Organozinc Pivalates for Cobalt-Catalyzed Difluoroalkylarylation of Alkenes and Mechanistic Insights

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**Article**

**Keywords:** cobalt-catalyzed regioselective difluoroalkylarylation, alkenes, mechanistic insights

**Posted Date:** February 8th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-156355/v1

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**Version of Record:** A version of this preprint was published at Nature Communications on July 16th, 2021. See the published version at https://doi.org/10.1038/s41467-021-24596-6.
Abstract

A set of cobalt-catalyzed regioselective difluoroalkylarylation of both activated and unactivated alkenes with bench-stable solid arylzinc pivalates and difluoroalkyl bromides through a cascade Csp$^3$–Csp$^3$–Csp$^2$ bond formation has been developed under mild reaction conditions. Indeed, a wide range of functional groups on difluoroalkyl bromides, olefins, 1,3-dienes as well as (hetero)arylzinc pivalates are well tolerated by the cobalt-catalyst, thus furnishing three-component coupling products in good yields and with high regio- and diastereoselectivity. Kinetic experiments comparing arylzinc pivalates and conventional arylzinc halides highlight the unique reactivity of these new organozinc pivalates. Detailed mechanistic studies strongly support that the reaction involves direct halogen atom abstraction via single electron transfer to difluoroalkyl bromides from the in situ formed cobalt(I) species, thus realizing a Co(I)/Co(II)/Co(III) catalytic cycle.

Introduction

Organometallic reagents, due to their versatile reactivity and high functional groups compatibility, have been broadly used for the synthesis of pharmaceuticals and agrochemicals. Especially, transition metal-catalyzed cross-coupling strategy, are of great importance for the development of modern organic chemistry.$^{[1−6]}$ Among them, boron$^{[7−10]}$ and zinc organometallics$^{[11−15]}$ have found extensive applications in such coupling reactions for the preparation of a wide range of highly complex molecules. As compared to the bench-stable, commercially available boronic derivatives, conventional organozinc reagents (RZnX, X = Cl, Br, I) displayed even more exquisite reactivity under mild reaction conditions in many coupling reactions, however, highly air and moisture sensitive still represent drawbacks for their synthetic applications. Remarkably, Knochel and coworkers recently developed a solid organozinc pivalates (RZnX·Mg(OPiv)$_2$·LiCl, which is abbreviated henceforth as RZnOPiv for the sake of clarity),$^{[16]}$ which show greatly enhanced air and moisture stability after solvent evaporation.$^{[17]}$ These novel organozinc reagents, including (hetero)aryl,$^{[17−22]}$ alkynyl,$^{[23−24]}$ and alkyl zinc pivalates,$^{[25]}$ exhibited good reactivity in Pd-catalyzed cross-coupling reactions with unsaturated halides, which further proved to be broadly applicable for the late-stage functionalizations of biologically active molecules.$^{[26]}$ Although palladium catalysts are very useful, the 3d transition-metals,$^{[27−34]}$ especially cobalt$^{[35−39]}$ have recently found numerous applications due to its low toxicity, low-cost and natural abundance. Recently, (hetero)arylzinc pivalates have been successfully used for cobalt-catalyzed cross-couplings with unsaturated halides,$^{[40]}$ alkenyl acetates,$^{[41]}$ N-hydroxylamine benzoates,$^{[42]}$ anthranils,$^{[43]}$ N-hydroxyphthalimide,$^{[44]}$ as well as thiopyridyl ester derivatives.$^{[45]}$ Therefore, the ease of preparation, stability and exquisite reactivity of these new solid zinc reagents have attracted considerable attention of synthetic chemists.

Transition metal-catalyzed regioselective difunctionalizations of olefins with two different functional groups have been recognized as an increasingly viable tool for preparing complex organic compounds from readily available starting materials.$^{[46−48]}$ However, due to the facile β-H elimination from the Csp$^3$–
[M] intermediate,[49–52] it still remained challenging to construct two new C–C bonds through transition-metal catalyzed multicomponent dicarbofunctionalization of alkenes (Scheme 1a).[53–55] Importantly, highly regioselective Ni-catalyzed alkylarylation of vinylarenes with alkyl halides and arylzinc iodides has recently developed by Giri and coworkers,[56] they further extended the substrate scope to α-halocarbonyl derivatives (Scheme 1a).[57] Besides, the installation of fluorine into bioactive molecules uniquely plays a vital role in their properties of relevance to biology or medicinal chemistry.[58–63] although major advances in transition-metal-catalyzed fluoroalkylation have been achieved in recent years.[64–68] It is worth noting that the elegant Ni-catalyzed tandem difluoroalkylation-(alkyl)arylation of enamides to the synthesis of difluoroalkylated amides were illustrated by Zhang and coworkers.[69–71] To the best of our knowledge, organozinc reagents for transition-metal-catalyzed difunctionalization of alkenes and 1,3-dienes to achieve fluorinated compounds was rather rare and limited to the use of nickel catalysis with activated alkenes.[71] In particular, the much less toxic and industrial friendly cobalt catalysts, have unfortunately thus far proven elusive for the aforementioned three component cascade coupling reactions.[72–73] As a part of our continuous program in fluorine installation via alkene difunctionalization strategy,[74–75] we herein report a versatile cobalt-catalyzed regioselective difluoroalkylarylation of (un)activated alkenes and 1,3-dienes with polyfunctionalized bench-stable arylzinc pivalates and difluoroalkyl bromides (Scheme 1b), which provides an expedient method to install fluorine into complex compounds. Of special interest in this cobalt-catalysis is that the arylzinc pivalates seem very crucial for promoting the overall catalytic efficacy.

Results And Discussion

We initiated our studies by optimizing reaction conditions for the envisioned cobalt-catalyzed regioselective three-component coupling of alkenylarene (2a) with bromodifuoroacetate (1a) and phenylzinc pivalate (3a, PhZnOPiv). A cascade cross-coupling reaction was observed in the presence of 10.0 mol % CoBr\textsubscript{2} under ligand-free conditions, thus affording the desired aryl-difuoroalkylated product 4 in 83% yield with high regioselectivity (Table 1, entry 1). Among a number of representative chelating ligands, bipyridines have given negative effects, and only trace amount of product was observed (entries 2–3), tridentate 2,6-bis(N-pyrazolyl)pyridine, 1,10-phenanthrolines, diimine, TMEDA, ME\textsubscript{4}DACH, as well as dpdz ligands gave poor to high yields, whereas the neocuproine (L5) afforded 4 in 92% (entries 4–11). Further testing reactions with different solvents verified the crucial importance of MeCN as the reaction medium (entry 11; See SI). Switching from CoBr\textsubscript{2} to other representative cobalt salts, such as CoCl\textsubscript{2}, CoCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, led to significant reduced yields (entry 12–13). In sharp contrast, replacement of CoBr\textsubscript{2} by using NiBr\textsubscript{2}, FeCl\textsubscript{2}, CrCl\textsubscript{2}, or CuBr failed to furnish the desired product 4 (entry 14).
Table 1. Optimization for cobalt-catalyzed difluoroalkylation of 4-methoxystyrene 2a.[a]

| Entry | Modified conditions | Yield (%)[b] |
|-------|---------------------|--------------|
| 1     | no ligand           | 83           |
| 2     | L1 instead of L5    | Trace        |
| 3     | L2 instead of L5    | Trace        |
| 4     | L3 instead of L5    | 62           |
| 5     | L4 instead of L5    | 16           |
| 6     | none                | 92           |
| 7     | L6 instead of L5    | 80           |
| 8     | L7 instead of L5    | 53           |
| 9     | L8 instead of L5    | 51           |
| 10    | L9 instead of L5    | 62           |
| 11    | THF, DMF, or NMP instead of MeCN | <12 |
| 12    | CoCl₂ instead of CoBr₂ | 49 |
| 13    | CoCl₂(PPh₃)₂ instead of CoBr₂ | 31 |
| 14    | NiBr₂, FeCl₃, CrCl₃, or CuBr instead of CoBr₂ | Trace |

[a] Reaction conditions: 1a (0.50 mmol, 2.0 equiv), 2a (0.25 mmol, 1.0 equiv), 3a (0.50 mmol, 2.0 equiv), CoBr₂ (10 mol %), L5 (11 mol %), MeCN (2.0 mL), 23 °C, 3 h. [b] Isolated yields.

Lei[76–78] demonstrated first that arylzinc reagents prepared by different methods possess very different kinetics in palladium- and nickel-catalyzed oxidative couplings, and further X-ray absorption spectroscopy studies show that changing the halide anion from Cl to Br or I will result in an increase of the Zn–C bond distance and thereby improve the transmetallation rate.[79] In order to preliminarily reveal the different kinetics between this solid zinc reagent and conventional zinc reagents, a series of control experiments with six different phenylzinc reagents, which prepared by transmetallation of the corresponding phenylmagnesium halides and zinc halides,[80] were also performed under the ligand-free cobalt catalysis (Scheme 2). Interestingly, all of these reactions were almost finished within remarkably short reaction times of only 15 min. It is worth noting that significantly reduced conversions of 4 were observed when using PhZnX (X = Cl, Br or I), Ph₂Zn□₂MgCl₂ or Ph₂Zn□₂Mg(OPiv)Cl instead of PhZnOPiv. Moreover, the results of comparison experiments between Ph₂Zn□₂Mg(OPiv)Cl and Ph₂Zn□₂MgCl₂ show the superiority of the former as well. Hence, these observations highlighted that the presence of M(OPiv)₂ (M = Mg or Zn) has made these new organozinc pivalates stand out amongst salt-supported organometallics, thus displaying the distinct advantage of reacting well in our regioselective cobalt-catalyzed difluoroalkylation of olefins.
Subsequently, the versatility of this optimized cobalt(II) catalyst was examined in a range of difluoroalkylation reactions with various polyfunctionalized arylzinc pivalates 3 (Scheme 3). All arylzinc pivalates were prepared from the corresponding aryl halides by Mg insertion in the presence of LiCl.\(^1\) Although the neocuproine (L5) gave the optimal results in the model reaction, in our efforts to extend the substrate scope of this domino reaction, ligand-free CoBr\(_2\) proved to be superior (see the results of products 7, 9, 11). A variety of para- and/or meta- substituted arylzinc pivalates were identified as viable nucleophiles for difluoroalkylation with bromodifuoroacetate (1a) and 4-methoxystyrene (2a) to afford the desired products 4–16 in moderate yields. More sterically hindered 4-chloro-2-methylphenylzinc pivalate was successfully employed, leading to the desired difluoroalkylated product 17 in 62% yield. Notably, ferrocenylzinc pivalate, as well as 3-thienylzinc pivalate also smoothly underwent the cobalt-catalyzed cascade cross-coupling, albeit yielding the products 18–19 in relatively lower yields.

Thereafter, we have explored the substrate scope of the difluoroalkylation reaction with a wide range of vinylarenes and bromodifuoroacetate/amides (Scheme 4). Remarkably, alkenylarenes bearing various valuable electrophilic functional groups, such as ether (22), fluoro (23), chloro (24), bromo (25, 35, 37), trifluoromethyl (26), methoxy (27–28, 31–32, 38–39), cyano (30), acetate (33), esters (36), isobutyl (34) substituents, as well as vinylnaphthalene (29) and unsubstituted styrenes (20–21), were well tolerated under the reaction conditions and converted to the corresponding difluorinated 1,1-diarylalkanes in moderate to excellent yields (40–98%), as were also observed when using different bromodifuoroacetamides as the fluorinating reagents. Also, internal alkene with (E)-β-methylstylene was examined under our cobalt catalysis, but only trace amount of desired product was detected by GC-analysis (See SI). In sharp contrast, coupling of arylzinc pivalate, bromodifuoroacetate with indene gave the desired difluoroalkylarylated product 40 in 55% yield, with high diastereoselectivity (\(dr > 20:1\)).

In addition, we further investigated the cross-coupling of various fluoroalkyl bromides with olefins and arylzinc pivalates (Scheme 5). Firstly, in contrast to bromodifuoroacetate, the bromomonofluoroacetate only gave 34% yield under the standard reaction conditions, and with a poor diastereoselectivity (\(dr = 1:1\)) (Scheme 5a). We were also pleased to find that bromodifuoroethylphosphonate smoothly underwent the envisioned cobalt-catalyzed difluoroethylarylilation to afford the desired 1,1-diarylalkylphosphonates 42–45 in 51–97% yields, and compound 45 was obtained with high diastereoselectivity (\(dr > 20:1\)). Besides, the unactivated alkene furnished the desired difluoroethylarylilated phosphonate 46 as well, albeit in a modest yield (Scheme 5b). Additionally, using as substrate of α-bromodifluoromethyl substituted benoxazole proved to be viable with versatile cobalt catalyst and, thereby, provided 47–48 as the products in 51–55% yields (Scheme 5c). Remarkably, this cobalt-catalyzed regioselective difluoroalkylation reaction was further extended to the decorated difluoroalkyl bromides (Scheme 5d). Functional groups, such as arylsulfonate, ester, were well tolerated under the standard reaction conditions, thus delivering the desired products 49–52 in good yields and with high diastereoselectivity of 51 (\(dr > 20:1\)).
Transformations of unactivated alkenes are acknowledged widely as a challenge in transition metal-catalyzed difunctionalization of alkenes. The reaction conditions previously optimized for the alkenylarenes led to an unsatisfactorily low yield of 53, because significant amounts of a Heck-type coupling product were formed as well. However, we were delighted to found that the transformation of the unactivated alkene difluoroalkylation process was significantly improved when using dppbz (L9, 11 mol %) as the ligand, leading to 53 in 54% yield. A number of unactivated alkenes were readily converted into the desired difluoroalkylated products 54–59 in moderate yields. Moreover, various synthetically valuable functional groups, including chloro, ether, and ester remained intact by the cobalt catalyst (Scheme 6a). Beyond that, the possibility of cobalt-catalyzed difluoroalkylation to form an allyl radical, which subsequently underwent 1,3-H-shift and Csp³–Csp² cross-couplings with arylzinc pivalates was also investigated (Scheme 6b). Indeed, difluoroalkyl bromide 1k and a quite range of functionalized (hetero)aryl-zinc reagents were realized 1,4-difunctionalization of 1,3-dienes with good regioselectivity and diastereoselectivity, thus furnishing 60–70 in 43–98% yields, albeit products 69 and 70 were obtained with 1:1 E:Z selectivity and 4:1 regioselectivity, respectively. To our delight, 1,3-octadiene was proven to be suitable substrate as well, giving the product 71 with high diastereoselectivity.

To further illustrate the potential applications of this cobalt-catalyzed regioselective difluoroalkylation in late-stage functionalizations of pharmaceutically active molecules, alkenylarenes derivatized from (pre-)drug molecules, such as febuxostat, canagliflozin, as well as indomethacin, were well difluoroalkylated with arylzinc pivalates and α-bromodifluorocarbonyl compounds or bromodifluoromethylphosphonate, leading to the corresponding products 72–77 in 30–96% yields. These results show the potential utility of this protocol for the discovery of novel bioactive drugs. Importantly, citronellol derivative was readily incorporated into the product 78 with remarkably high regioselectivity and chemoselectivity. Moreover, an unactivated alkene bearing a 4-hydroxycoumarin proved to be viable substrate as well, albeit delivering the phosphonate 79 in a rather modest yield. Finally, we showed that isopropenylzinc pivalate is well suited for the cobalt-catalyzed difluoroalkylalkenylation, although the reaction proceeded with lower yield (Scheme 7).

Intrigued by the high regioselectivity and efficacy of our cobalt-catalyzed difluoroalkylation, a series of intermolecular competition experiments were performed (Scheme 8). A competition experiment between bromodifluoroacetate (1a) and 2-bromo-2-methylpropanoate showed that BrCF₂CO₂Et reacted much faster than these α-bromocarbonyl compounds. These findings can be rationalized in terms of a prioritized direct halogen atom abstraction from difluoroalkyl bromides via single electron transfer from a cobalt catalyst (Scheme 8a). Intermolecular competition experiments with different alkenylarenes, and arylzinc pivalates revealed electron-rich styrenes and electron-deficient arylzinc pivalates to be slightly reactive substrates (Scheme 8b and 8c). These results suggested that vinylarenes and arylzinc reagents might not be involved in the rate-determine step.

Beyond that, radical-clock experiment with substrate 83 bearing a radical clock cyclopropane moiety, the ring-opened difluoroalkylarylated product 84 was generated in 11% yield. Similarly, both three- and two-
component coupling products were observed when using N,N-diallyl-2-bromo-2,2-difluoroacetamide (85) as a radical probe under the standard reaction conditions, the cyclized products 86 (dr = 2:1) and 87 were generated in 17% and 34% yields, respectively. Moreover, a difluoroalkylated benzylic radical homocoupling dimer 88 was detected by GC as well. With these findings, we propose this cobalt-catalyzed difluoroalkylarlylation involves a single-electron-transfer (SET) process (Scheme 9a).

According to the earlier mechanistic studies for cobalt-catalyzed cross-coupling reactions with using organomagnesium reagents, an in situ low-valent Co(0) was proposed as the catalytically active species. On the other hand, a mechanism involving Co(I)/(III) couple was also proposed for many cobalt-catalyzed cross-couplings. Therefore, we performed experiments of CoBr$_2$ (1.0 equiv) with excess of ArZnOPiv under typical reaction conditions for 30 min. These reactions furnished the corresponding homo-products of 89a and 89b in near 0.5 equiv ratio to that of CoBr$_2$, respectively. These findings support the formation of a Co(I)-species based on the stoichiometry shown in scheme 9b. In this context, the well-defined Co(I)-complex, such as CoCl(PPh$_3$)$_3$ was proved to be active for the desired difluoroalkylated process, yielding product 4 in 66%, while Co$_2$(CO)$_8$ gave a poor yield (Scheme 9c). Further experiments to examine the catalytic activity of the in situ generated low-valent cobalt(I) species were performed. A mixture of vinylarene 2a (0.25 mmol) and CoBr$_2$ (0.025 mmol) was treated with 2.0 equiv of 3,4-(methylenedioxy)phenylzinc pivalate (0.05 mmol) at 23 °C for 30 min to generate the proposed Co(I)-species, followed by addition of bromodifuoroacetate 1a (0.3 mmol) and another 0.5 mmol of phenylzinc pivalate. The difluoroalkylated product 4 was isolated in 57% yield as the sole product, while the product 11 was obtained in 79% yield when exchanging the order of the two arylzinc reagents (Scheme 9d). These findings are consistent with the in situ generated low-valent cobalt(I)-species might be the active catalyst for the current three-component cross-coupling reaction. A series of EPR spin-trapping experiments show the existence of C-centered radicals trapped by DMPO ($g$=2.0066, $A_H$ = 13.9 G, $A_N$ = 19.3 G), which was considered to be •CF$_2$R. These results strongly supported the single electron transfer progress for the activation of BrCF$_2$R was only promoted by the in situ formed Co(I)-species (Scheme 9e).

Based on the above experimental findings, along with previous mechanistic insights, a mechanism for this regioselective cobalt-catalyzed difluoroalkylarylation of alkenes has been proposed as shown in Scheme 10. The reduction of the precatalyst CoBr$_2$ with arylzinc pivalates forms the catalytically active Co(I)-species (A), which reduces difluoroalkyl bromides (1) by SET and generates difluoroalkyl radical B, then followed by a facile radical addition of B into olefins (2) to afford a secondary alkyl radical species, along with subsequent rapid trapping with $L_n$Co(II)XBr (X = Br) into intermediate C, which undergoes transmetalation with ArZnOPiv (3) to lead to the organocobalt(III) species D. Subsequent reductive elimination finally delivers the difluoroalkylated product and regenerate the active cobalt(I)-catalyst (path a). In addition, another possible pathway is that transmetalation of arylzinc pivalates could also occurred after the initial reduction step, thus in situ forming the $L_n$Co(I)X (X =
Ar) species as the catalyst to promote the SET process. Radical addition and reductive elimination give rise to the desired products and regenerate the active Co(I)-species (path b).

We were also pleased to find that this cobalt-catalyzed difluoroalkylation can be easily scaled up to gram level. Under the optimized reaction conditions, the difluoroalkylated product 90 was afforded with high efficacy (65% yield, Scheme 10a). Finally, we further demonstrated the synthetic potential of this cobalt-catalyzed difluoroalkylation strategy through the late-stage modification of the obtained difluoroalkylated products. For example, the resulting N-morpholino amide 90 can be readily converted into various ketones by treating with Grignard reagents, thus furnishing the products 92a–b in moderate yields. Moreover, the reduction of the ester group of substrate 4 by using NaBH₄ provides the corresponding alcohol 93, which readily undergoes various derivatization (Scheme 11b).

**Conclusion**

In conclusion, we have reported the first practical cobalt-catalysis for regioselective difluoroalkylation of alkenes or 1,3-dienes with functionalized arylzinc pivalates and difluoroalkyl bromides. This simple cobalt-catalyst enables three-component cross-couplings through cascade Csp³−Csp³/Csp³−Csp² bond formation in one-pot fashion, thus generating difluoroalkylated products with predictable regioselectivity and high diastereoselectivity. The reaction proceeds under remarkable mild conditions with high efficacy, excellent functional group tolerance, as well as a broad substrate scope. Notable features of this approach are the use of less toxic and low-cost cobalt catalyst, as well as user-friendly solid zinc reagents. Straightforward late-stage functionalizations of pharmaceutically active molecules shown the potential applications of this protocol for the discovery of novel bioactive drugs. Beyond that, among a series of kinetic experiments with six type of phenylzinc reagents, these bench-stable solid arylzinc pivalates displayed the distinct advantage of reactivity for the current reaction. Detailed mechanistic studies demonstrated the reaction undergoes a direct halogen atom abstraction via single electron transfer from the in situ formed cobalt(I) species to difluoroalkyl bromides.

**Declarations**

**Acknowledgements**

We thank the National Natural Science Foundation of China (Grant No. 21602083) and Start Funding of Soochow University (Grant No. Q410900520) for financial support. We are grateful to Prof. Yi-hung Chen for their kind discussions, and Jianlin Yao, Chen Zhu for their kind support and accessing to laboratory.

**Author Contributions**

X.C., X.L. and S.W. contributed equally to this work and they planned, conducted and analysed the experiments. X.C., X.L., S.W., Y.H., and B.H. performed the experiments. J.L., and A.L. designed and directed the project and wrote the manuscript with contributions from all co-workers.
Methods

General procedure for the cobalt-catalyzed difluoroalkylarylation: A suspension of CoBr$_2$ (10 mol %), olefin (0.25 mmol, 1.0 equiv), difluoroalkyl bromide (0.5 mmol, 2.0 equiv) and aryl zinc pivalates (0.5 mmol, 2.0 equiv) in degas MeCN (1.0 mL) was stirred at 23 °C for 3 h under an atmosphere of Ar. At ambient temperature, the solvent was evaporated *in vacuo* and the remaining residue was purified by column chromatography on silica gel (n-hexane/EtOAc) to yield the desired products.

Additional Information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to J.L., and A.L..

Competing financial interests

The authors declare no competing financial interests.

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80. Note: PhZnOPiv was prepared from PhMgCl and Zn(OPiv)₂ with 1:1.2 ratio; Ph₂Zn₂Mg(OPiv)Cl was prepared from PhMgCl and Zn(OPiv)₂ with 2:1 ratio; PhZnX was prepared from PhMgX and ZnX₂ with 1:1.2 ratio; Ph₂Zn₂MgCl₂ was prepared from PhMgCl and ZnCl₂ with 2:1 ratio.

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82. See more details from the Supporting Information.

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**Figures**
Previous work:
(a) Overview of alkene (di)functionalization with organometallic reagents

\[
\text{Pd, Ni, Co...} \quad \begin{array}{c}
\beta-H \text{ Elimination} \\
\text{Ar/Alk} - M \\
M = \text{MgX or ZnX}
\end{array} \\
\text{Pd, Ni} \quad \begin{array}{c}
\text{Cascade Couplings} \\
\text{Ar/Alk} - M \\
M = \text{ZnX or Li}
\end{array}
\]

\[
\text{X} = \text{Hal, OTf, N hydroxyphthalimide}
\]

This work:
(b) Cobalt-catalyzed difluoroalkylative Negishi coupling

\[
\begin{array}{c}
\text{R} \\
\text{Br} \\
\text{F} \\
\text{F}
\end{array} + \begin{array}{c}
\begin{array}{c}
\text{R'} \\
\text{Ar} \\
\text{ZnOPiv}
\end{array} \\
\text{Co}
\end{array} \rightarrow \begin{array}{c}
\begin{array}{c}
\text{R} \\
\text{F} \\
\text{F}
\end{array} \\
\text{R'} \\
\text{Ar}
\end{array}
\]

\[
\text{MeCN, 23 °C}
\]

HOMOGENEOUS CATALYSIS
- unique reactivity of organozinc pivalates
- robust cobalt enabled difluoroalkylarylation
- (un)activated alkenes and 1,3-dienes
- high regio- and diastereoselectivity
- Co(I/II/III) pathway

Figure 1

Scheme 1. Organometallic reagents for difunctionalization of olefins.
Figure 2

Scheme 2. Kinetic experiments with different phenylzinc reagents of 3a–X.
Figure 3

Scheme 3. Scope of cobalt-catalyzed cascade cross-coupling reaction with aryl zinc pivalates of type 3. Reaction conditions: 1a (0.50 mmol, 2.0 equiv), 2a (0.25 mmol, 1.0 equiv), arylzinc pivalates (0.50 mmol, 2.0 equiv), CoBr$_2$ (10 mol %), MeCN (2.0 mL), 23 °C, 3–6 h. [a] 11 mol % of L5 was used. [b] CoBr$_2$ (20 mmol %) was used. [c] Ar$_2$Zn$_2$Mg (OPiv)Cl (2.0 equiv) was used.
Figure 4

Scheme 4. Substrate scope with alkenylarenes and bromodifluoroacetate/amides. Reaction conditions: difluoroalkyl bromides (0.50 mmol, 2.0 equiv), vinylarenes (0.25 mmol, 1.0 equiv), arylzinc pivalates (0.50 mmol, 2.0 equiv), CoBr2 (10 mol %), MeCN (2.0 mL), 23 °C, 3–6 h.
Figure 5

Scheme 5. Regioselective cobalt-catalyzed di-/monofluoroalkylation with fluoroalkyl bromides. Reaction conditions: difluoroalkyl bromides (0.5 mmol), alkenes (0.25 mmol), arylzinc pivalates (0.5 mmol), CoBr$_2$ (10 mol %), MeCN, 23 °C, 3–6 h. [a] Ph$_2$Zn·2Mg(OPiv)Cl (2.0 equiv) was used.
Figure 6

Scheme 6. Difluoroalkylarylation of unactivated alkenes and 1,3-dienes. Reaction conditions: 1k (0.25 mmol), unactivated alkenes or 1,3-dienes (0.5 mmol), arylzinc pivalates (0.5 mmol), CoBr2 (10 mol %), dppbz (10 mol %), MeCN, 23 °C, 12 h.
Figure 7

Scheme 7. Late-stage difluoroalkylationlation of drug derivatives and natural products. [a] A second portion of 1a and isopropenylzinc pivalate was added.
**Figure 8**

Scheme 8. Competition experiments.
Figure 9

Scheme 9. Mechanistic studies for cobalt-catalyzed cascade difluoroalkylarylation.
Figure 10

Scheme 10. Proposed catalytic cycle
Scheme 11. (a) Gram-scale reaction. (b) Modification of difluoroalkylarylated products.

**Figure 11**

Scheme 11. (a) Gram-scale reaction. (b) Modification of difluoroalkylarylated products.

**Supplementary Files**

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