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C–F Activation

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Nickel-Catalyzed Cyclization of Difluoro-Substituted 1,6-Enynes with Organozinc Reagents through the Stereoselective Activation of C–F Bonds: Synthesis of Bicyclo[3.2.0]heptene Derivatives[**]

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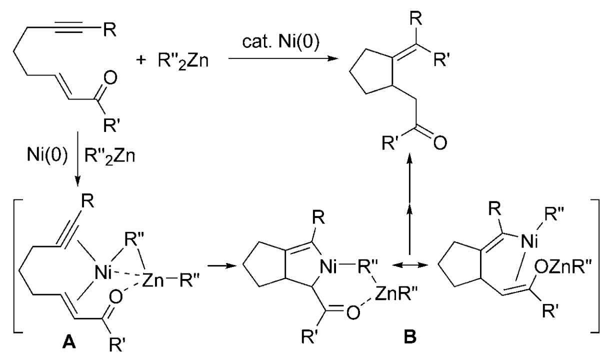
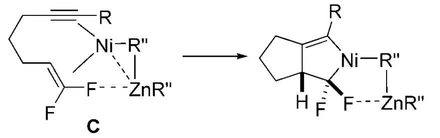
Multicomponent reactions have been a subject of intense study because they provide for a variety of transformations that are not easily achieved by current methods.[1] Among such reactions, transition-metal-catalyzed three-component coupling reactions of alkynes (or dienes), electron-deficient olefins (having ketone, ester, imide, and nitro groups at the olefinic moiety), and organometallic reagents (or metal hydrides) have been extensively studied because such alkylative (or reductive) coupling results in the stereoselective formation of synthetically important skeletons in a one-pot reaction.[2–6] In 1994, Ikeda and Sato reported on the nickel-catalyzed intermolecular coupling of alkynes, enones, and organostannanes.[3a] Montgomery and Savchenko also reported the nickel-catalyzed cyclization of intramolecular alkynyl enones with organozinc reagents leading to alkylative cyclization products (Scheme 1).[4a] At the initial stage, a nickelacycle, simply derived from the oxidative cyclization of an intramolecular alkynyl enone and Ni^0, was proposed as a potential intermediate. However, based on computational investigations, they concluded that organozinc is also involved in the oxidative cyclization step. Thus, an alternate mechanism that involves both the Lewis acid activation of the carbonyl oxygen atom and the Lewis base activation of a Ni^0 species by the organozinc, as shown in **A**, was proposed.[7] The involvement of an organozinc species may accelerate the oxidative cyclization leading to the production of **B**, which then undergoes reductive elimination/protonation to give the final product. Lei and co-workers recently reported the nickel-catalyzed reductive cyclization of simple, nonactivated enynes through the use of $i\mathrm{Pr}_2\mathrm{Zn}$, and proposed that the transmetalation of a C–Ni bond with $i\mathrm{Pr}_2\mathrm{Zn}$ occurs.[8]



Scheme 1. Nickel-catalyzed alkylative cyclization of enynes.

We became interested in reactions of difluoro-substituted enynes with organozinc reagents, as a fluorine atom at the olefinic terminus may also interact with the organozinc (**C**; Scheme 2) in a manner analogous to a carbonyl group. The fluorine atom would also affect the reactivity of the olefin component in terms of electronic factors.[9] Herein we report an unprecedented cyclization of 1,6-enynes bearing a gem-difluoro group at the olefinic terminus that leads to the formation of bicyclo[3.2.0]heptene derivatives, in which one of the fluorine atoms is stereoselectively replaced by the R″ group of $\mathrm{R''_2Zn}$. Although the cross-coupling reaction of C–F bonds is known,[10] the present reaction involves a new type of coupling reaction with cyclization.



Scheme 2. Working hypothesis.

The reaction of **1a** with $\mathrm{Et_2Zn}$ in the presence of $[\mathrm{Ni(cod)_2}]/\mathrm{PCy_3}$ (cod = 1,5-cyclooctadiene) as the catalyst in 1,4-dioxane at 50 °C for 2 hours gave **2a**,[11] as the sole product, in 56 % yield (Scheme 3). Products containing an ethyl group were not detected.[12] The use of $\mathrm{PPh_3}$ improved the product yield to 77 %. $\mathrm{P(4\text{-}MeOC_6H_4)_3}$ was found to be the ligand of choice given the following results: $\mathrm{P(4\text{-}MeOC_6H_4)_3}$ gave 83 % **2a**; $\mathrm{P(4\text{-}CF_3C_6H_4)_3}$ gave 75 % **2a**; $\mathrm{PPh_3}$ gave 77 % **2a**; $\mathrm{P(2\text{-}MeC_6H_4)_3}$ and $\mathrm{P}t\mathrm{Bu_3}$ each gave complex reaction mixtures. A comparable yield (76 %) was observed when THF was used as a solvent. The use of other solvents also gave the product, albeit in less satisfactory yields [toluene 60 %; DMA 51 % (DMA = *N,N*-dimethylaniline)].

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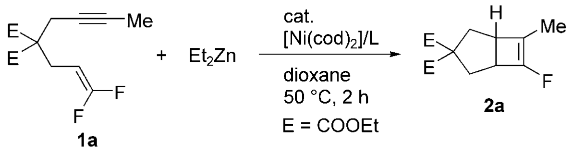
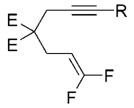
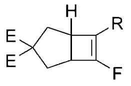
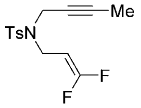
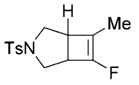
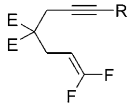
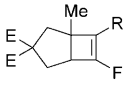
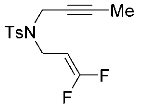
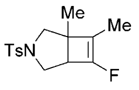
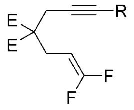
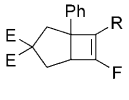
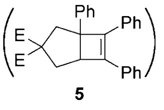


Scheme 3.

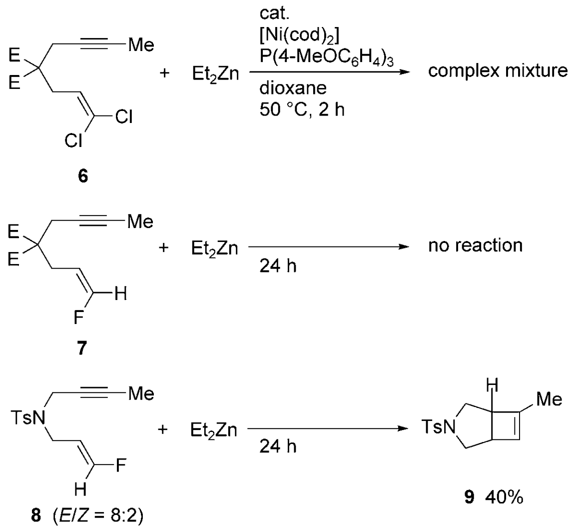
The results of the reaction of various difluoro-substituted enynes with organozinc reagents are shown in Table 1. Enynes bearing internal alkynes served as good substrates in the reaction with Et$_2$Zn, and the corresponding bicyclo[3.2.0]heptene derivatives **2a**–**2e** (entries 1–5) were obtained in high yields (72–83% yields). The structure of the product was confirmed by X-ray analysis of **2d**.[13] Use of a terminal alkyne as in **1f** also resulted in the corresponding reductive cyclization product **2f** (entry 6). An enyne having a nitrogen functionality in the tether (e.g., **1g**) also gave the corresponding cyclobutene **2g** (entry 7) in 65% yield. As expected, the use of Me$_2$Zn resulted in methylative cyclization to give products **3** (entries 8–11). It was found that a phenyl group can also be introduced at a bridgehead by the use of Ph$_2$Zn to give products **4** (entries 12–14). However, the reaction of **1c** with Ph$_2$Zn gave a mixture of **4c** and **5** (entry 13). The reaction of **4c** under standard reaction conditions did not give **5**. A route to the formation of **5** is not clear at present.

Table 1: Nickel-catalyzed reaction of difluoro-substituted 1,6-enynes with organozinc reagents.[a]

Entry	Difluoro enyne	R$_2$Zn	Product[b]
		Et$_2$Zn	
1	R = Me (**1a**)		**2a** (83%)
2	R = cyclopropyl (**1b**)		**2b** (81%)
3	R = Ph (**1c**)		**2c** (83%)
4	R = 2-naphthyl (**1d**)		**2d** (72%; 4 h)
5	R = SiMe$_3$ (**1e**)		**2e** (77%; 4 h)
6	R = H (**1f**)		**2f** (41%)
		Et$_2$Zn	
7	**1g**		**2g** (65%)
		Me$_2$Zn	
8	R = Me (**1a**)		**3a** (86%)
9	R = Ph (**1c**)		**3c** (63%)
10	R = H (**1f**)		**3f** (31%)
		Me$_2$Zn	
11	**1g**		**3g** (80%; 6 h)
		Ph$_2$Zn	 () **5**
12	R = Me (**1a**)		**4a** (50%; 5 h)
13	R = Ph (**1c**)		**4c** (42%) + **5** (14%)
14	R = H (**1f**)		**4f** (28%)

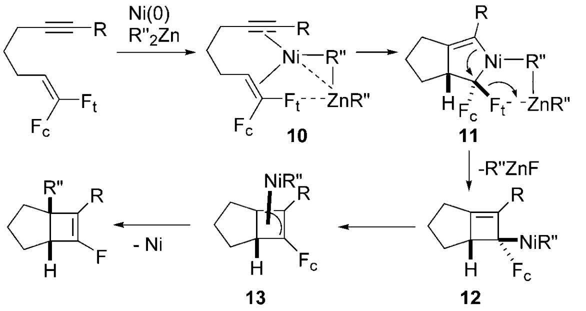
[a] Reaction conditions: difluoro-substituted 1,6-enyne (0.3 mmol), organozinc (0.636 mmol), [Ni(cod)$_2$] (0.015 mmol), P(4-MeOC$_6$H$_4$)$_3$ (0.06 mmol), 1,4-dioxane (1.5 mL) at 50 °C for 2 h. [b] Yields of isolated products.

We investigated the reaction of **6**, a chloro analogue of **1a**, under the standard reaction conditions, but a complex mixture was obtained, indicating that the presence of a fluorine atom is required for the reaction to proceed (Scheme 4). We next examined whether two fluorine atoms were required for the reaction to occur by using monofluoro-substituted enynes **7** and **8**. Interestingly, only the *trans* isomer **8** gave the corresponding product **9**, but the *cis* isomer **7** was completely unreactive. Although the reaction involves the stereoselective activation of a *trans* C–F bond, the reaction required an extended period of time for completion [compare **1g** (2 h) and **7** (24 h)], indicating that the presence a *cis* fluorine atom also has a significant effect on the reactivity of the substrate, even though the *cis* fluorine atom itself does not appear to participate in the reaction.



Scheme 4. Halogen atom effects. Ts = 4-toluenesulfonyl.

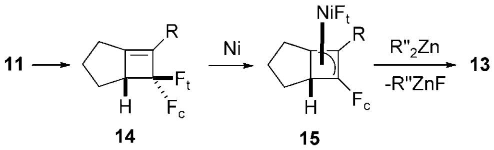
A proposed mechanism for the reaction is shown in Scheme 5. The intermediate **10**, corresponding to **C** as shown in Scheme 2, is proposed as the key intermediate in which Ni is activated by a Lewis base interaction with the R″ group on the organozinc, and the olefin is activated by a Lewis acid through coordination of the fluorine atom to Zn.[14] In the latter activation, only the *trans* C–F bond can coordinate to Zn. Both activations by organozinc facilitate the oxidative cyclization leading to the production of the nickelacyclopentene **11**,[15] which is then transformed into the σ-allyl nickel complex **12**. Reductive elimination directly from **12** or from the π-allyl nickel complex **13**[16] gives the final product. In the case of Et$_2$Zn, β-hydride elimination occurs in **12** or **13** to



Scheme 5. Proposed reaction mechanism. F_t = *trans* F, F_c = *cis* F.

introduce a hydride. This mechanism explains the experimental results showing that the stereoselective cleavage of the *trans* C–F bond occurred, as shown in Scheme 4.

An alternative mechanism is depicted in Scheme 6. The reductive elimination from **11** gives cyclobutene **14**, which again reacts with Ni^0 in a *syn* fashion to give the π-allyl nickel fluoride complex **15**. Transmetalation of **14** with R'_2Zn leading to **13** and subsequent reductive elimination affords the final product. However, the formation of a π-allyl nickel complex by the reaction of allyl fluorides with Ni^0 has been reported in only one paper and provided no details.[16,17] Although this alternative mechanism cannot be excluded, the path from **14** to **15**, which proceeds in a *syn* fashion, is not likely.



Scheme 6. Alternative steps.

In summary, we report the development of a new catalytic system based on the assumption that organozinc functions as both a Lewis base with respect to Ni^0 and a Lewis acid with respect to the C–F bond. As a result, an unprecedented type of cyclization using difluoro-substituted 1,6-enynes was achieved. The nickel-catalyzed reaction of difluoro-substituted enynes with organozinc reagents gives bicyclo-[3.2.0]heptene derivatives, in which one of the fluorine atoms is replaced in a stereoselective manner by the R'' group of R''_2Zn. The reaction involves the regioselective activation of C–F bonds. The extension of the methodology[18] to the coupling of difluoro-substituted enynes with other organometallic reagents and reducing reagents is currently underway.

Experimental Section

General procedure for nickel-catalyzed reaction of difluoro-substituted 1,6-enynes with organozinc reagents: The enyne (0.3 mmol), $[Ni(cod)_2]$ (0.015 mmol), and $P(4\text{-}MeOC_6H_4)_3$ (0.06 mmol) were introduced into a 10 mL two-necked round-bottom flask, and then dissolved in 1,4-dioxane (1.5 mL). The organozinc (0.636 mmol; 1.06 M Et_2Zn in *n*-hexane, 2.0 M Me_2Zn in toluene, Ph_2Zn solid) was then added to the flask, and the flask was immersed in an oil bath at 50 °C. The reaction was monitored by GC methods. After the starting enyne had disappeared, the flask was cooled to room temperature, the solvent removed by evaporation, and the product was separated by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1). In the reaction with Me_2Zn, a 10 mL screw-top vial was used in place of a 10 mL two-necked round-bottom flask. When a 10 mL two-necked round-bottom flask was used, yields were dramatically decreased.

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Keywords: C–F activation · cyclization · enynes · nickel · organozinc

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[12] Use of *N*,*N*-tetramethylethylenediamine as a ligand in the reaction of **1a** gave an ethylation product in 52% yield. This catalytic system was not applicable to other reactions.

[13] CCDC 762355 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi..

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