Aldol Reaction

International Edition: DOI: 10.1002/anie.201508266
German Edition: DOI: 10.1002/ange.201508266

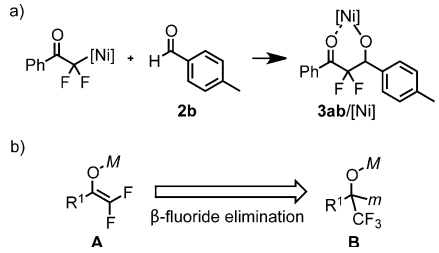
Copper-Catalyzed Reaction of Trifluoromethylketones with Aldehydes via a Copper Difluoroenolate

*Ryohei Doi, Masato Ohashi, and Sensuke Ogoshi**

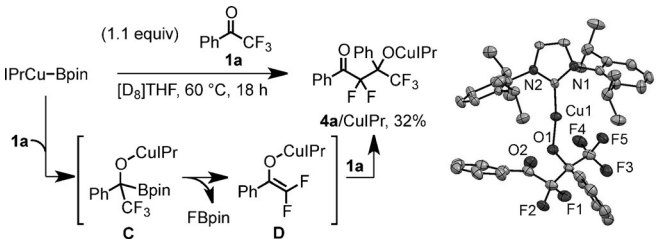
Abstract: *A copper-catalyzed reaction of easily accessible α,α,α-trifluoromethylketones with various aldehydes affords difluoro-methylene compounds in the presence of diboron and NaOtBu. The key process of the reaction is the formation of a copper difluoroenolate by 1,2-addition of a borylcopper intermediate to α,α,α-trifluoromethylketones and subsequent β-fluoride elimination. Mechanistic studies including the isolation and characterization of a possible anionic copper alkoxide intermediate are also described.*

Difluoroenolates are powerful synthetic tools for preparing difluoro-methylene compounds which are important intermediates or products in medicinal chemistry.[1] Several protocols to generate difluoroenolates by the Reformatsky reaction using relatively expensive α-bromo-α,α-difluorocarbonyl compounds and other stepwise procedures have been reported.[2–4] Herein, we disclose the copper-catalyzed reactions of trifluoromethylketones with aldehydes via a copper difluoroenolate which enables direct transformation of trifluoroacetic acid derivatives into difluoro-methylene compounds. A possible reaction path concerning the reactivity and equilibrium of difluoroenolate is also discussed based on the mechanistic studies.

We have previously reported a novel synthetic method of a nickel difluoroenolate [(PhCOCF$_2$)Ni(dcpe)][FB(C$_6$F$_5$)$_3$] [dcpe = 1,2-bis(dicyclohexylphosphino)ethane] by B(C$_6$F$_5$)$_3$-promoted C–F bond activation of α,α,α-trifluoroacetophenone (**1a**), which is coordinated to nickel(0) (Scheme 1a).[5] Furthermore, a rapid C–C bond-forming reaction of the nickel difluoroenolate with 4-tolualdehyde (**2b**) occurred quantitatively to afford the aldol product **3ab**/[Ni]. However, B(C$_6$F$_5$)$_3$ could not be regenerated because of the stability of the B–F bond of which formation was the driving force behind the C–F bond-cleavage step. Another efficient method for cleaving a C–F bond is β-fluoride elimination, which is known to proceed under relatively mild reaction conditions.[6] With this strategy in mind, the retrosynthetic analysis suggested the α-metallated alkoxide **B** as a synthon of a difluoroenolate (**A**; Scheme 1b). Sadighi reported that the 1,2-addition of [(IPr)CuBpin] [IPr = 1,3-bis(2′,6′-diisopropylphenyl)imidazole-2-ylidene, pin = 2,3-dimethyl-2,3-butanediolate] to an aldehyde generates an α-borylated copper alkoxide in situ.[7,8] Inspired by this reaction, we conducted the reaction of [(IPr)CuBpin] with **1a** to observe the copper alkoxide **4a**/CuIPr in a 32% yield (Scheme 2). The molecular



Scheme 1. a) The C–C bond formation of a nickel difluoroenolate with **2b**. [Ni] = [Ni(dcpe)][FB(C$_6$F$_5$)$_3$]. b) Retrosynthetic analysis of the difluoroenolate **A** (M, m = metal).



Scheme 2. Reaction of [(IPr)CuBpin] with **1a** via formation of the copper difluoroenolate **D**. Molecular structure of **4a**/CuIPr. THF = tetrahydrofuran. Thermal ellipsoids are shown at 30% probability and hydrogen atoms were omitted for clarity.

structure of **4a**/CuIPr was confirmed by X-ray crystallography.[9] This result suggests the formation of the difluoroenolate **D** via the intermediate **C**. Motivated by this outcome, we attempted the reaction of **1a** with the aldehyde **2b** in the presence of a catalytic amount of CuCl, IPr, and NaO*t*Bu, and 1.5 equivalents of bis(pinacolato)diboron (B$_2$pin$_2$), and it afforded a trace amount of the coupling product **3ab**/Bpin along with a 4% yield of the homoadduct **4a**/Bpin (see Table S1 in the Supporting Information).[10] By increasing the amount of NaO*t*Bu to 0.6 and 1.5 equivalents, the yield of **3ab**/Bpin was improved to 32 and 56%, respectively. Next, several auxiliary ligands were screened. Various phosphine ligands were tested, however the yields were compatible to that obtained in the absence of a ligand. Contrary to these results, nitrogen-based ligands such as 1,10-phenanthroline (Phen), 2,2′-bipyridine, and 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline, BPhen) improved the yields to 81–82%. The choice of an inorganic base was also crucial:

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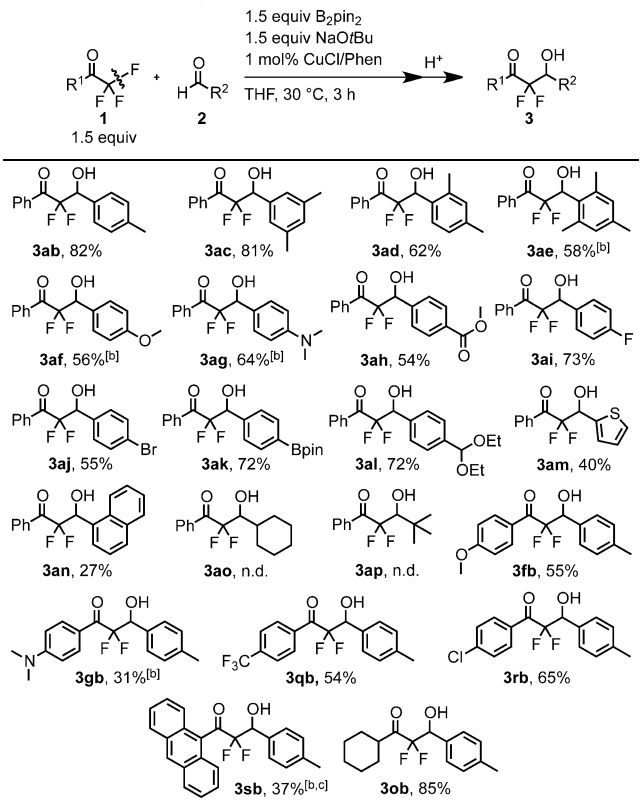
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201508266.

a reaction using LiO*t*Bu resulted in a lower yield and KO*t*Bu gave a trace amount of **3ab**/Bpin. The reaction even proceeded at 30 °C, and no reaction occurred in the absence of copper catalyst.

The catalyst loadings could be reduced to 1 mol %, and with these reaction conditions the corresponding alcohol product **3ab** was isolated in an 82 % yield (Table 1). Then, we

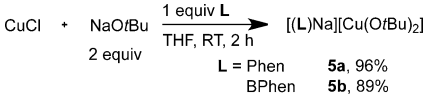
Table 1: Substrate scope.[a]



[a] Yields of isolated purified products. n.d. = not detected. [b] Reaction was conducted at 60 °C. [c] Reaction time was 24 h.

explored the substrate scope of this reaction. The reaction was affected by the steric hindrance of benzaldehydes (**3ac**, **3ad**, **3ae**). The reactions of benzaldehydes bearing an electron-donating methoxy (**2f**) and an *N*,*N*-dimethylamino group (**2g**) gave the corresponding products **3af** (56 %) and **3ag** (64 %). Functional groups such as ester (**3ah**), fluorine and bromine attached to the aromatic ring (**3ai**, **3aj**), Bpin (**3ak**), and acetal (**3al**) survived under the reaction conditions. 2-Thiophenecarboxaldehyde and 1-naphthaldehyde also gave the desired products **3am** and **3an**, respectively. Contrary to aromatic aldehydes, aliphatic aldehydes such as **2o** and **2p** could not be applied to these reaction conditions. We next examined the scope of the trifluoromethyl ketone. The reactions of trifluoroacetophenones bearing an electron-donating methoxy, *N*,*N*-dimethylamino group and an electron-withdrawing CF_3 group afforded the desired products **3fb**, **3gb**, and **3qb** in moderate yields. The reaction of **1r**, bearing chlorine at the 4-position of the benzene ring, afforded the product **3rb**, and the C–Cl bond was not reduced under the same reaction conditions. The bulky ketone **1s** afforded the corresponding product **3sb** in a 37 % yield even at 60 °C. The cyclohexyl trifluoromethyl ketone **1o** reacted with **2b** to yield coupling product **3ob** in an 85 % yield. Although NMR analysis of crude reaction mixtures indicated full conversions of aldehydes, the formation of some unidentified by-products was observed, and possibly account for decreased yields. Ethyl trifluoroacetate could not be applied under the reaction conditions.

To gain deeper insights into the reaction mechanism, a mixture of CuCl and Phen was treated with excess NaO*t*Bu in [D_8]THF. NMR analysis of the reaction mixture indicated the formation of a complex bearing two *t*BuO groups relative to Phen. In fact, [(L)Na][Cu(O*t*Bu)$_2$] (**5**, where L = Phen or BPhen) was successfully isolated from the reaction of CuCl, ligand, and 2 equivalents of NaO*t*Bu (Scheme 3).[11] The



Scheme 3. Formation of the complexes **5**.

crystal structures of **5** were determined by X-ray crystallography (for **5b** see Figure 1; and, for **5a** see the Supporting Information).[9] The complexes formed dimers through coordination of *t*BuO groups to sodium atoms. The copper atoms

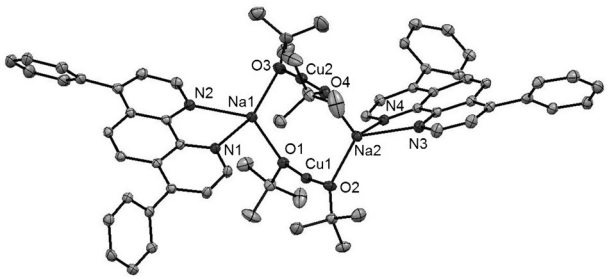
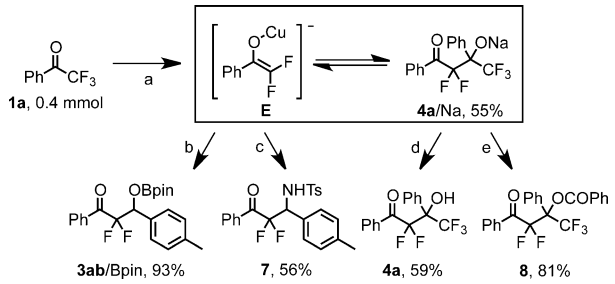


Figure 1. The molecular structure of complex **5b**.Thermal ellipsoids are shown at 50 % probability and hydrogen atoms were omitted for clarity. Selected bond lengths [Å]: Cu1–O1 1.820(3), Cu1–O2 1.819(3), Na1–O1 2.241(3), Na1–O3 2.208(3), Na1–N1 2.417(3), Na1–N2 2.470(3), angles [°]: O1-Cu1-O2 170.14(10), O1-Na1-O3 118.15(11), O1-Na1-N1 96.29(10), O1-Na1-N2 129.19(10), O3-Na1-N1 124.59(11), O3-Na1-N2 109.95(11), N1-Na1-N2 67.26(10).

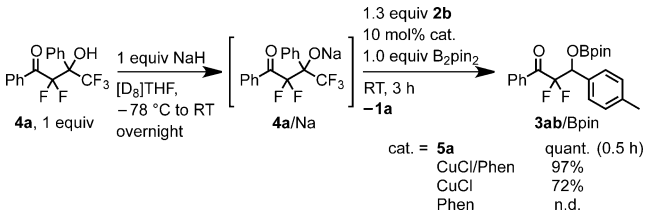
adopted a two-coordinate linear structure while the conformation of the sodium atoms could be described as a distorted tetrahedral coordinated by either Phen or BPhen and two *t*BuO groups. It is noteworthy that **5a** acts as a catalyst in our system.

In the catalytic reaction, the addition of a difluoroenolate to either a trifluoromethylketone (**1**) or aldehyde (**2**) could occur. We monitored the reaction, by NMR spectroscopy, in the absence of an aldehyde and observed the sodium alkoxide of homoadduct **4a**/Na in a 55 % yield along with some unidentified products (Scheme 4). It merits note that **4a**/Bpin was not detected even though ^{11}B NMR analysis revealed the



Scheme 4. Generation, reactivity, and equilibrium of **4a**/Na. Reaction conditions: a) 5 mol% CuCl/Phen, 1 equiv B_2pin_2, 1 equiv NaO*t*Bu, [D_8]THF, RT, 30 min. b) 0.27 mmol aldehyde **2b**, RT, 12 h. Yield is based on **2b**. c) 0.2 mmol imine **6**, RT 5 h, then $NaOH_{aq.}$ Yield of the isolated product is given. d) Excess *i*PrOH, RT, 5 min. Yield is based on **1a**. e) 0.2 mmol benzoyl chloride, RT, 9 h. Yield is based on benzoyl chloride.

existence of a considerable amount of residual B_2pin_2. These observations indicate the sluggish transmetallation of **4a**/Na with B_2pin_2 under the catalytic reaction conditions. The addition of the aldehyde **2b** resulted in the formation of the cross-adduct **3ab**/Bpin in a high yield even at room temperature (Scheme 4). An analogous reaction with *N*-(4-*m*ethylbenzylidene)-4-methylbenzenesulfonamide (**6**) afforded the corresponding product **7** (Scheme 4). In contrast, protonolysis of the reaction mixture did not afford $PhCOCF_2H$, but did afford the alcohol **4a** (Scheme 4). The alkoxide **4a**/Na was also trapped by the addition of benzoyl chloride to deliver the ester **8** (Scheme 4). These observations indicate that in the presence of anionic copper species like **5a**, **4a**/Na is in equilibrium with the anionic enolate **E** which produces **3ab**/Bpin by a reaction with **2b**. In fact, in the presence of a catalytic amount of **5a** and a stoichiometric amount of B_2pin_2, the reaction of **2b** with **4a**/Na, which was generated by treatment of **4a** with NaH, yielded **3ab**/Bpin quantitatively (Scheme 5). In this case, we confirmed formation of **1a** by



Scheme 5. Copper-catalyzed reaction of **4a**/Na with **2b** in the presence of B_2pin_2.

means of ^{19}F NMR analysis. The reaction also proceeded in the presence of 10 mol% of either CuCl/Phen or CuCl, whereas the product was not obtained at all in the absence of CuCl.

A possible reaction mechanism is depicted in Figure 2. First, the reaction of CuCl, Phen, and NaO*t*Bu gives the cuprate **5a**. Reaction of **5a** with B_2pin_2 affords an anionic borylcopper species **F** which reacts with **1** to give the intermediate **G**. β-Fluoride elimination of **G** affords the

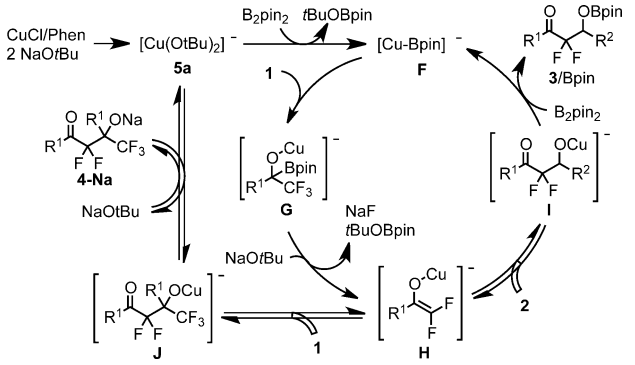


Figure 2. A possible reaction mechanism.

difluoroenolate **H**. In this step, NaO*t*Bu would act as a promoter of β-fluoride elimination since the β-fluoride elimination of a fluoroalkyl copper complex is promoted by the addition of sodium salt.[6k] The reaction of **H** with **2** gives the alkoxide **I**, which reacts with B_2pin_2 to generate the cross-adduct **3**/Bpin.[12] The enolate **H** also can react with **1** to form the alkoxide **J** which is in equilibrium between **4**/Na and **5a** in the presence of NaO*t*Bu. The selective formation of **3** could be rationalized by the equilibrium and the difference in basicity between **I** and **J**. The alkoxide **I** is sufficiently basic to give a thermodynamically stable borate ester of cross-adduct **3**/Bpin, while the reaction of **J** with B_2pin_2 is much slower, probably because of the electron-withdrawing nature of five fluorine atoms attached to the β-carbon atoms.

In summary, we have achieved the copper-catalyzed reaction of trifluoromethylketone with aldehyde by C–F bond cleavage using B_2pin_2 as a reductant in the presence of NaO*t*Bu. This novel methodology is a potential alternative to the known procedures for synthesis of difluoro compounds by circumventing the use of expensive mixed-halogen compounds and lengthy procedures. Further exploration on the improvement of yields, scope, and extension to an asymmetric version are currently underway in our group. The catalytic reaction was highly selective to give the cross-adducts, although the copper difluoroenolate generated in situ reacts with either trifluoromethylketone to give the homoadducts or aldehyde to give the cross-adducts. The mechanistic investigation rationalized this high selectivity by revealing the existence of an equilibrium between alkoxides of the homo-adducts and those of cross-adducts, which more easily give the thermodynamically stable borate ester rather than those of homo-adducts.

Acknowledgements

This work was supported by a Grant-in-Aid for Young Scientist (A) (25708018) and Scientific Research on Innovative Area "Molecular Activation Directed toward Straightforward Synthesis" (23105546) from MEXT, and ACT-C from JST. R.D. is grateful for support as a JSPS Research Fellow.

Keywords: aldol reaction · boron · C–F activation · copper · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 341–344
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[12] We confirmed that **3ab** produces **2b** under the catalytic reaction conditions in the presence of the aldehyde **2i**. Therefore, the addition of **H** with **2** would be reversible.

Received: September 4, 2015
Revised: September 15, 2015
Published online: October 30, 2015

