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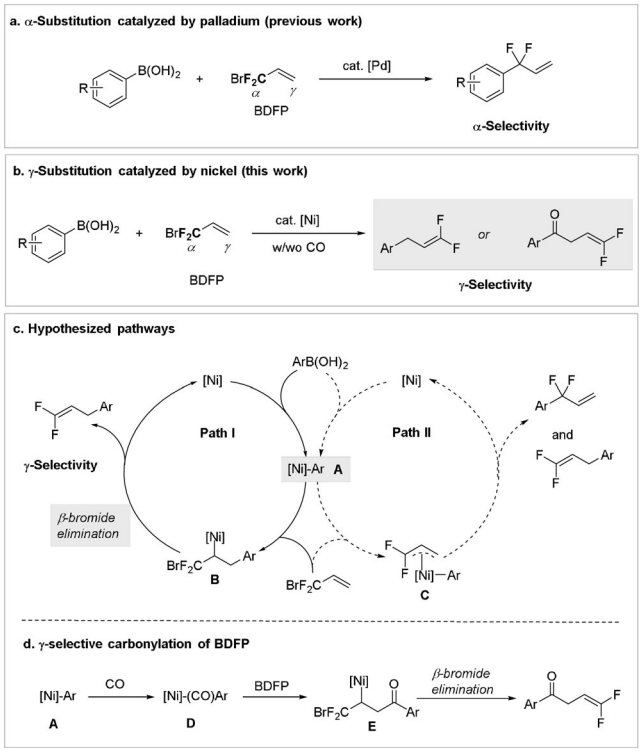
Highly γ-Selective Arylation and Carbonylative Arylation of 3-Bromo-3,3-difluoropropene via Nickel Catalysis

Ran Cheng, Yueqian Sang, Xing Gao, Shu Zhang, Xiao-Song Xue, and Xingang Zhang**

Abstract: *A nickel-catalyzed highly γ-regioselective arylation and carbonylative arylation of 3-bromo-3,3-difluoropropene has been developed. The reaction proceeds under mild reaction conditions, providing the gem-difluoroalkenes with high efficiency and good functional group tolerance. The resulting gem-difluoroalkenes can serve as versatile building blocks for diversified synthesis. Preliminary mechanistic studies and density functional theory calculations reveal that both non-radical and radical pathways are possible for the reaction, and the radical pathway is more likely. The high γ-regioselectivity results from the β-bromide elimination of alkylnickel(II) species or from the reductive elimination of nickel(III) species [(aryl)(CF_2=$CHCH_2$)$Ni^{III}(L_n)X$]. The γ-selective carbonylation of 3-bromo-3,3-difluoropropene under 1 atm CO gas also provides a new way for nickel-catalyzed carbonylation.*

Introduction of one or more fluorine atoms into organic molecules can dramatically change their physical, chemical, and biological properties.[1] Specifically, the binding of fluorinated groups at different sites in the same organic molecule can also lead to different properties. Therefore, extensive efforts have been made to develop general and efficient methods for controllable incorporation of fluorinated groups into organic compounds.[2] In addition to the traditional fluoroalkylating reactions,[3] recently, transition-metal-catalyzed fluoroalkylations have emerged as an attractive strategy to construct C–R_f bonds (R_f = fluoroalkyl).[2a–c,4] Among these catalytic methodologies, however, the controllable site-selective fluoroalkylation by the same fluoroalkylating reagent to access different fluorinated isomers has only been reported scarcely. One of the possible reasons is the lack of efficient catalytic systems and suitable fluoroalkylating reagents to discriminate one reaction site among the multiple functional bonds.

3-Bromo-3,3-difluoropropene (BDFP)[5] is a useful building block owing to the synthetic versatility of its carbon–carbon double bond and tunable reaction sites. Efficient methods that enable the highly selective substitution on both α- and γ-sites of BDFP would provide structural diversified fluorinated compounds of great interest in medicinal chemistry and advanced functional materials. Recently, we developed an efficient method for the highly α-selective arylation of BDFP with arylboronic acids using a palladium catalyst, representing the first example of catalytic synthesis of *gem*-difluoroallylated arenes with BDFP (Scheme 1a).[6] Considering that the nature of the palladium catalyst is critical for the high α-substitution selectivity of BDFP, we envisioned that using a different transition-metal catalyst to modulate the reactivity of arylboronic acids towards BDFP would make it possible to access *gem*-difluoroalkenes, γ-substituted BDFP products (Scheme 1b), a versatile structural motif that has



Scheme 1. Transition-metal-catalyzed regioselective substitution of 3-bromo-3,3-difluoropropene.

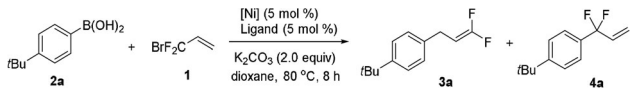
[*] R. Cheng, X. Gao, Prof. Dr. X. Zhang
Key Laboratory of Organofluorine Chemistry
Center for Excellence in Molecular Synthesis
Shanghai Institute of Organic Chemistry
University of Chinese Academy of Sciences
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: xgzhang@mail.sioc.ac.cn
Y. Sang, Prof. Dr. X.-S. Xue
College of Chemistry, Nankai University
Tianjin 300071 (P. R. China)
E-mail: xuexs@nankai.edu.cn
Prof. Dr. S. Zhang
School of Materials and Energy
University of Electronic Science and Technology of China
2006 Xiyuan Avenue, West High-Tech Zone, Chengdu, Sichuan 611731 (China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202015921.

important applications in medicinal chemistry and advanced functional materials.[7]

The common methods to synthesize *gem*-difluoroalkenes rely on the difluoromethylenation of aldehydes and ketones[8] or β-F elimination of trifluoromethylated compounds.[8a,9] Following our studies on the nickel-catalyzed fluoroalkylation reactions,[10] we hypothesized that the γ-selective substitution of BDFP could be obtained by choosing an appropriate nickel catalyst, which can facilitate the transmetalation of nickel with arylboronic acid,[11] followed by insertion of the resulting arylnickel complex [Ar-Ni] (**A**) into the carbon–carbon double bond and β-bromide elimination (Scheme 1c, path I). Furthermore, this strategy could also be extended to the γ-selective carbonylation of BDFP (Scheme 1b), as we recently found that the [Ar(CO)Ni^{II}(L$_n$)X] complex (**D**) could be easily formed between [Ar–Ni^{II}] species and CO,[11] which may benefit the γ-selective carbonylation of BDFP through a similar pathway as mentioned above (Scheme 1d). One crucial issue to be addressed in this strategy is how to suppress the competitive α-substitution of the BDFP reaction (Scheme 1c, path II). We carried out a systematic investigation to resolve this challenge. Herein, we describe a nickel-catalyzed, highly γ-selective arylation and carbonylation of BDFP, providing an efficient access to *gem*-difluoroalkenes.

On the basis of the above hypothesis, we began this study by choosing (4-(*tert*-butyl)phenyl)boronic acid **2a** as a model substrate (Table 1). We found that the combination of $NiCl_2$·DME (5 mol%) with 1,10-phenathroline (phen, 5 mol%) in the presence of K_2CO_3 in dioxane at 80°C could provide the γ-selective product **3a** in 48% yield, with only trace amounts of α-selective product **4a** observed (Table 1, entry 1). Further examination of different ligands (for details, see the Supporting Information) showed that 2,2′-bypyridine (bpy) performed better than others, providing **3a** in 86% yield with excellent γ-selectivity (γ/α = 86:1, Table 1, entry 2), but no product was observed with tripyridine (tpy) as the ligand (Table 1, entry 3). The reaction was also sensitive to the nickel sources. $NiCl_2$·DME turned out to be the optimal one in terms of yield and regioselectivity (see the Supporting Information). Among the tested solvents and bases, THF and Cs_2CO_3 could also afford **3a** in comparable yields (see the Supporting Information), thus providing complementary reaction conditions. Finally, an 84% isolated yield of **3a** with almost single γ-selectivity was obtained by prolonging the reaction time to 24 h (Table 1, entry 5). Under these reaction conditions, good repeatability of the reaction could be obtained. No product was observed in the absence of nickel catalyst (Table 1, entry 6) and only 6% yield of **3a** was obtained without ligand (Table 1, entry 7), thus demonstrating the essential role of [Ni/L] in promoting the reaction.

Table 1: Representative results for the optimization of Ni-catalyzed 3,3-difluoroallylation of arylboronic acids.[a]

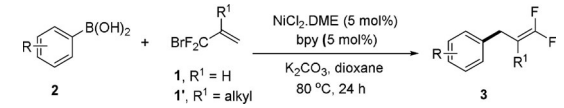


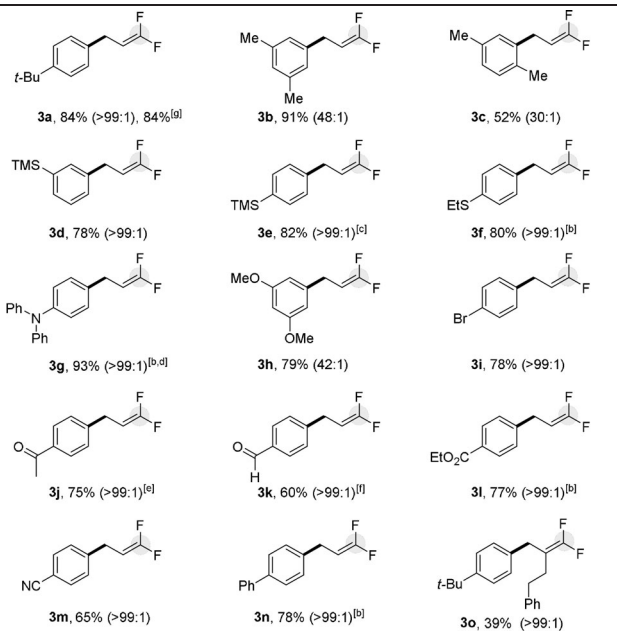
entry	[Ni]	Ligand	**3a**/**4a**, yield [%][b]
1	$NiCl_2$·DME	Phen	48/traces
2	$NiCl_2$·DME	Bpy	86/1
3	$NiCl_2$·DME	Tpy	nd/nd
4	$NiBr_2$·DME	Bpy	30/traces
5[c]	$NiCl_2$·DME	Bpy	86 (84)/trace
6	none	Bpy	nd/nd
7	$NiCl_2$·DME	none	6/1

[a] Reaction conditions (unless otherwise specified): **2a** (0.9 mmol, 1.50 equiv), **1** (0.6 mmol, 1.0 equiv), dioxane (4 mL), 8 h. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard, the number in parentheses is the isolated yield; nd = not detected. [c] Reaction run for 24 h.

With viable reaction conditions in hand, we next examined the reaction of BDFP **1** with a variety of arylboronic acids (Table 2). Overall, good to high yields of *gem*-difluoroalkenes **3** with excellent γ-selectivity (γ/α = 30:1 to > 99:1) were obtained. Arylboronic acids bearing an electron-donating or an electron-withdrawing substituent showed reliable reaction efficiency. The nickel-catalyzed process exhibited good functional group tolerance. Versatile functional groups, such as trimethylsilyl, thioether, enolizable ketone, formyl, ester, and cyano moieties, were compatible with the reaction conditions (**3d**–**3f**, **3j**–**3m**). Importantly, an aryl-bromide-containing substrate was also a competent coupling partner and provided the corresponding product **3i** in 78% yield, thus offering opportunities for subsequent derivatization. The steric effect of the arylboronic acid slightly influenced the reaction efficiency, but moderate yield was still obtained (**3c**).

Table 2: Ni-catalyzed γ-selective arylation of *gem*-difluoropropene bromide with arylboronic acids.[a]



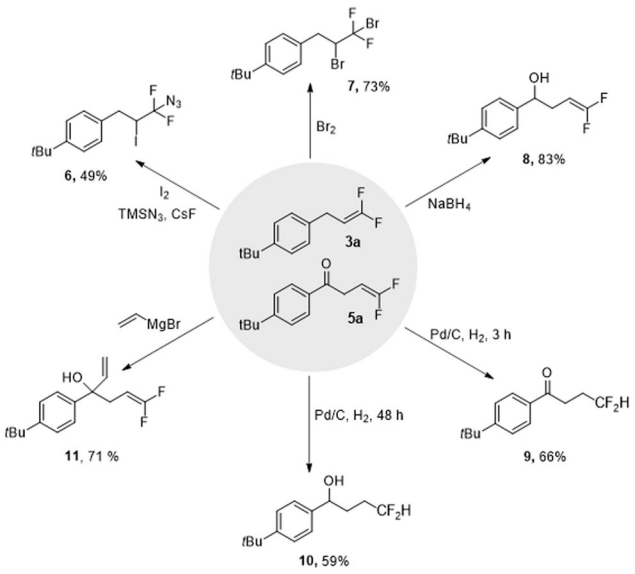


[a] Reaction conditions (unless otherwise specified): **2** (0.9 mmol, 1.5 equiv), **1** or **1′** (0.6 mmol, 1 equiv), K_2CO_3 (2.0 equiv), dioxane (4 mL). [b] Reaction run for 48 h. [c] 2 equiv of Cs_2CO_3 were used as base. [d] 2.0 equiv of CsF were used. [e] 0.5 equiv of H_2O was used. [f] THF was used as solvent. [g] Gram-scale reaction.

The reaction can be readily scaled up, as demonstrated by the gram-scale synthesis of **3a** without erosion of the reaction efficiency. Branch-substituted BDFP was also applicable to the reaction, providing the corresponding product **3o** in 39% yield without observation of the β-H elimination side product.

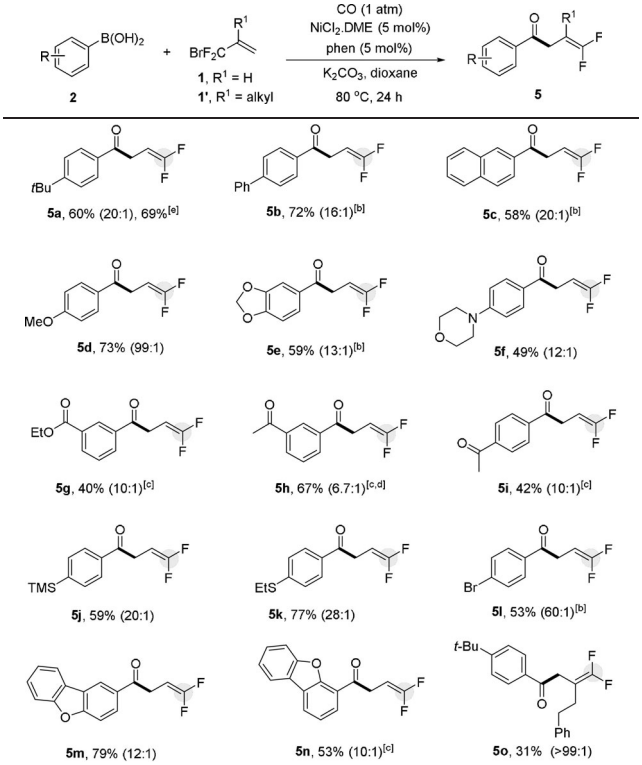
The high efficiency and excellent γ-selectivity of this nickel-catalyzed process encouraged us to evaluate the γ-selective carbonylation of BDFP. We found that the γ-selective carbonylation of BDFP could be obtained with high efficiency and moderate to excellent regioselectivity (γ/α = 6.7:1–99:1) under 1 atm of CO using $NiCl_2$·DME as the catalyst and phen as the ligand (Table 3). An even higher yield was obtained on gram-scale synthesis of the carbonyl compound (**5a**). These result suggests that the current catalytic system is highly compatible with the nickel-catalyzed carbonylation reaction using inexpensive CO gas, which remains challenging because of the easy formation of highly toxic and unreactive $Ni(CO)_4$ species.[12–14] Both electron-rich and electron-deficient arylboronic acids were applicable to the reaction, and good functional group tolerance was observed in such a transformation (**5f–5l**). However, for the electron-deficient substrates, moderate γ-selectivity was observed (**5g–5i**).

The resulting *gem*-difluoroalkenes **3** and **5** can serve as a versatile building block for the diversified synthesis of fluorinated compounds. As shown in Scheme 2, difunctionalization of the carbon–carbon double bond in **3a** with $TMSN_3$ and I_2 provided the azide-substituted difluoroalkylated compound **6** in synthetically useful yield. To the best of our knowledge, such a transformation has not been reported yet. The introduced azide and iodide moieties offer additional opportunities for downstream transformations. Bromination of **3a** efficiently produced difluoroalkyl bromide **7**, which could be employed as a good coupling partner for transition-metal-catalyzed cross-coupling reactions. The transformation of carbonyl compound **5a** was also conducted. Selective reduction of **5a** with $NaBH_4$ afforded alcohol **8** in 83% yield, while hydrogenation of **5a** over a short time (3 h) could provide difluoromethylated alkane **9** with the carbonyl intact. Prolonging the reaction time, both carbon–carbon double bond and carbonyl group in **5a** were reduced, providing difluoromethylated alcohol **10** in moderate yield. The nucleophilic addition of vinylmagnesium bromide to ketone **5a** also proceeded smoothly and furnished allylic alcohol **11** in 71% yield.



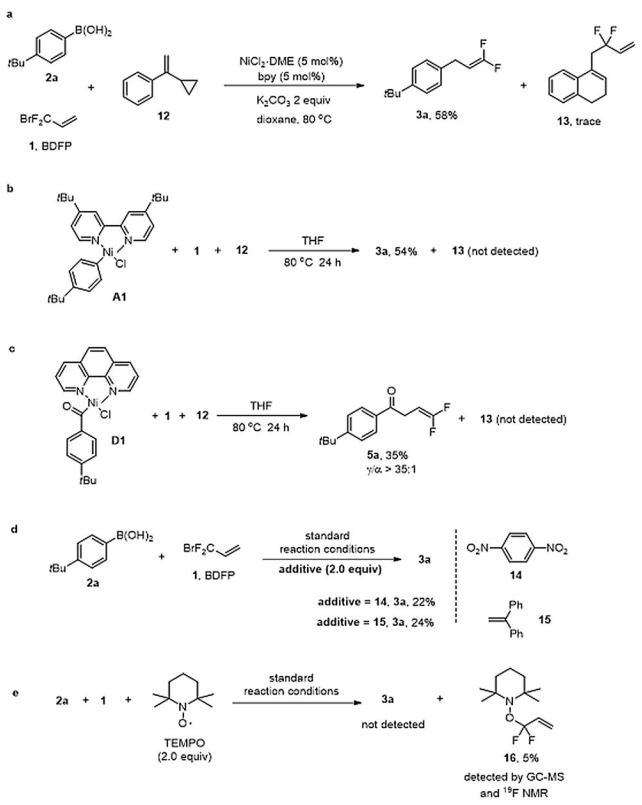
Scheme 2. Transformations of compounds **3a** and **5a**.

Table 3: Ni-catalyzed γ-selective carbonylation of *gem*-difluoropropene bromide with arylboronic acids under 1 atm of CO.[a]

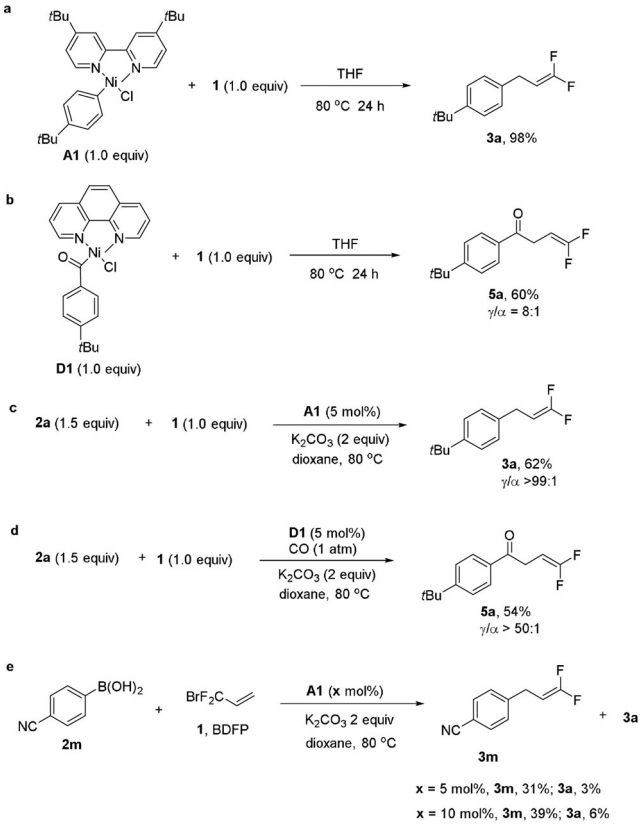


[a] Reaction conditions (unless otherwise specified): **2** (0.9 mmol, 1.5 equiv), **1** (0.6 mmol, 1 equiv), K_2CO_3 (2.0 equiv), dioxane (4 mL). [b] Reaction run for 12 h. [c] Reaction run for 48 h. [d] Using 4,7-dimethoxy-1,10-phenanthroline as the ligand. [e] Gram-scale reaction.

To identify whether a radical pathway was involved in the reaction, we conducted radical clock experiments (Scheme 3). Treatment of α-cyclopropyl styrene **12** with the reaction mixture of arylboronic acid **2a** and BDFP **1** under standard reaction conditions did not lead to the ring-opening expansion product **13** (Scheme 3a). We also prepared an arylnickel(II) complex (**A1**)[10c,15] and an arylacylnickel(II) complex (**D1**).[11] Stoichiometric reaction of **A1** or **D1** with **12** in the presence of BDFP **1** did not provide **13** either (Scheme 3b). Instead, the *gem*-difluoroalkene **3a** and **5a** were obtained in 54% and 35% yield, respectively. However, density functional theory (DFT) calculations showed that trapping of *gem*-difluoroallyl radical with **12** is kinetically disfavored over the combination of the *gem*-difluoroallyl radical with nickel complex **D1** (see Supporting Information, Figures S9 and S11), indicating that the pathway involving a radical cannot be excluded. We also conducted radical inhibition experiments and found that the yield of **3a** was dramatically decreased for



Scheme 3. Radical trapping experiments.



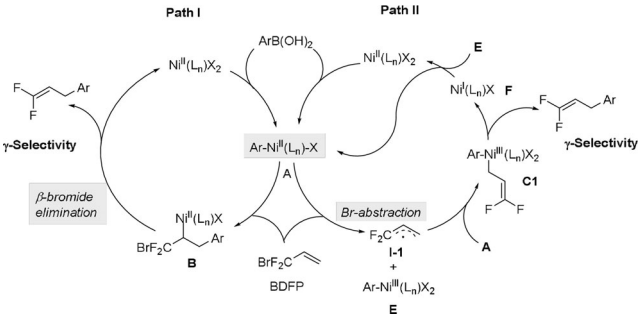
Scheme 4. Stoichiometric reactions using **A1** and **D1** as the catalysts.

the reaction of arylboronic acid **2a** with **1** in the presence of an electron transfer inhibitor, 1,4-dinitrobenzene **14**, or a radical scavenger, α-phenyl styrene **15**, under standard reaction conditions (Scheme 3d). In addition, the addition of TEMPO to the reaction totally inhibited the reaction, and an adduct **16** was observed in 5% yield (Scheme 3e). These results suggested that a radical pathway is likely involved in the reaction.

To gain more detailed mechanistic insight into the reaction, we conducted a stoichiometric reaction of **A1** with BDFP **1**, leading to **3a** in almost quantitative yield (98%, Scheme 4a). Kinetic studies showed that this stoichiometric reaction is faster than the standard catalytic reaction with 4,4′-di*t*Bubpy as the ligand (Figures S1 and S2). The reaction of complex **D1** with BDFP **1** could also provide corresponding carbonylated *gem*-difluoroalkene **5a** (60% yield, $\gamma/\alpha = 8{:}1$, Scheme 4b), and it is also faster than the standard catalytic carbonyl reaction.

Additionally, nickel(II) complexes **A1** and **D1** could also serve as the catalysts to produce the *gem*-difluoroalkenes (Scheme 4c,d).[16] Kinetic studies showed that the reaction rate of the **A1**-catalyzed reaction is similar to the standard reaction using 4,4′-di*t*Bubpy as the ligand (Figures S2 and S3). Furthermore, in addition to the formation of desired product **3m**, the reaction of arylboronic acid **2m** with **1** catalyzed by **A1** led to a small amount of **3a** (Scheme 4e), and with increasing the loading amount of **A1** from 5 mol% to 10 mol%, the formation of **3a** increased from 3% to 6% yield. Thereby, these results indicated that the arylnickel(II) complex or arylacylnickel(II) complex may be the key intermediate in the current nickel-catalyzed process.

Finally, we conducted DFT calculations to shed further light on the reaction mechanism (for details, see the Supporting Information, Figures S4–S12). Interestingly, both the non-radical and radical pathways are possible for the reaction (Scheme 5). The key steps of these two pathways require a similar free energy of activation from arylnickel(II) [Ar–$Ni^{II}(L_n)X$] complex **A**. For the non-radical pathway (Scheme 5, Path I), the insertion of arylnickel(II) complex **A** into the carbon–carbon double bond of BDFP **1** requires 27.1 kcal mol^{-1} from [Ph–$Ni^{II}(L_n)X$] **A2** via transition state ^{3}**TS1a** (Figures 1a, S4, and S5). A similar free energy barrier is also found for the key step in the radical pathway (Scheme 5, Path II), in which the formation of a *gem*-difluoroallyl radical **I-1** and [Ph–$Ni^{III}(L_n)X_2$] **E1** via transition state ^{3}**TS1b** from **A**



Scheme 5. Proposed mechanism.

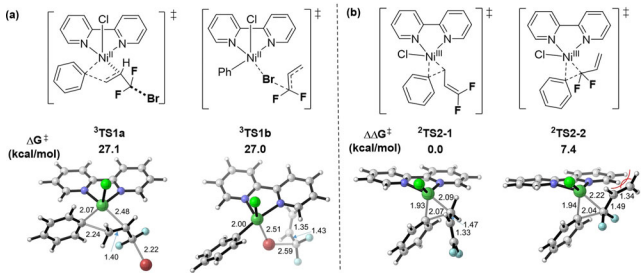


Figure 1. DFT-calculated transition states for a) the rate-determining step of the non-radical pathway (**^{3}TS1a**: the insertion of arylnickel(II) complex **A** into the double bond of BDFP **1**) and the radical pathway (**^{3}TS1b**: bromine abstraction from **1** by **A**); b) the reductive elimination process in the radical pathway.

and BDFP requires 27.0 kcal mol^{-1} (Figures 1a and S9). Additionally, in path I, after the formation of key intermediate alkylnickel(II) **B**, β-bromide elimination is faster than the β-H elimination step (Figure S8); as a result, a γ-selective *gem*-difluoroalkene is produced. DFT calculations also show that the possibility of an S_N2' pathway through attack of **A2** to BDFP is thermodynamically disfavored, as the dissociation of a bromide anion from BDFP requires a very high free energy barrier (51.7 kcal mol^{-1}, Figure S6). For Path II, the γ-selective formation of *gem*-difluoroalkenes **3** from reductive elimination of key intermediate [(aryl)(CF_2=$CHCH_2$)Ni^{III}-(L_n)X] **C1** is the kinetically favorable pathway, as a higher free energy barrier is required from intermediate [(aryl)(CH_2=$CHCF_2$)Ni^{III}(L_n)X] **C2** to generate **3** likely due to the steric interaction between the allyl group and the bpy ligand (Figures 1b and S9).

Overall, two possible pathways are proposed for the current reaction as illustrated in Scheme 5. In Path I, the reaction starts with the formation of [Ar–Ni^{II}(L_n)X] **A**, and a β-bromide elimination from **B** is responsible for the high γ-regioselectivity. Alternatively, for Path II, after formation of **A**, **A** undergoes a bromine abstraction from BDFP to generate [Ar–Ni^{III}(Ln)X_2] **E** and *gem*-difluoroallyl radical **I-1**. Recombination of the resulting radical with another **A** provides key intermediate [(aryl)(CF_2=$CHCH_2$)Ni^{III}(L_n)X] **C1**, which undergoes reductive elimination to produce **3** and [Ni^{I}(L_n)X] **F** in a kinetically favorable manner. Finally, **F** reacts with nickel(III) complex **E** via a comproportionation reaction to regenerate complex **A** and nickel(II) catalyst.[11] In the case of the formation of carbonylated product, **A** undergoes CO insertion to give arylacylnickel(II) complex **D**, which then follows similar pathways to give final product **5**.

In conclusion, we have developed an efficient method for highly γ-selective arylation and carbonylation of BDFP via nickel catalysis. The reaction exhibited good functional group tolerance and provided the *gem*-difluoroalkenes with high efficiency and regioselectivity. The resulting products can serve as versatile building blocks for diversified synthesis. Preliminary mechanistic studies and DFT calculations revealed that the reaction starts with the transmetalation of nickel(II) with arylboronic acids to form an arylnickel(II) complex, and both non-radical and radical pathways are possible for the current reaction, but the radical pathway is more likely.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 3-bromo-3,3-difluoropropene · arylboronic acids · carbonylation · *gem*-difluoroalkenes · nickel catalysis

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[16] The lower yield of **3a** compared to the standard reaction conditions is because of using 4,4′-di*t*BuBpy as the ligand. Replacing bpy with 4,4′-di*t*BuBpy under standard reactions led to **3a** in 57% yield, see the Supporting Information.

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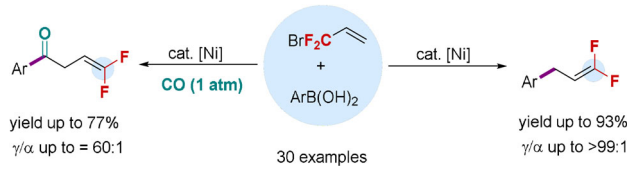
Communications

Homogeneous Catalysis

R. Cheng, Y. Sang, X. Gao, S. Zhang, X.-S. Xue,* X. Zhang* ——— ■■■■–■■■■

Highly γ-Selective Arylation and Carbonylative Arylation of 3-Bromo-3,3-difluoropropene via Nickel Catalysis



A nickel-catalyzed highly γ-regioselective arylation and carbonylation of 3-bromo-3,3-difluoropropene has been developed. The reaction provides a variety of *gem*-difluoroalkenes with good functional group tolerance and high efficiency. Preliminary mechanistic studies and DFT calculations revealed that both non-radical and radical pathways are possible for the reaction.