation of ketones. Herein we report the development of a palladium-catalyzed coupling of aldehyde hydrazones with halodifluoromethylated reagents which affords difluoromethylketone hydrazones.

Preliminary studies have focused on the reaction of the *p*-nitrobenzaldehyde-derived N,N-dimethylhydrazone **1a** as a model substrate with ethyl bromodifluoroacetate ($BrCF_2CO_2Et$; **2**; Table 1). The latter reagent is particularly attractive as it is practical, inexpensive, and provides a convenient functional handle for further elaboration or increase in molecular complexity. The reaction was initially evaluated at 80 °C using 1,4-dioxane as the solvent, AcOK as the base, and a catalytic amount [$Pd_2(dba)_3$] as a source of palladium(0). Several phosphorus ligands were thus screened under the selected reaction conditions. The use of monodentate phosphine ligands led essentially to no conversion (entries 1–4). The bidentate diphenylphosphine ligand Xantphos, known as an efficient ligand for reductive elimination from fluoroalkyl palladium(II) complexes, also proved ineffective (entry 9).[17a,19] However, we were pleased to discover that the related *t*BuXantphos, bearing bulkier *tert*-butyl groups on the P atoms, was an extremely efficient ligand for promoting the reaction, thus affording the desired difluorinated product **3a** in an excellent 93% yield as determined by ^{19}F NMR spectroscopy (entry 10). Among other bidentate ligands tested (entries 5–8), only *rac*-binap and the ferrocenyl-based ligand dppf showed potent activity, but proved far less efficient compared to *t*BuXantphos. Note that essentially no reaction was observed in the absence of a ligand (entry 12). Other combinations of bases (*t*BuOK, K_2CO_3, K_3PO_4, Et_3N) and solvents (MeCN, toluene, DMF, DMSO) were also examined but did not lead to any significant improvement.[20]

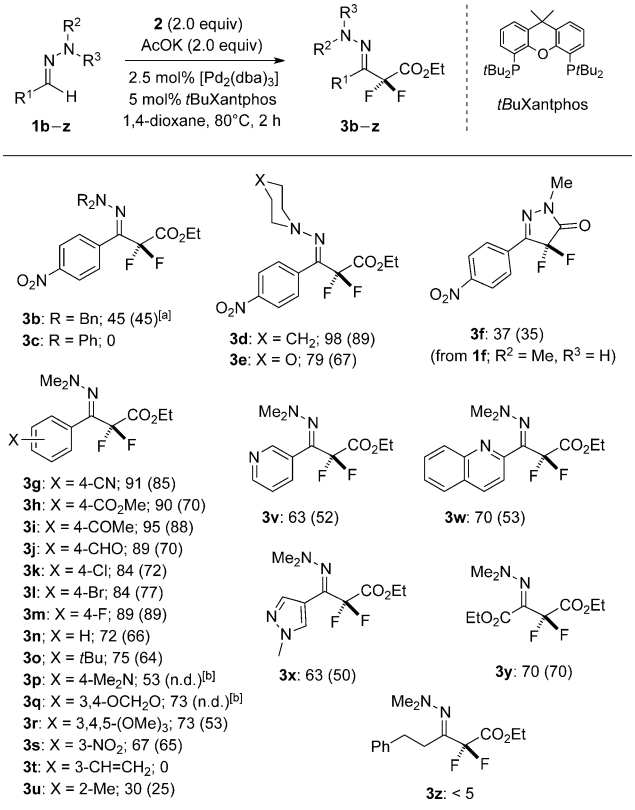
With the optimized reaction conditions in hand, the scope of the coupling reaction was then examined (Scheme 2). First we investigated the effect of varying the nature of the terminal amino group of the *p*-nitrobenzaldehyde-derived

Table 1: Selected optimization experiments for difluoromethylation of the 4-nitrobenzaldehyde-derived N,N-dimethylhydrazone **1a** with **2**.[a]



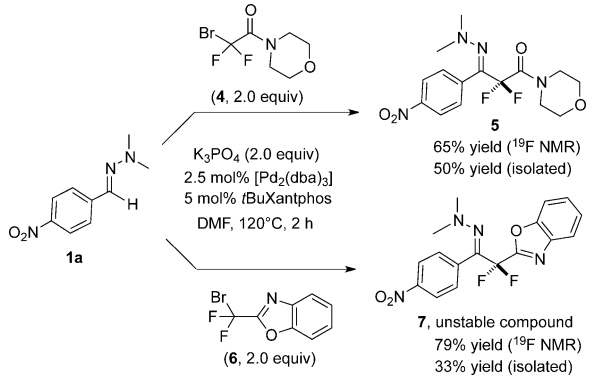
Entry	Ligand (mol%)	*t* [h]	Yield [%][b]
1	$tBu_3P{\cdot}HBF_4$ (10)	24	trace
2	*t*BuXPhos (10)	24	5
3	RuPhos (10)	24	trace
4	DavePhos (10)	24	trace
5	*rac*-binap (5)	24	16
6	dppf (5)	24	29
7	*t*Bu-dppf (5)	24	trace
8	DPEPhos (5)	24	trace
9	Xantphos (5)	24	trace
10	*t*BuXantphos (5)	2	93 (76)[c]
11	*t*BuXantphos (10)	2	63
12	none	2	6

[a] Reaction conditions: **1a** (0.3 mmol), **2** (2.0 equiv), AcOK (2 equiv), [Pd_2dba_3] (2.5 mol%). and ligand in 1.0 mL solvent. [b] Determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [c] Yield of the isolated product. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, DavePhos = 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl, dba = dibenzylideneacetone, DPEPhos = bis(2-diphenylphosphinophenyl)ether, dppf = 1,1′-bis(diphenylphosphino)ferrocene, Ruphos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.



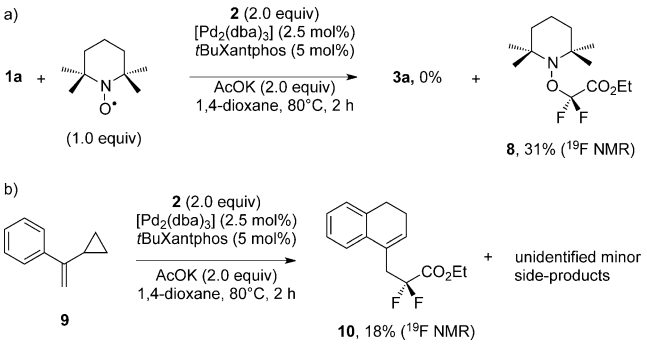
Scheme 2. Scope of the palladium-catalyzed difluoromethylation of aldehyde hydrazones with $BrCF_2CO_2Et$. Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), AcOK (1.0 mmol), [$Pd_2(dba)_3$] (0.0125 mmol), and *t*BuXantphos (0.025 mmol) in 1.5 mL 1,4-dioxane at 80 °C. Yields (%) were determined by ^{19}F NMR analysis of the crude reaction mixture using α,α,α-trifluorotoluene as an internal standard. Yield of the isolated product is given within parentheses. [a] 89% yield of isolated product based on recovered starting material. [b] N.D. = not determined; the products are contaminated with unreacted starting material (see the Supporting Information).

hydrazones. While the dibenzylhydrazone still furnished the expected product **3b**, albeit in moderate yield, the much less electron-donating diphenylhydrazone resulted in essentially no reaction (**3c**). Hydrazones bearing cyclic amino groups, that is, 1-piperidinyl and 4-morpholinyl, participated efficiently in the coupling reaction giving the desired products **3d** and **3e**, respectively, in high yields. Most interestingly, the monosubstituted N-methylhydrazone yielded the ring-fluorinated 4,4-difluoropyrazol-5-one **3f** as the sole product, which presumably originates from spontaneous lactamization of the amino ester coupling product.[22] Next we investigated the effect of substituents on the aryl moiety of various benzaldehyde-derived N,N-dimethylhydrazones. Good results were obtained with *para*- and *meta*-substituted aryls. Notably, substrates with electron-withdrawing *para* substituents afforded the products **3g**–**m** in higher yields than those bearing electron-donating substituents (**3o**–**r**). However, sterically hindered *ortho*-substituted aryls afforded the desired coupling product in low yield (**3u**). The reaction tolerated a wide range of substituents/functional groups, including nitro, cyano, carboxylic ester, formyl, acetyl, and halide (Cl, Br), thus offering opportunities for further diversification. However, the presence of a vinyl substituent on the aryl moiety (**3t**) led only to decomposition of the substrate. Importantly, several heterocyclic aldehyde-derived hydrazones [i.e. pyridinyl, quinolinyl, and pyrazolyl (**3v**–**3x**)] proved suitable substrates for the transformation wherein the heterocyclic ring was untouched. An ethyl glyoxylate hydrazone participated also efficiently in the reaction (**3y**). Unfortunately, as illustrated with **3z**, aliphatic aldehyde-derived hydrazones proved to be more challenging substrates for this reaction, thus giving only small amounts of the desired product under the standard reaction conditions. Finally, the robustness of this transformation was further demonstrated by performing the synthesis of **3m** on a 2.5 mmol scale (64% yield).[23] Importantly, the scope of the reaction coupling partners was not restricted to ethyl bromodifluoroacetate **2** (Scheme 3). Indeed, the coupling reaction of **1a** with the bromodifluoroacetamide **4**,[17b] or even 2-(bromodifluoromethyl)benzo[*d*]oxazole (**6**),[17d] was made possible with some modifications of the reaction conditions (potassium phosphate as the base in DMF at 120 °C) to afford the desired coupling products **5** and **7**, respectively.



Scheme 3. Scope of coupling partners. DMF = *N*,*N*-dimethylformamide.

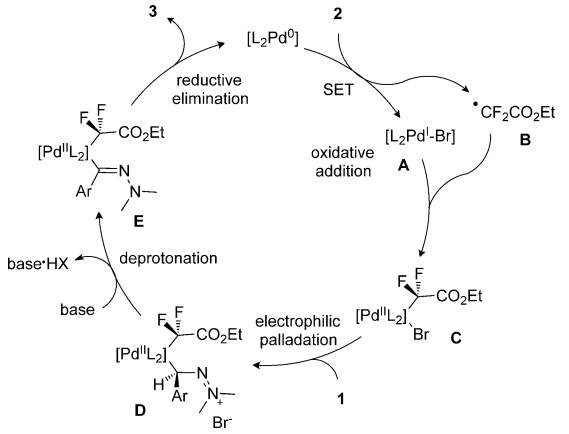
The mechanistic details of the catalytic coupling reaction remain unclear at the present stage. However, given the known propensity of Pd^0 species to promote the formation of difluoromethyl radicals from fluoroalkyl halides through SET,[10–13,16,17] the possibility of a radical/SET pathway that would initiate the catalytic reaction was briefly explored. Our standard coupling reaction of **1a** with **2** (93% yield) was thus repeated in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 1.0 equiv). Interestingly, formation of coupling product **3a** was completely inhibited, and the TEMPO–CF_2CO_2Et adduct **8**[24] was formed in 31% yield as estimated by ^{19}F NMR spectroscopy (Scheme 4a). The reaction was also conducted in the presence



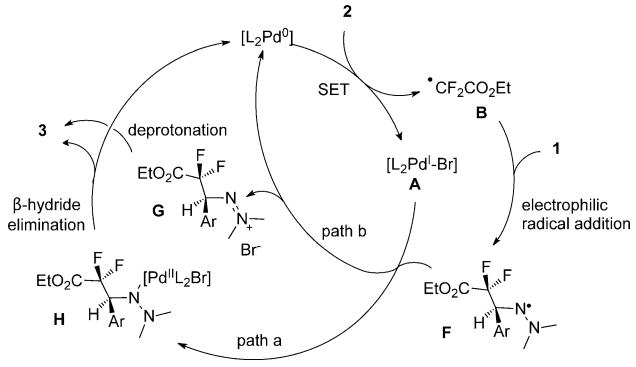
Scheme 4. Preliminary mechanistic studies. a) Inhibition experiment using TEMPO. b) Radical clock experiment with α-cyclopropylstyrene.

of 2,6-di-*tert*-butyl-4-methylphenol (BHT; 1.0 equiv) which again led to inhibition of the coupling process. Moreover, repeating the reaction in the presence of 5 mol% of the electron transfer scavenger *p*-dinitrobenzene (1:1 ratio with respect to the metal) caused a dramatic drop in the reaction yield (25%). Finally, we performed a radical clock experiment using α-cyclopropylstyrene (**9**) as a radical trapping agent.[25] When **9** was reacted with **2**, formation of the known ring-expanded product **10** was observed (18% yield as estimated by ^{19}F NMR spectroscopy), thus confirming that a free CF_2CO_2Et radical can be generated under our standard reaction conditions (Scheme 4b).[16b]

These preliminary experiments seem to confirm that a radical/SET pathway may initiate the coupling reaction. Furthermore, deuterium-labeling studies showed no primary kinetic isotope effect (KIE; $k_H/k_D = 1.14$) in the experiment using a deuterated benzaldehyde-derived N,N-dimethylhydrazone (**1n**-***d***) thus indicating that cleavage of the azomethine C–H bond is not involved in the rate-determining step of the process.[20] A plausible mechanism is depicted in Scheme 5 and takes into account the previous observations. The process would begin with single-electron transfer from the Pd^0 metal complex to the fluoroalkyl bromide to form the $Pd^I Br$ complex **A** and difluoroalkyl radical intermediate **B**, with subsequent recombination of these two species to give the regular Pd^{II} oxidative addition adduct **C**.[26] Subsequent electrophilic palladation of the hydrazone, followed by deprotonation of the resulting cationic intermediate **D** would generate the azomethinyl Pd^{II} complex **E**. Finally, reductive elimination would form the coupling product and



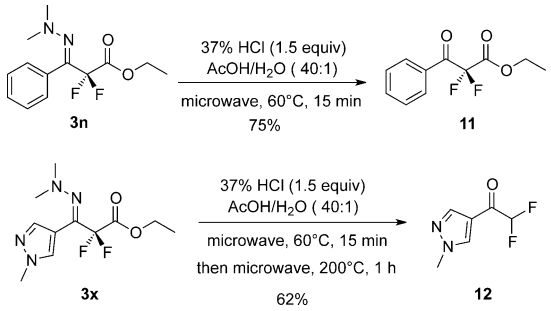
Scheme 5. SET-initiated mechanism involving electrophilic palladation.



Scheme 6. SET-initiated mechanism involving electrophilic radical addition.

recycle the active Pd^0 catalytic species. However, other mechanistic pathways that would involve addition of **B** across the C=N bond of the hydrazone as a key step and result in the formation of the aminyl radical **F**, cannot be ruled out at this stage (Scheme 6). In this case, H-elimination would then proceed by two possible pathways. The radical **F** may be oxidized by Pd^I to the cationic intermediate **G**, thereby regenerating the active Pd^0 species. Subsequent deprotonation would restore the C=N bond of the hydrazone moiety to yield the final product. Alternatively, **F** may be trapped by Pd^I to give the Pd^{II} complex **H**. The C=N bond would then be restored by β-hydride elimination.[27] It is noteworthy that no TEMPO–hydrazone adduct was detected in the trapping experiment. Although conclusive evidence is still pending, detection of reaction intermediates by positive ion electrospray mass spectrometry revealed molecular ions at *m*/*z* 685.1 and 727.3, with the predicted isotope pattern resulting from the palladium atom, and they are attributed to the $[(t\text{BuXantphos})PdBr]^+$ and $[(t\text{BuXantphos})PdCF_2CO_2Et]^+$ cations, respectively, thereby providing evidence for difluoroalkyl palladium intermediates.[20]

The hitherto unknown hydrazones **3** are compounds with great potential for further synthetic manipulation, notably as intermediates for different classes of α,α-difluoro carbonyl derivatives. For instance, the carbonyl function of **3n** could be restored by simple acidic treatment under microwave irradiation at 60 °C to afford the corresponding β-ketoester **11** in 75 % yield upon isolation (Scheme 7). α,α-Difluoro-β-ketoesters are particularly attractive as precursors of optically active fluorinated β-hydroxy esters which are important building blocks for the synthesis of various organofluorine compounds, notably bioactive fluorinated peptides.[28] Interestingly, it was also established that further microwave irradiation at a more elevated temperature (200 °C) allows subsequent deethoxycarbonylation of the difluoro ketoesters[29] to afford the corresponding α,α-difluoro ketones ($RCOCF_2H$). This transformation was illustrated by the one-pot, two-step synthesis[30] of the difluorinated pyrazolyl-ethanone **12** (62 % yield), on account of the important role played by fluorinated pyrazoles in medicinal and agro chemistry.[31] Overall, these valuable α,α-difluoro carbonyl derivatives are made accessible in three steps from simple aldehydes.[32]



Scheme 7. Elaboration of the hydrazone products **3**.

In summary, we have developed a practical procedure for the synthesis of hitherto unknown α,α-difluoroketone hydrazones based on the coupling of readily available (hetero)-aromatic aldehyde-derived hydrazones with halodifluoromethylated reagents under palladium catalysis. In addition, applications of the methodology to functional-group transformations have been illustrated, notably through the straightforward conversion of aldehydes, via their hydrazones, into α,α-difluoro-β-ketoesters and α,α-difluoroketones. We have also shown that 4,4-difluoropyrazol-5-one derivatives are directly accessible from N-monosubstituted hydrazones, although the transformation would require further optimization. Further studies into the scope and limitations as well as the mechanistic understanding of this reaction are currently underway in our laboratories and will be reported as events merit.

Experimental Section

Preparation of the difluoropropanoate hydrazones **3**: In a glass tube equipped with a magnetic stir bar, the selected hydrazone (0.5 mmol), dry potassium acetate (98.2 mg, 1.0 mmol), and ethyl 2-bromo-2,2-difluoroacetate (128.2 μL, 1.0 mmol) were successively added to a suspension of $[Pd_2dba_3]$ (11.5 mg, 2.5 mol %) and *t*BuXantPhos (12.5 mg, 5 mol %) in 1,4-dioxane (1.5 mL). The reactor was flushed with argon, sealed, and heated at 80 °C for 2 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, appropriate mixture of *n*-pentane/ethyl acetate) to afford the corresponding difluoropropanoate hydrazone.

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Keywords: fluorine · homogeneous catalysis · hydrazones · palladium · reaction mechanisms

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