ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-10-2015-008950
Article Type:	Communication
Date Submitted by the Author:	28-Oct-2015
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Journal Name

COMMUNICATION

Catalytic C-F Bond Activation of Geminal Difluorocyclopropanes by Nickel(I) Complexes via a Radical Mechanism

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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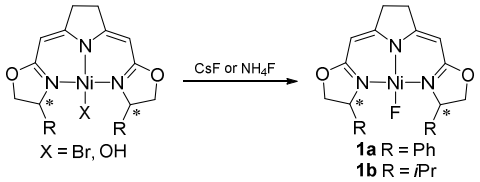
Nickel(II) fluorido complexes bearing NNN-pincer ligands were found to be catalysts in the hydrodefluorination of geminal difluorocyclopropanes which undergo ring-opening to form the corresponding monofluoroalkenes in good yield and high Z-selectivities. Evidence for a radical based mechanism involving nickel(I) and nickel hydrido complexes as key intermediates was obtained in the corresponding stoichiometric reactions.

The activation and functionalization of C-F bonds is considered a major challenge in organometallic chemistry[1] and has received growing attention due to the importance that organofluorine compounds have gained in recent years.[2] The increasing demand for ways of introducing fluorine into new materials or into biologically active molecules has inspired the development of diverse synthetic strategies. [1a]

Hydrodefluorination (HDF) is regarded as a promising approach to access partially fluorinated building blocks from readily available fluorinated bulk chemicals.[3] At present HDF is rarely used in preparative contexts but a range of transition metal catalysts have been described to date, including titanium[4], zirconium[5], rhodium[6], ruthenium[7], gold[8], palladium[9] and nickel.[1a,10]

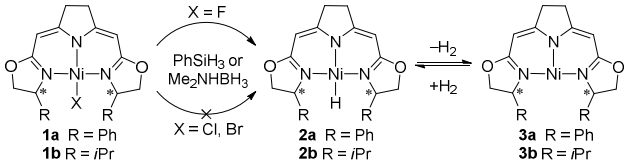
Despite the availablity of several synthetic methods for the construction of geminal difluorocyclopropanes,[11] their application as substrates in catalytic transformations is barely examined. Very recently, Fu *et al.* reported a general and efficient Pd(0)/Pd(II)-catalyzed regioselective functionalization of geminal difluoro-cyclopropanes leading to 2-fluoroallylic amines, ethers, esters, and alkylation products with high Z-selectivities. Their contribution represents the first general application of geminal difluorocyclopropanes in this context.[12]

The pincer ligands used in this work[13] are capable of stabilizing T-shaped nickel(I) complexes[14], which have been used to reduce prochiral geminal dichlorides and dibromides enantioselectively to the corresponding secondary halides in combination with a hydride source.[14b] A detailed mechanistic investigation on the reaction mechanism revealed a catalytic cycle that is based on the interplay between these nickel(I) complexes and corresponding nickel(II) hydrido species and involves the generation of α-halogenalkyl radicals.



Scheme 1 Synthesis of nickel fluorido complexes **1a** and **1b**.

Here we report the activation of geminal difluorocyclopropanes by these nickel complexes inducing ring-opening of the cyclopropane and leads to fluoroalkenes with high Z-selectivity. The nickel(II) fluorido complexes **1a** and **1b** were used in the catalytic transformation. Salt metathesis of CsF or NH_4F with the corresponding halogenido or hydroxo complexes in wet THF led to a clean formation of air and moisture stable fluorido complexes **1a,b** which were isolated and characterized. [15,16]The addition of water helps to dissolve the fluoride salts. Under these conditions the nickel fluorido complexes were found to be stable and no hydroxo species were formed. Notably, the ^{19}F NMR resonances of the fluorido ligands are observed at unusually high field (-444.0 ppm (**1a**), -452.1 ppm(**1b**)) compared to the range reported in the literature (-160 ppm to -410 ppm).[16,17]



Scheme 2 Conversion of the fluoridonickel complexes **1a** and **1b** with ammoniaboranes and silanes to the corresponding hydrido complexes **2a** and **2b** and their H_2-pressue dependent equilibrium with the T-shaped nickel(I) species.

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Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [Synthesis, NMR, crystal data and structure refinement]. See DOI: 10.1039/x0xx00000x

The high affinity of fluorine towards silicon[3a] and boron[3c] results in an increased reactivity of the fluorido complexes **1a** and **1b** with silanes and boranes in their conversion to the hydrido complexes **2a** and **2b** compared to the corresponding chlorido and bromido complexes.[1a,18] The formation of the hydrido species (Scheme 2), which were previously shown to exist in a hydrogen pressure dependent equilibrium with the nickel(I) complexes (**3a,b**), plays a crucial role in the catalytic hydrodefluorination. Generally, hydride transfer reagents such as $PhSiH_3$ and Me_2NHBH_3 were found to be suitable stoichiometric hydride sources for the conversion of the fluorido to the hydrido complexes instead of the highly reactive $LiEt_3BH$ used in the previous catalytic hydrodehalogenations.[14b]

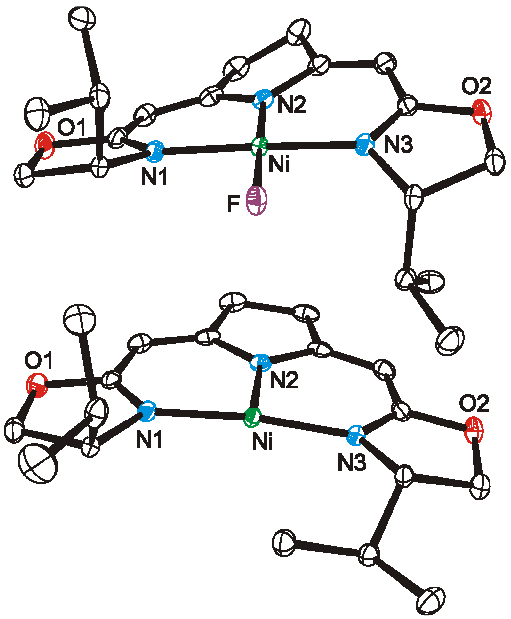
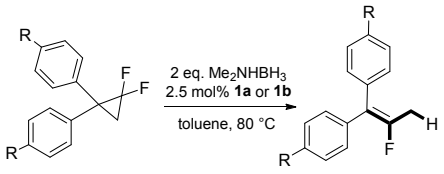


Figure 1 Molecular structures of **1b** (top, only one of the two independent molecules is shown; cocrystallized toluene and hydrogen bonded H_2O are not shown) and **3b** (bottom). Hydrogen atoms are omitted for clarity. Selected bond length [Å] and angles [°]: (**1b**) Ni-F 1.8308(17), Ni-N(1) 1.8847(18), Ni-N(2) 1.885(2), Ni-N(3) 1.8884(18), F-Ni-N(1) 87.30(6), F-Ni-N(2) 178.96(6), F-Ni-N(3) 88.04(6), N(2)-Ni-N(1) 92.34(7), N(3)-Ni-N(1) 175.28(7); (**3b**) Ni-N(2) 1.9301(18), Ni-N(1) 1.8955(19), Ni-N(3) 1.8903(18), N(1)-Ni-N(2) 95.26(8), N(2)-Ni-N(3) 96.12(8), N(3)-Ni-N(1) 168.60(7).

Single-crystal X-ray diffraction studies of **1b** and **3b** established small differences in the coordination of the pincer ligand to the nickel center for both oxidation states (Figure 1).[†] While **1b** displays an almost ideal square planar coordination geometry, the absence of the fluoride ligand in **3b** results in a slightly disordered T-shaped arrangement, which has already been shown for the corresponding complex **3a**.[14b] The change in oxidation state is mainly reflected by an elongation of the central Ni-N(2) bond from 1.885(2) Å (**1b**) to 1.9301(18) Å (**3b**), which is attributed to the larger ionic radius of the nickel(I) center.

In the presence of a hydride source the nickel(II) fluorido complexes **1a,b** were able to catalytically activate 1,1-difluoro-2,2-diphenylcyclopropane above 60 °C leading to a C-C bond cleavage to form 1,1-diphenyl-2-fluoropropene (Scheme 3).

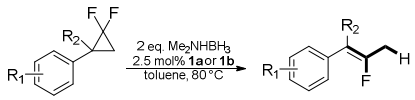


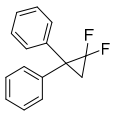
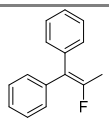
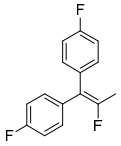
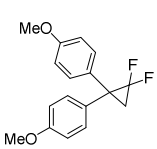
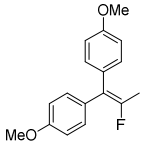
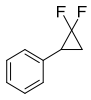
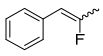
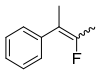
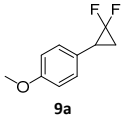
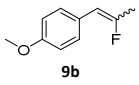
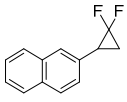
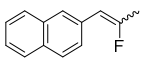
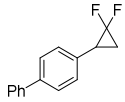
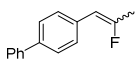
4a R = H
5a R = F

4b R = H
5b R = F

Scheme 3 Catalytic hydrodefluorination of the 1,1-difluoro-2,2-diphenylcyclopropanes **4a** and **4b**.

Table 1 Results of the catalytic hydrodefluorination for different geminal difluoro-cyclopropanes.



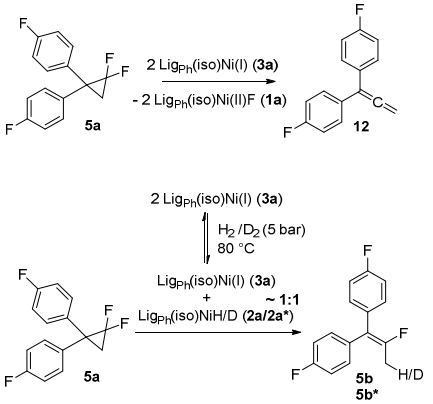
Substrate	Product	dr[a] (Z/E)	yield [%] (NMR[a])
 **4a**	 **4b**	-	89 (99) (**1a**) (96) (**1b**)
 **5a**	 **5b**	-	86 (99) (**1a**) (88) (**1b**)
 **6a**	 **6b**	-	92 (98) (**1a**) (75) (**1b**)
 **7a**	 **7b**	9:1 (**1a**)	67 (90) (**1a**)
 **8a**	 **8b**	7:3 (**1a**) 6:4 (**1b**)	65 (74) (**1a**)
 **9a**	 **9b**	19:1 (**1a**) 13:1 (**1b**)	61 (78) (**1a**) (53) (**1b**)
 **10a**	 **10b**	9:1 (**1a**) 9:1 (**1b**)	89 (96) (**1a**) (60) (**1b**)
 **11a**	 **11b**	9:1 (**1a**) 9:1 (**1b**)	81 (99) (**1a**) (64) (**1b**)

[a] determined by ^{19}F-NMR before work-up using 1,4-bis(trifluoromethyl)benzene as internal standard.

When the reaction was monitored by ^{19}F NMR spectroscopy, the disappearance of the starting material

[triplet resonance at −130.0 ppm ($^3J_{H,F}$ = 8.7 Hz)] was accompanied by the appearance of a quartet at −97.4 ppm ($^3J_{H,F}$ = 17.7 Hz) which correspond to the fluoroalkene **4b**. The conditions of the reaction were optimized using the difluorocyclopropane derivative **5a**. The best results were obtained with dimethylammonia borane as hydride source and the Ph-substituted nickel fluorido complex **1a** in toluene as solvent at a temperature at 80 °C (Supporting Information). Under these optimized conditions a range of difluorocyclopropanes (**4a**-**11a**) was tested (Table 1). After a reaction time of 16 h, the complete conversion of the starting material had occurred in all cases and the formation of the corresponding fluoroalkenes with high Z-selectivity and yield was observed. Notably, the nickel system described in this work is capable of activating the sterically demanding 1,1'-disubstituted difluorocyclopropanes.

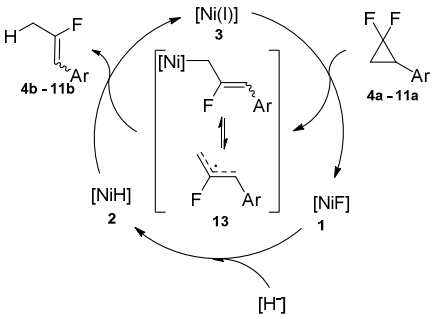
In the case of chiral geminal difluorocyclopropanes, which were employed as racemates, a mixture of both possible diasteriomeric fluoroalkenes was obtained (Entry **7a**-**11a**) and the diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis. The characteristic *trans* and *cis* hydrogen fluorine coupling constants of $^3J_{H,F(trans)} \approx 45$ Hz and $^3J_{H,F(cis)} \approx 18$ Hz were used to determine the configuration of the double bond of each isomer.[19] In each case the Z-diastereomer was obtained as the major product with moderate to excellent diastereoselectivity. Since the observed product ratio was found to be independent of the conversion, the possibility of a kinetic resolution as the reason for preferred formation of one stereoisomer can be ruled out. DFT modelling of E- and Z-diastereomers revealed slightly greater stability of the latter, except for **8b** (see SI).



Scheme 4 Stoichiometric reactions of **5a** with the nickel complexes **2a** and **3a**. Top: Formation of a 1,1'-diphenylallene derivative via double defluorination of **5a**. Bottom: Monodefluorination and subsequent hydrogen/deuterium atom transfer in the presence of an in situ generated mixture of **2a/2a*** and **3a**.

In analogy to the previously studied hydrodechlorinations, the activation of the C-F bonds by the nickel catalysts employed in this work is thought to involve the in situ generated nickel(I) species **3a,b** which abstract halogen atoms via one electron steps involving radical species. It was thus essential to probe whether the significantly stronger C-F bond could be activated by the *isolated* nickel(I) species. To this end, stoichiometric transformations involving the geminal difluorocyclopropane **5a** were carried out. The reaction of **5a** with one equiv. of the nickel(I) complex **3a** at 80 °C in toluene led to a 1:1 mixture of the starting material and diphenylallene **12** along with one equivalent of the fluorido complex **1a**. On the other hand, reaction with two molar equivalents of **3a** gave near quantitative formation of the reaction product **12** (Scheme 4).[‡] The exclusive observation of the doubly defluorinated product indicated that the second defluorination step occurs more rapidly than the initial fluorine atom abstraction.

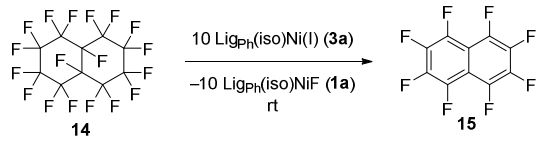
In order to probe the reactivity of the elusive monodefluorinated intermediate and to obtain insight into the reaction paths leading to the fluoroalkene products of the catalytic process discussed above, the solution of the Ni(I) complex **3a** was placed under 5 bar of hydrogen at 80°C to generate in situ a ratio of roughly 1:1 between both nickel hydride species **2a** and the nickel(I) complex **3a** (which are in equilibrium with each other under these conditions). Performing the same stoichiometric transformation under these conditions gave the hydrodefluorination product **5b** exclusively. The H atom transfer from the hydrido complex **2a** onto an allylic (radical) intermediate is thus kinetically favoured over a second F atom abstraction by the nickel(I) species **3a**. If, instead of hydrogen, deuterium was used the exclusive formation of the mono deuterated product **5b*** was observed. Due to the reaction temperature of 80 °C under which these transformations occur, an investigation of the nature of the intermediate species by the usual radical traps was not possible.



Scheme 5 Proposed mechanism for the catalytic cycle of the hydrodehalogenation of geminal difluorides.

However, the observations are generally consistent with a mechanism which is similar to the one established previously for the hydrodehalogenation of geminal dichlorides: In a first step the nickel(I) complex activates the geminal difluorocyclopropane **4a** - **11a** by homolytic C-F cleavage and subsequent ring-opening[20] liberating the monofluoroallylic radical species **13** which may be either metal-stabilized or dissociated (Scheme 5). The latter is transformed to the corresponding fluoroalkene **4b** - **11b** via hydrogen atom abstraction from the nickel hydrido complex **2** (as demonstrated in the stoichiometric reaction discussed above) regenerating the nickel(I) species **3**. The rapid conversion of the fluorido complex **1**, formed in the first defluorination step, to the hydrido complex **2** by the hydride source closes the catalytic cycle.

To further support the mechanistic proposal in which a C-F bond is activated by the nickel(I) species in the initial step of the catalytic cycle, we probed to see whether non-constrained geminal fluorides would be disposed to defluorination under these conditions. Indeed, the reaction of perfluorinated decalin **14** with 10 equiv. of the isolated nickel(I) species at room temperature led to the quantitative formation of perfluorinated naphthalene **15** as well as the nickel fluorido complex **1a**. The formation of the unsaturated compound during this reaction reflects the general reactivity pattern observed for the dehalogenation of dihalogenated alkanes by Ni(I) (TMC) complexes[21] and, therefore, supports the proposed occurrence of radical intermediates in the defluorination reaction of difluorocyclopropanes presented in this work.



Scheme 6 Stoichiometric defluorination of **14** by **3a**.

The results of this work demonstrate that the previously developed nickel(I/II) system, which was found to be catalytically active for the hydrodechlorination and -bromination of corresponding geminal dihalides is also capable of activating the geminal difluorocyclopropanes. The products, most probably formed via an analogous radial mechanism are vinylic fluorides which are obtained in high yield and Z-selectivity.

Acknowledgements

We thank Alexander Ahrens and Steffen Ott for experimental support. We acknowledge funding by the Deutsche Forschungsgemeinschaft (Ga 488/9-1) as well as the University of Heidelberg.

Notes and references

† CDC 1427461-1427465 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

‡. The product 1,1-diphenylallene was synthesized separately according to literature procedure (Doering–LaFlamme allene synthesis) to verify its formation during the reaction.[22]

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