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Stereoselective Reactions |*Hot Paper*|

Generation of ε,ε-Difluorinated Metal-Pentadienyl Species through Lanthanide-Mediated C–F Activation

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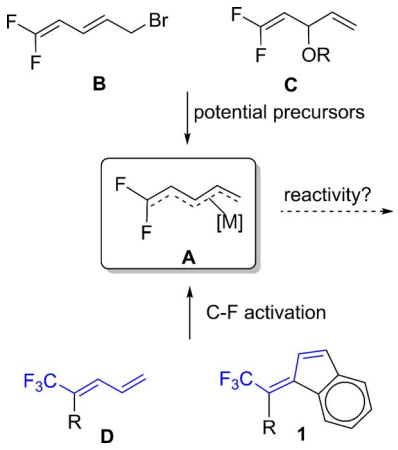
Abstract: Heavy metal on Lewis acid: The combination of lanthanide metals and $AlCl_3$ has been employed for selective single C–F activation in benzofulvenes comprising an exocyclic CF_3 substituent. Intermediate ε,ε-difluorinated metal-dienyl species react with a large variety of aldehydes in a highly regio- and diastereoselective fashion to afford 1,1-disubstituted indenes bearing a difluorovinyl group. These new building blocks have been further transformed through a hydrogenation–cyclization process into fluorinated heterocyclic spiro compounds.

Metal-pentadienyl complexes display structural diversity as shown by experimental and theoretical investigations and are valuable synthons in organic chemistry.[1] Depending on the metal, regioselective transformations with electrophiles have been observed and exploited, for example, in the synthesis of terpenes or dendralenes.[2] Only few examples of ε,ε-disubstituted metal-dienyl complexes have been described and, to our knowledge, no report on ε,ε-difluorinated derivatives **A** exists (Scheme 1).[3] Derivatives of type **A** could function as nucleophilic entities to readily access new classes of difluoroalkenes, which have found important applications in organic synthesis and in certain cases display biological activities.[4]

Difluoropentadienyl-metal species could arise from precursors **B** or **C** (Scheme 1) through insertion reactions with low-valent metals or metal complexes.[5] However, owing to the limited synthetic methods to access such fluorinated substrates,[6] we envisaged the generation of the metalpentadienyl



Scheme 1. Synthetic strategies to access ε,ε-difluorinated metal-pentadienyl complexes.

complexes through single C–F activation of trifluoromethylated dienes **D** with zero-valent metals,[7] focusing on lanthanides.

Lanthanide complexes have been studied in C–F activation of polyfluorinated arenes since the pioneering works by Deacon and Andersen.[8] Recently, selective transformations of alkyl fluorides have been achieved using SmI_2, YbI_3, or La[N-$(SiMe_3)_2]_3$.[9] In the case of CF_3 groups, only very few examples have been described leading mostly to fully defluorinated products.[10] For zero-valent lanthanides, there has been only one report on C–F activation, that is, the *para*-selective reaction of ytterbium metal with pentafluorobenzene giving straightforward access to an YbF_2 salt and 1,2,4,5-tetrafluorobenzene.[11] The strong reduction potential of elemental lanthanides prompted us to investigate their behavior towards CF_3-dienes for the generation of difluorinated metal-dienyl species. The chemical behavior of these uncommon conjugated systems was investigated through reaction with aldehydes. The study was conducted by using readily accessible trifluoromethylated benzofulvene derivatives of general structure **1** as model substrates.

The new trifluoromethylated benzofulvene **1a** was synthesized using the standard Thiele method for fulvene synthesis, that is, heating indene with trifluoroacetophenone and NaOMe in refluxing ethanol (Scheme 2).[12,13] Compound **1a** was initially obtained as a 65:35 mixture of *E*/*Z* isomers. Crystallization from hexanes at −35 °C selectively afforded the *E* isomer which

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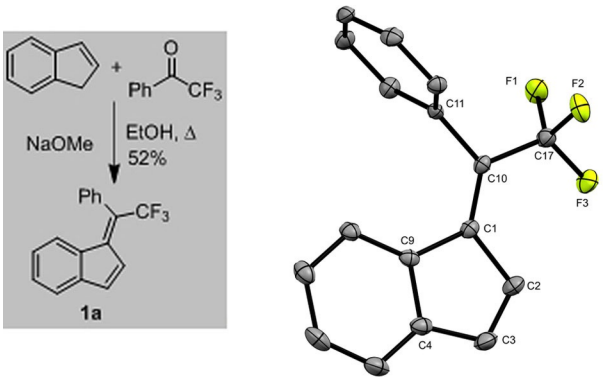
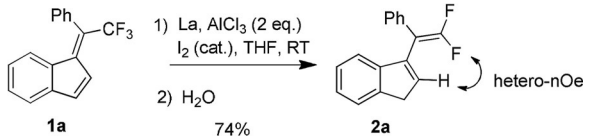


Scheme 2. Synthesis and X-ray crystal structure of CF_3- benzofulvene **1a**.

could be analyzed by X-ray studies. Despite the presence of the electron-withdrawing CF_3 group no significant deviation of the exocyclic double bond from the planar indene system was observed.

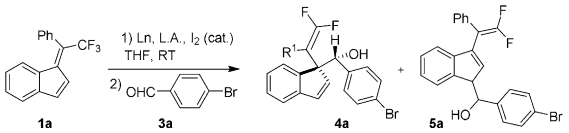
Initially, the reaction of **1a** with stoichiometric amounts of lanthanum metal did not lead to any reaction. However, upon activation of the metal by catalytic amounts of iodine or $AlCl_3$,[14] the formation of trace amounts of difluorovinylindene **2a** was observed when water was used as a trap for the transient metal species. After further screening of reaction parameters, the yield of **2a** could be raised to 74% by increasing the amount of $AlCl_3$ (2 equiv) and including a catalytic amount of iodine (Scheme 3).



Scheme 3. Initial results on C–F activation.

Under these optimized conditions, the reaction was next investigated using *p*-Br-benzaldehyde **3a** as electrophilic counterpart. The formation of two regioisomeric homoallylic alcohols **4a** and **5a** was observed, which were formed in 46% and 19% yield, respectively, (Table 1, entry 1). Compound **4a** was obtained as a single diastereoisomer whereas **5a** was isolated as a 7:3 mixture of diasteroisomers. Variation of the metal reductant along the lanthanide series revealed contrasting yields and selectivities of **4a** and **5a** (entries 2–8). Whereas samarium was clearly not efficient (entry 4), dysprosium gave the highest yield with excellent selectivity in favor of **4a** (entry 6). When an equimolar mixture of ***E*-1a** and ***Z*-1a** was employed, a similar reaction outcome was observed (entry 6). The reason as to why certain lanthanide metals gave lower yields or no reaction at all could not be elucidated, but precedent is found in the literature.[15] Further variation of the reaction conditions by using different additives showed that, besides $AlCl_3$, only $ZrCl_4$ gave a satisfying result (entries 9–13). We therefore focused on the Dy/$AlCl_3$ combination and found that the yield of **4a** could be further improved to 93% by using 3 equiv of $AlCl_3$ and 1.3 equiv of benzofulvene (entry 14).

Table 1. Optimization of C–F activation procedure toward selective formation of product **4a**.[a]



Entry	Ln	LA[b]	**4a** yield [%][c,d]	**5a** yield [%][c]	*d.e.* [%]
1	La	$AlCl_3$	46	19	44
2	Ce	$AlCl_3$	20	15	34
3	Nd	$AlCl_3$	27	18	60
4	Sm	$AlCl_3$	Trace[e]	trace[e]	–
5	Gd	$AlCl_3$	37	6	40
6	Dy	$AlCl_3$	60 (58)[f]	–	–
7	Yb	$AlCl_3$	14[e]	–	–
8	Y	$AlCl_3$	30	5	34
9	Dy	$ZrCl_4$	52	–	–
10	Dy	$Sc(OTf)_3$	–[e]	–	–
11	Dy	TMSOTf	–[e]	–	–
12	Dy	$BF_3{\cdot}OEt_2$	–[e]	–	–
13	Dy	$ZnCl_2$	–	trace[e]	–
14[g]	Dy	$AlCl_3$[h]	93	–	–

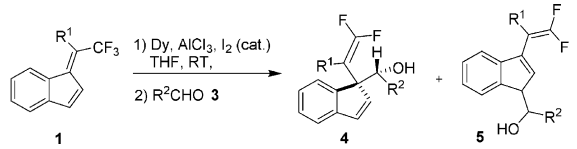
[a] a) Reaction conditions: benzofulvene (0.5 mmol), aldehyde (0.5 mmol), La (0.5 mmol), LA (1.0 mmol) and catalytic amount of iodine (20 mg) in THF at RT. [b] Lewis acid; 2 equiv added unless noted. [c] Isolated yields after silica gel column chromatography. [d] One single diastereoisomer was observed. [e] Benzofulvene was recovered. [f] Equimolar mixture of ***E*-1a** and ***Z*-1a** was employed. [g] Benzofulvene (0.65 mmol) and $AlCl_3$ (1.5 mmol) used. [h] 3 Equiv.

Under optimal reaction conditions, the scope of this new C–F activation procedure was investigated with various benzofulvenes **1** and aldehydes and the results are summarized in Table 2.

Firstly, we used the phenylsubstituted benzofulvene **1a** as the substrate, which after C–F activation was reacted with a range of aromatic, heteroaromatic, or aliphatic aldehydes. In almost all cases, isomer **4** was obtained as the sole reaction product in good yield (entries 1–10, 14, 15). Substitution at the aromatic ring of the electrophile with either electron-withdrawing (halogen, CF_3) or electron-donating (Me, OMe) groups did not affect the stereoselectivity (entries 1–6). Conversely, steric effects had a strong impact on the reaction outcome. Mesitaldehyde **3l** led to a mixture of regioisomers **4l** (22% yield) and **5l** (57% yield, entry 11) and pivaldehyde **3o** afforded **4o** (17%) and **5o** (30%) (entry 16), the less crowded isomer **5** being favored in both cases. Interestingly, when the reaction with mesitaldehyde was carried out at 40 °C, **5l** formed as the major product (64% yield), whereas the reaction at −40 °C delivered **4l** in 65% yield, with trace amounts of the other regioisomer formed in both cases.

An X-ray structure of product **4e** was obtained, which supports the proposed structure of the branched regioisomer, and reveals a sterically crowded character of the quaternary indene carbon (Figure 1).

Table 2. Scope of aldehydes/benzofulvene reactivity with Dy/$AlCl_3$ system.[a]



Entry	1	R^1	3	R^2	4	Yield [%][b,c]	5	Yield [%][b]	*d.e.* [%]
1	**1a**	C_6H_5	**3b**	4-Cl-C_6H_4	**4b**	80	–	–	–
2	**1a**	C_6H_5	**3c**	4-F-C_6H_4	**4c**	85	–	–	–
3	**1a**	C_6H_5	**3d**	4-CF_3-C_6H_4	**4d**	69	–	–	–
4	**1a**	C_6H_5	**3e**	C_6H_5	**4e**	82	–	–	–
5	**1a**	C_6H_5	**3f**	4-Me-C_6H_4	**4f**	80	–	–	–
6	**1a**	C_6H_5	**3g**	4-MeO-C_6H_4	**4g**	69	–	trace	–
7	**1a**	C_6H_5	**3h**	2-naphthyl	**4h**	69	–	–	–
8	**1a**	C_6H_5	**3i**	1-naphthyl	**4i**	68	–	–	–
9	**1a**	C_6H_5	**3j**	2-furyl	**4j**	66	–	–	–
10	**1a**	C_6H_5	**3k**	3-pyridyl	**4k**	71	–	–	–
11	**1a**	C_6H_5	**3l**	2,4,6-Me-C_6H_2	**4l**	22[f]	**5l**	57	80
12[d]	**1a**	C_6H_5	**3l**	2,4,6-Me-C_6H_2	–	trace	**5l**	64	80
13[e]	**1a**	C_6H_5	**3l**	2,4,6-Me-C_6H_2	**4l**	65[f]	–	trace	–
14	**1a**	C_6H_5	**3m**	$-CH_2(CH_2)_2CH_3$	**4m**	57	–	–	–
15	**1a**	C_6H_5	**3n**	$-CH_2(CH_2)_5CH_3$	**4n**	73	–	–	–
16	**1a**	C_6H_5	**3o**	$-C(CH_3)_3$	**4o**	18	**5o**	30	100
17	**1b**	4-Cl-C_6H_4	**3a**	4-Br-C_6H_4	**4p**	72	–	–	–
18	**1c**	4-Me-C_6H_4	**3a**	4-Br-C_6H_4	**4q**	89	–	–	–
19	**1d**	2-thiophene	**3a**	4-Br-C_6H_4	**4r**	72	–	–	–
20	**1e**	4-NMe_2-C_6H_4	**3a**	4-Br-C_6H_4	–	–[g]	–	–	–

[a] Reaction conditions: benzofulvene (0.65 mmol), aldehyde (0.5 mmol), Dy (0.5 mmol), $AlCl_3$ (1.5 mmol), catalytic amount of iodine (20 mg) in THF at RT. [b] Isolated yields after silica gel column chromatography. [c] One single diastereoisomer observed. [d] 40 °C. [e] −40 °C. [f] Crude yield determined by ^{19}F NMR spectroscopy owing to instability of product on silica gel. [g] Benzofulvene was recovered.

We further studied the influence of the aryl group next to the CF_3 group on the reactivity. Benzofulvenes **1b–d** with a *p*-Cl or *p*-methyl substituted phenyl group or a thiophene ring afforded the expected products **4p–r** in good to excellent yields upon reaction with *p*-bromobenzaldehyde **3a** under standard conditions (entries 17–19). In contrast, no C–F activation reaction was observed in the case of the strongly electron-donating NMe_2 group at the *para* position of benzofulvene **1e** (entry 20).

To shed some light on the reaction mechanism and to understand the observed selectivities in the reaction, further experiments were conducted involving reaction monitoring by ^{19}F NMR spectroscopy and characterization by electrospray mass spectrometry. It has been well established that under kinetic control, reactions of allyl-lanthanide-halide species with aldehydes or ketones afforded selectively the linear homoallylic alcohols,[16] whereas allyl-aluminum species led to the branched products in a highly diastereoselective manner.[16a,17] Assuming a similar behavior for dienyl-metal species, the observation of the linear product **5** and the branched product **4** in the case of our reaction with lanthanum (Table 1, entry 1) points toward the presence of two different metallic intermediates (one based on lanthanum and one based on aluminum) in the reaction course. This was confirmed by investigating the reaction mixture obtained after 30 min from the reaction of La/$AlCl_3$/**1a** by ^{19}F NMR spectroscopy. Two major compounds could be identified, each as two characteristic doublet signals for the vinyl-CF_2 group, one at −85.4 (J = 43.1 Hz) and −96.3 ppm (J = 43.1 Hz) for a lanthanum species and one at −87.1 (J = 35.4 Hz) and −91.9 ppm (J = 35.4 Hz) for an aluminum species (see the Supporting Information for all ^{19}F spectra). This attribution was confirmed by using Nd instead of La in this reaction as the peaks for the Al compound did not change, whereas two broad peaks for the lanthanide complex were now observed at −81.5 and −84.5 ppm. Furthermore, a lanthanum-dienyl species was prepared and characterized in the absence of aluminum by reacting 2 equiv of La metal with 1 equiv of iodine and 1 equiv of **1a** in THF. The ^{19}F NMR spectrum showed two doublets at −83.8 (J = 40.4 Hz)

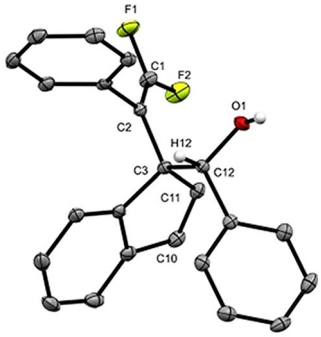
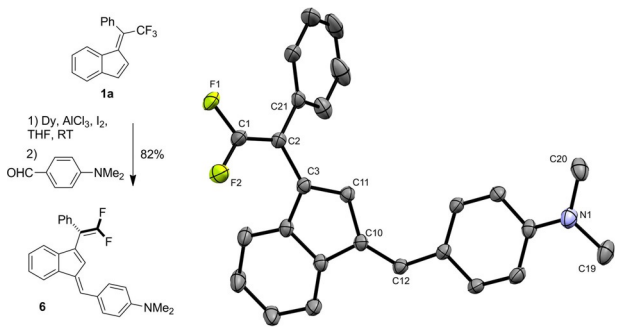


Figure 1. ORTEP plot of compound **4e**.

Interestingly, when *p*-dimethylaminobenzaldehyde was employed under standard conditions, complete inversion of the regioselectivity was observed. However, instead of formation of the corresponding homoallylic alcohol, dehydration occurred and the new benzofulvene derivative **6** was isolated (Scheme 4). An interplay of the strongly electron-donating properties of the dimethylamino group and its basicity might be at the origin of this observation. It should be noted that only the *E* isomer of **6** was formed and the exocyclic difluoroalkenyl moiety is nearly perpendicular to the benzofulvene system as shown by X-ray studies.

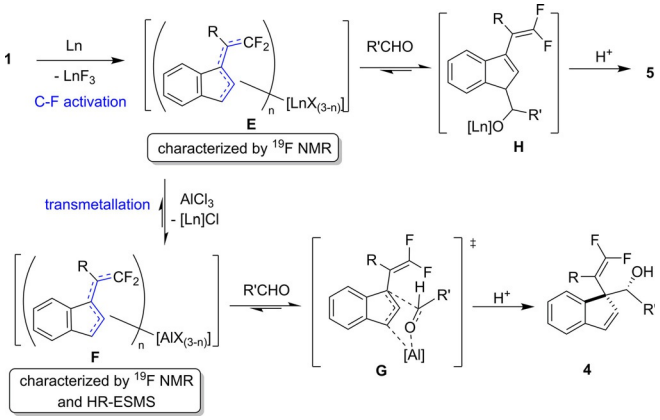


Scheme 4. Reaction with *p*-dimethylaminobenzaldehyde.

and −95.2 ppm (J = 40.4 Hz) (see above) for this complex in good agreement with the above observations. When 1 equiv $AlCl_3$ was added to this solution the peaks corresponding to an aluminum-dienyl species appeared and further increased with the addition of another equiv $AlCl_3$, in agreement with a transmetallation process from La to Al. It should be further noted that addition of *p*-bromobenzaldehyde to the reaction of La/I_2/**1a** selectively afforded the linear compound **5a** as the sole product. Similar ^{19}F NMR experiments were attempted involving Dy, however, the strong paramagnetism did not allow the observation of any Dy-containing species. Nevertheless, the ^{19}F spectrum of the reaction Dy/$AlCl_3$/**1a** again showed the peaks corresponding to the aluminum-dienyl complex. As from this reaction only the branched products **4** were obtained upon addition of aldehydes, one can assume a very efficient transmetallation process from Dy to Al. We could further establish the formation of aluminum-dienyl complexes by ESMS from the reaction Dy/$AlCl_3$/**1a**. Two complexes [(dienyl)$AlCl_2$] and [(dienyl)$_2$AlCl] were observed in the negative ion mode and confirmed with HRMS and correct isotope patterns (see the Supporting Information). Despite numerous attempts, no lanthanide-dienyl species could be observed by ESMS.

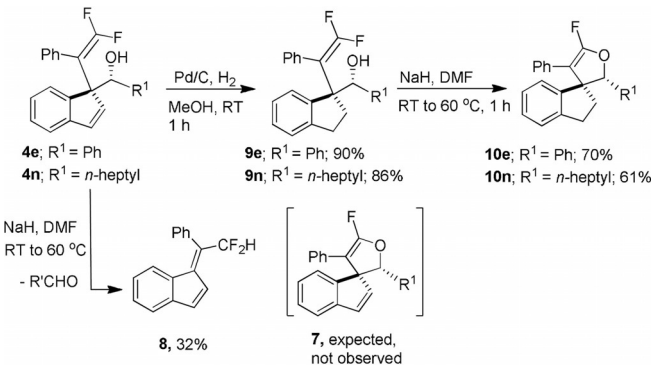
From these findings we conclude the following mechanistic pathways for this new transformation (Scheme 5):

1) The initial lanthanide-metal-mediated C–F activation process in **1** affords lanthanide-dienyl species **E**. This step may proceed in analogy to the Mg/TMSCl system with α-CF_3-substituted carbonyl groups owing to the similar electronic properties of carbonyl and fulvene systems.[18] However, more in-depth studies are required to elucidate this process.
2) Transmetallation of intermediates **E** with $AlCl_3$ affords the aluminum complexes **F**. Depending on the lanthanide metal used this process proceeds more or less efficiently.
3) The intermediates **E** and **F** react with the aldehyde either through direct insertion or via six-membered intermediate **G** to afford the linear or branched products **5** and **4**, respectively. Steric bulk on aldehydes may have an important impact on the equilibrium between intermediates. In the case of sterically hindered aldehydes, such as mesitaldehyde and pivaldehyde, the equilibrium may lie towards **F**, which could explain the formation of the mixture of products **4** and **5**.



Scheme 5. Mechanistic proposal for major reaction pathways.

Difluoroalkenes have recently attracted considerable attention as synthetic building blocks.[4] Among the various transformations, the intramolecular 5-*endo*-trig cyclization with nucleophiles developed by Ichikawa has given access to a wide range of fluorinated heterocycles.[19] In the case of substrates **4**, this cyclization may lead to the unprecedented formation of fluorinated heterocyclic spiroindenes.[20] Similar scaffolds are known to exhibit biological activities.[21] When representative **4e** was subjected to cyclization under standard NaH/DMF conditions, cyclization to product **7** did not occur but instead a mixture of products was formed, including the new benzofulvene **8** (Scheme 6). Compound **8** may derive from a retro-allylation reaction leading to a sodium-pentadienyl complex, which protonates in the ε-position, as previously observed for other alkali-pentadienyl complexes.[1b,3c] We therefore envisaged to hydrogenate the ring double bond in **4e** to avoid the retro-allylation process. The reaction of **4e** with hydrogen under Pd/C catalysis proceeded smoothly to the formation of **9e** and was completely selective toward the ring double bond (Scheme 6). Next, the hydrogenated product **9e** was subjected to standard NaH/DMF conditions whereby intramolecular cyclization took place and delivered the new heterocyclic spiroindane **10e** as a single diastereoisomer in good yield (70%).[22] The same hydrogenation–cyclization procedure was also successful in the case of the aliphatic chain-containing substrate **4n**.



Scheme 6. Selective hydrogenation and 5-*endo*-trig cyclization to spiroindanes.

In conclusion, we have shown that trifluoromethyl-substituted benzofulvenes can serve as model substrates for the generation of ε,ε-difluorinated metal-dienyl species through selective C–F activation by lanthanide metals. Some dienyl-metal complexes could be characterized by ^{19}F NMR spectroscopy and ESMS. Depending on the metal (Ln vs. Al), the reaction with aldehydes afforded different regioisomers. Further work along this line is in progress, namely the extension to other CF_3-containing dienes and variation of electrophiles.

Experimental Section

In a glovebox under argon atmosphere, a mixture of freshly filed dysprosium metal (82 mg, 0.5 mmol, 1.0 equiv), $AlCl_3$ (200 mg, 1.5 mmol, 3 equiv), and benzofulvene **1** (0.65 mmol, 1.3 equiv) was prepared in a Schlenk tube. After addition of THF (1.5 mL) and a small piece of iodine, the mixture was stirred for 2 h at room temperature. Benzaldehyde (0.5 mmol, 1.0 equiv) was added and stirring continued for another 3 h. The reaction was quenched with aq. HCl (1 M, 5 mL) and extracted with diethyl ether (15 mL × 3) and the combined organic phase was dried over anhyd. $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE 5:95–20:80).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–F activation · difluoroalkenes · lanthanides · pentadienyl complexes · spirocycles

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