

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

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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 $\text{Csp}^3\text{--Csp}^3/\text{Csp}^3\text{--Csp}^2$ 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 , $\text{X} = \text{Cl}, \text{Br}, \text{I}$) 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 ($\text{RZnX} \cdot \text{Mg}(\text{OPiv})_2 \cdot \text{LiCl}$, 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 $\beta\text{-H}$ elimination from the $\text{Csp}^3\text{--}$

[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 bromodifluoroacetate (**1a**) and phenylzinc pivalate (**3a**, PhZnOPiv). A cascade cross-coupling reaction was observed in the presence of 10.0 mol % CoBr₂ under ligand-free conditions, thus affording the desired aryl-difluoroalkylated 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, ME₄DACH, as well as dppbz ligands gave poor to high yields, whereas the neocuproine (**L5**) afforded **4** in 92% (entries 4–10). Further testing reactions with different solvents verified the crucial importance of MeCN as the reaction medium (entry 11; See SI). Switching from CoBr₂ to other representative cobalt salts, such as CoCl₂, CoCl₂(PPh₃)₂, led to significant reduced yields (entry 12–13). In sharp contrast, replacement of CoBr₂ by using NiBr₂, FeCl₂, CrCl₂, or CuBr failed to furnish the desired product **4** (entry 14).

Table 1. Optimization for cobalt-catalyzed difluoroalkylarylation 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	CoCl ₂ instead of CoBr ₂	49
13	CoCl ₂ (PPh ₃) ₂ instead of CoBr ₂	31
14	NiBr ₂ , FeCl ₂ , CrCl ₂ , or CuBr instead of CoBr ₂	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 transmetalation 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 transmetalation 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 difluoroalkylarylation of olefins.

Subsequently, the versatility of this optimized cobalt(II) catalyst was examined in a range of difluoroalkylarylation 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.^[81] 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 CoBr₂ 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 difluoroalkylarylation with bromodifluoroacetate (**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 difluoroalkylarylated 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 difluoroalkylarylation reaction with a wide range of vinylarenes and bromodifluoroacetate/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**), methyloxy (**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 bromodifluoroacetamides as the fluorinating reagents. Also, internal alkene with (*E*)- β -methylstyrene 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, bromodifluoroacetate 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 bromodifluoroacetate, 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 bromodifluoromethylphosphonate smoothly underwent the envisioned cobalt-catalyzed difluoromethylarylation 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 difluoromethylarylated phosphonate **46** as well, albeit in a modest yield (Scheme 5b). Additionally, using as substrate of α -bromodifluoromethyl substituted benzoxazole 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 difluoroalkylarylation 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.^[49–56, 69–71] 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 difluoroalkylarylation 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 difluoroalkylarylated products **54–59** in moderate yields.^[82] 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 $\text{Csp}^3\text{--Csp}^2$ 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 difluoroalkylarylation in late-stage functionalizations of pharmaceutically active molecules, alkenylarenes derivatized from (pre-)drug molecules, such as febuxostat, canagliflozin, as well as indomethacin, were well difluoroalkylarylated 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 difluoroalkylarylation, a series of intermolecular competition experiments were performed (Scheme 8). A competition experiment between bromodifluoroacetate (**1a**) and 2-bromo-2-methylpropanoate showed that $\text{BrCF}_2\text{CO}_2\text{Et}$ 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).^[83] 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.^[56]

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 difluoroalkylarylation 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.^[52, 72–73, 84–85] On the other hand, a mechanism involving Co(I)/(III) couple was also proposed for many cobalt-catalyzed cross-couplings.^[37–39, 83] Therefore, we performed experiments of CoBr₂ (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 CoBr₂, 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(PPh₃)₃ was proved to be active for the desired difluoroalkylarylated process, yielding product **4** in 66%, while Co₂(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 CoBr₂ (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 bromodifluoroacetate **1a** (0.3 mmol) and another 0.5 mmol of phenylzinc pivalate. The difluoroalkylarylated 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_N* = 13.9 G, *A_H* = 19.3 G), which was considered to be •CF₂R.^[86] These results strongly supported the single electron transfer progress for the activation of BrCF₂R was only promoted by the in situ formed Co(I)-species (Scheme 9e).

Based on the above experimental findings, along with previous mechanistic insights,^[37–39, 74, 83] a mechanism for this regioselective cobalt-catalyzed difluoroalkylarylation of alkenes has been proposed as shown in Scheme 10. The reduction of the precatalyst CoBr₂ 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_nCo(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 difluoroalkylarylated product and regenerate the active cobalt(I)-catalyst (path a). In addition, another possible pathway is that transmetallation of arylzinc pivalates could also occurred after the initial reduction step, thus in situ forming the L_nCo(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 difluoroalkylarylation can be easily scaled up to gram level. Under the optimized reaction conditions, the difluoroalkylarylated product **90** was afforded with high efficacy (65% yield, Scheme 10a). Finally, we further demonstrated the synthetic potential of this cobalt-catalyzed difluoroalkylarylation strategy through the late-stage modification of the obtained difluoroalkylarylated 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 difluoroalkylarylation 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 difluoroalkylarylated 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

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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.

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Competing financial interests

The authors declare no competing financial interests.

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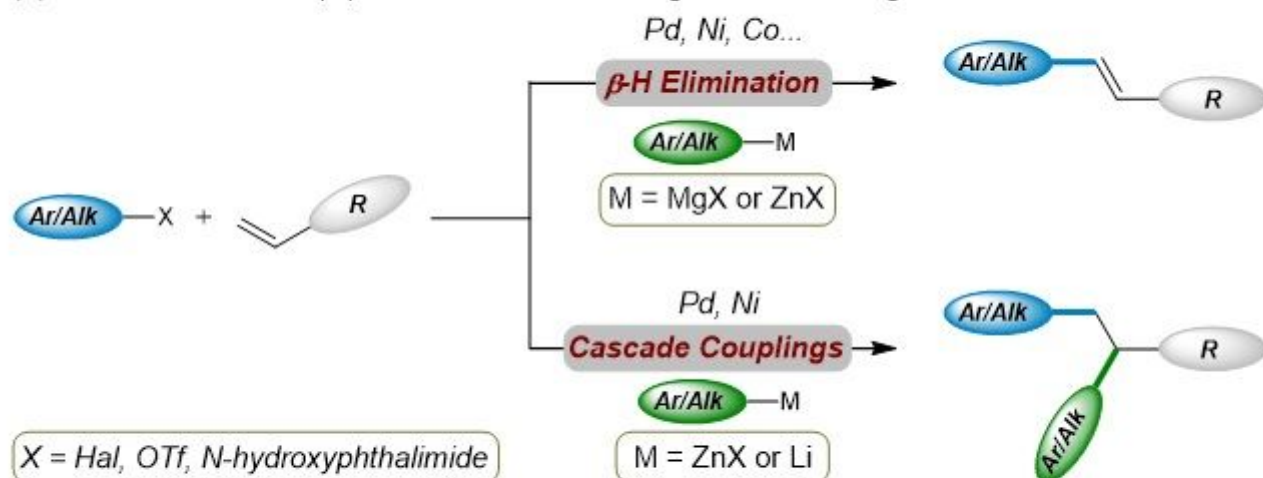
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80. Note: PhZnOPiv was prepared from PhMgCl and Zn(OPiv)_2 with 1:1.2 ratio; $\text{Ph}_2\text{Zn} \cdot 2\text{Mg(OPiv)Cl}$ was prepared from PhMgCl and Zn(OPiv)_2 with 2:1 ratio; PhZnX was prepared from PhMgX and ZnX_2 with 1:1.2 ratio; $\text{Ph}_2\text{Zn} \cdot 2\text{MgCl}_2$ was prepared from PhMgCl and ZnCl_2 with 2:1 ratio.
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Figures

Previous work:

(a) Overview of alkene (di)functionalization with organometallic reagents



This work:

(b) Cobalt-catalyzed difluoroalkylarylation Negishi coupling

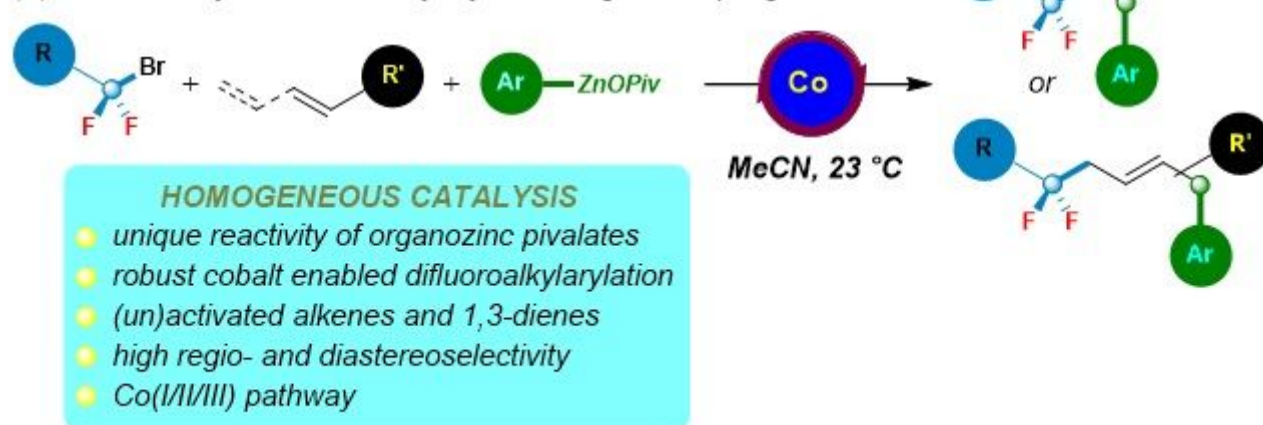


Figure 1

Scheme 1. Organometallic reagents for difunctionalization of olefins.

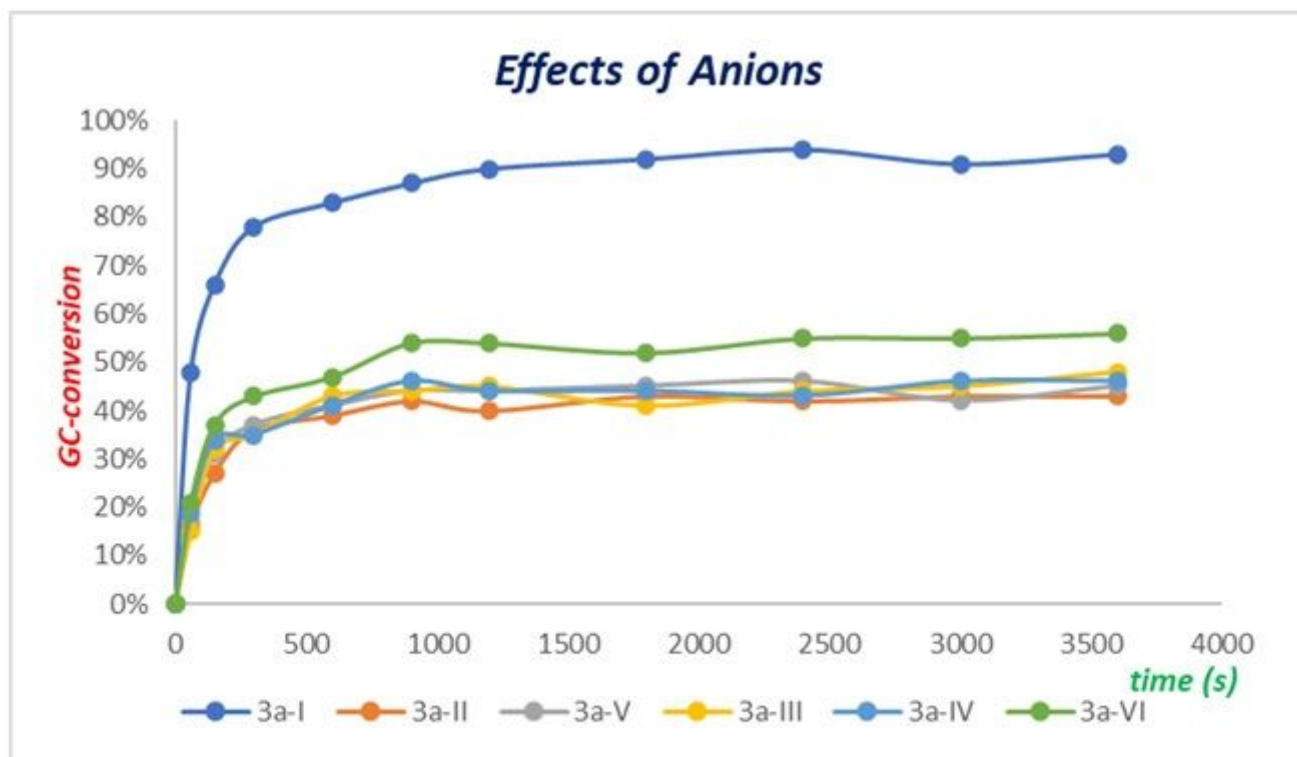
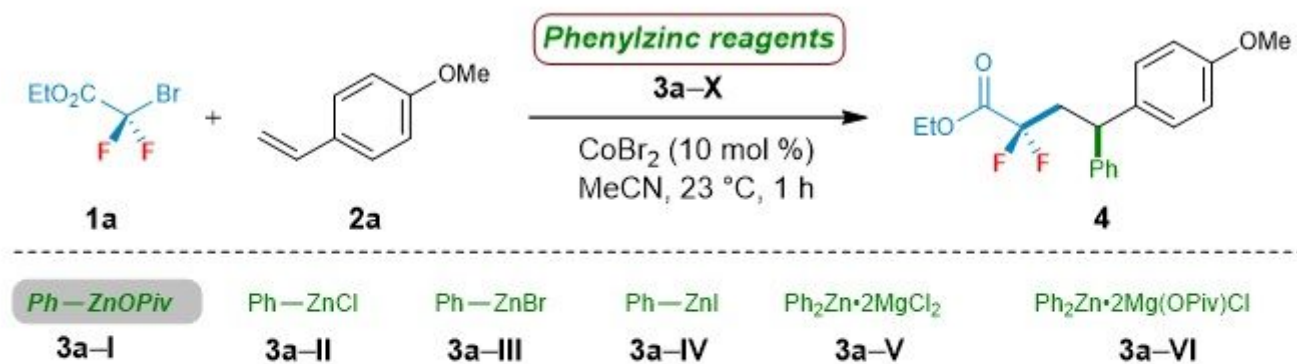


Figure 2

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

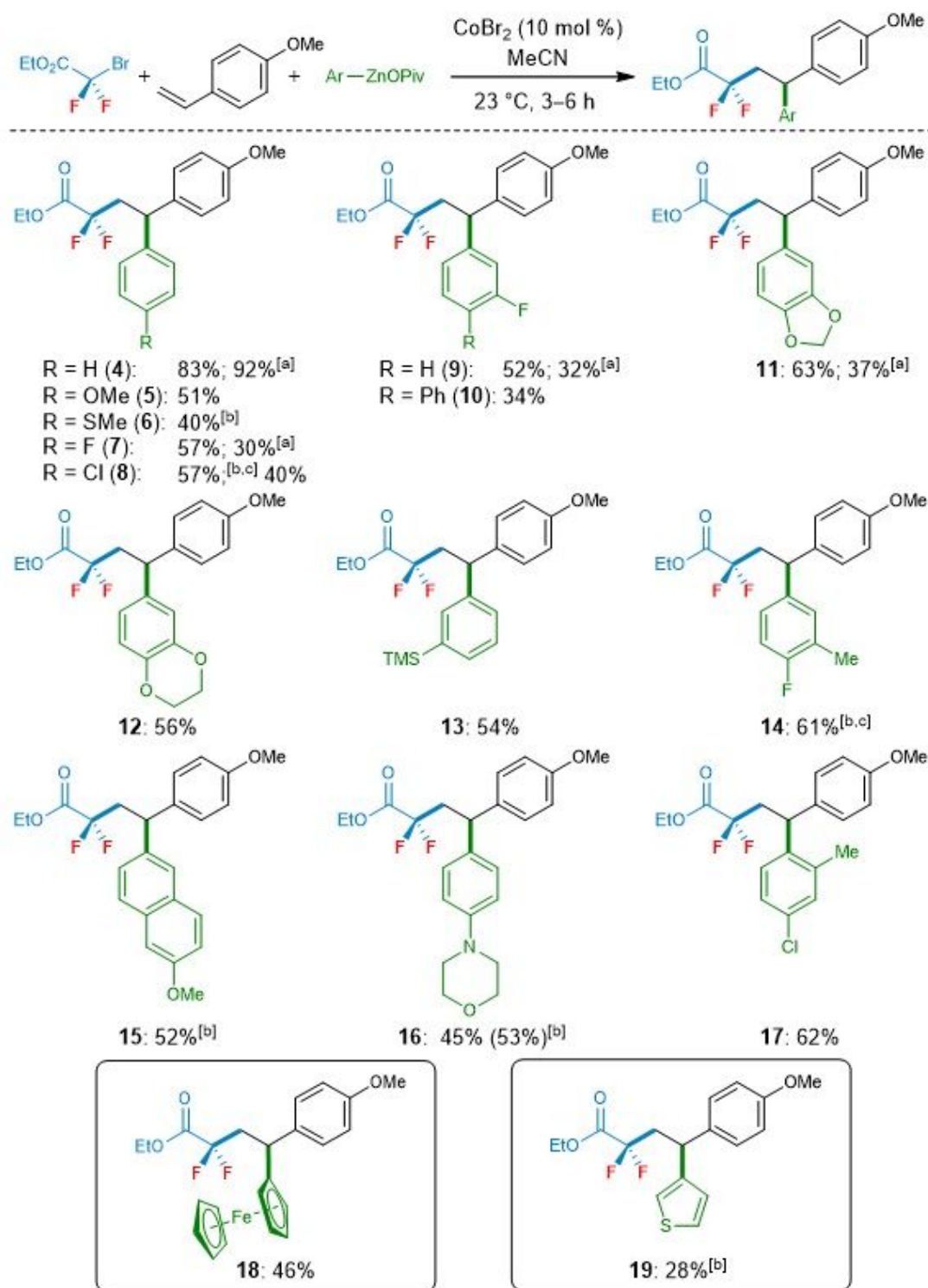


Figure 3

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), CoBr₂ (10 mol %), MeCN (2.0 mL), 23 °C, 3–6 h. [a] 11 mol % of L5 was used. [b] CoBr₂ (20 mmol %) was used. [c] Ar₂Zn·2Mg(OPiv)Cl (2.0 equiv) was used.

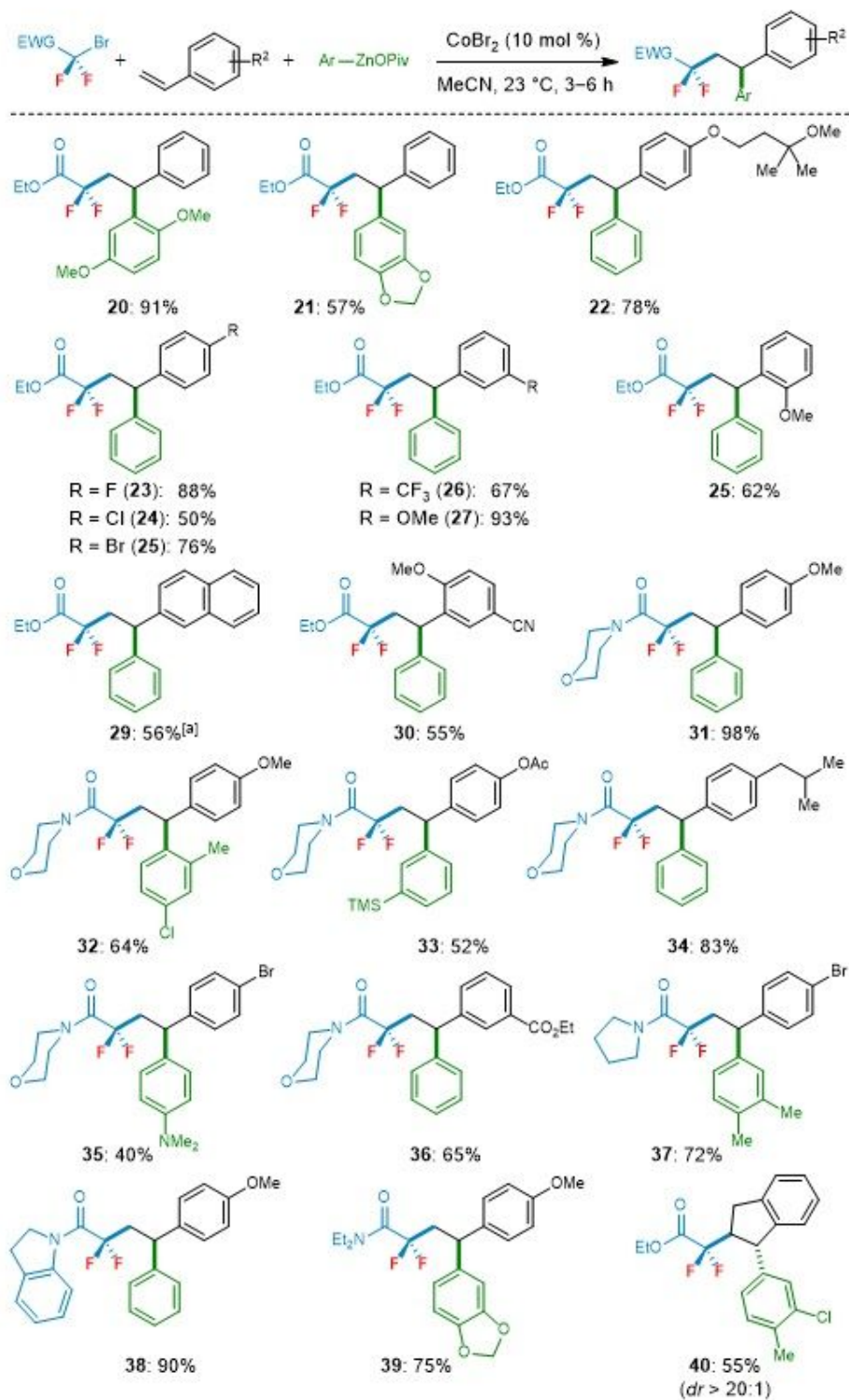


Figure 4

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), CoBr_2 (10 mol %), MeCN (2.0 mL), 23 °C, 3–6 h.

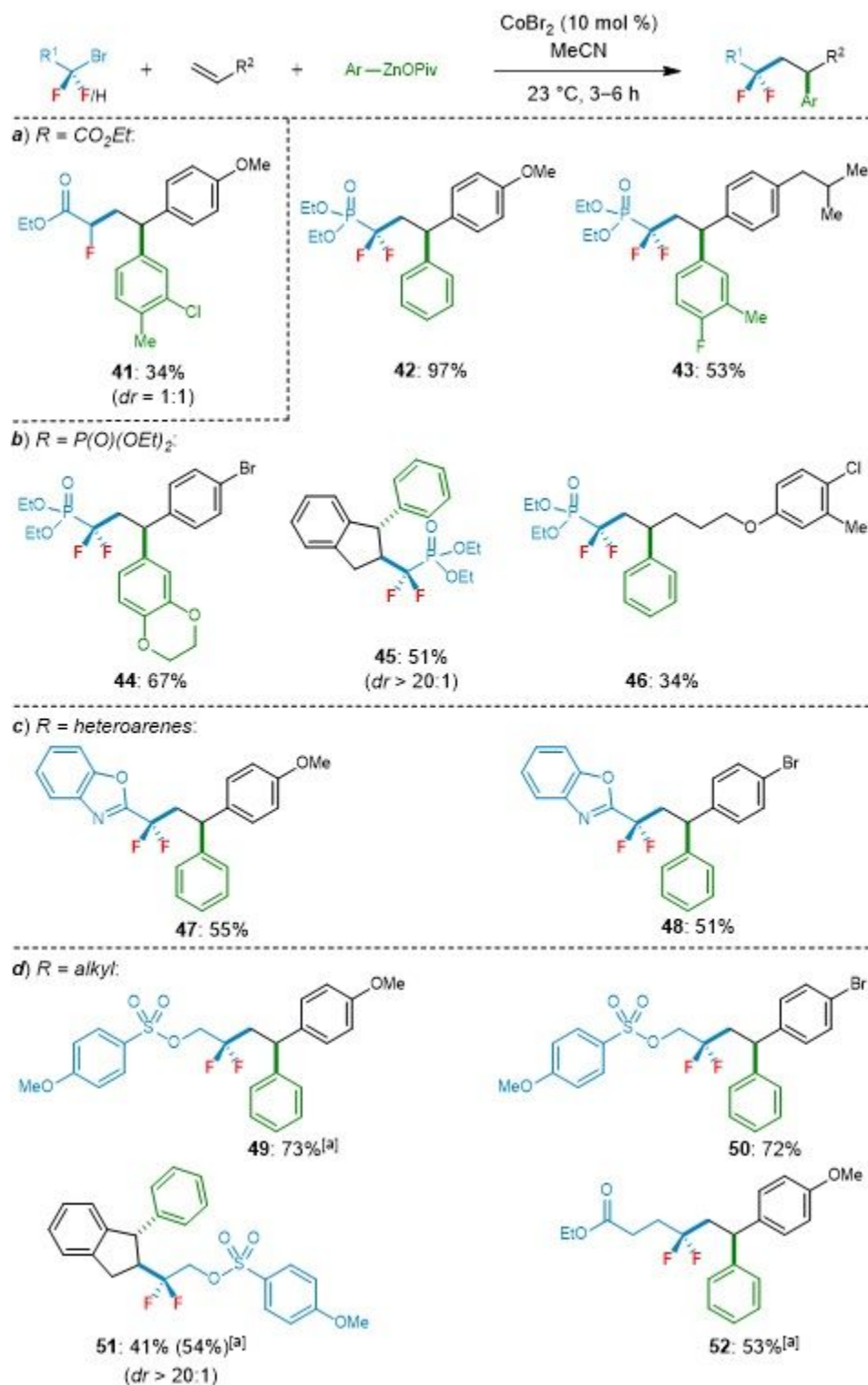
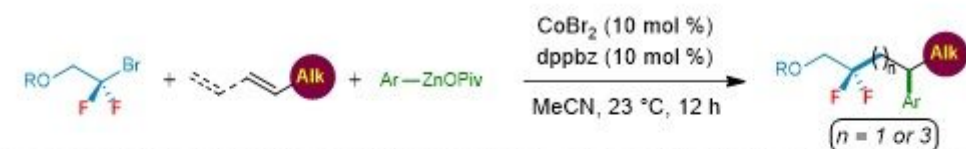
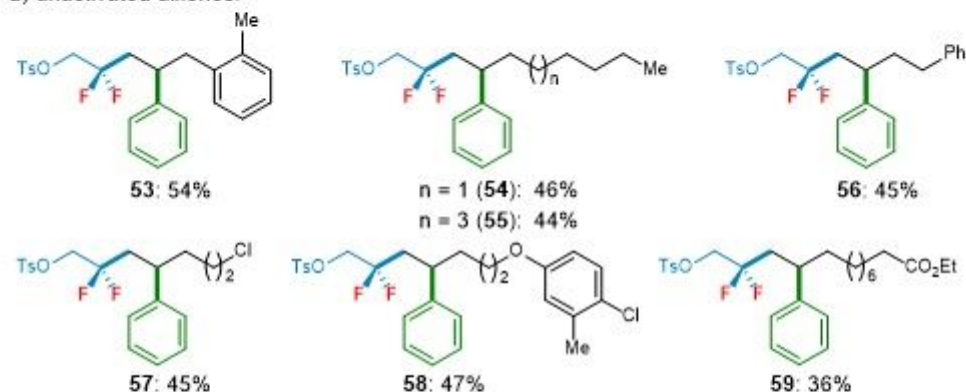


Figure 5

Scheme 5. Regioselective cobalt-catalyzed di-/monofluoroalkylarylation 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] $\text{Ph}_2\text{Zn} \cdot 2\text{Mg}(\text{OPiv})\text{Cl}$ (2.0 equiv) was used.



a) unactivated alkenes:



b) 1,3-dienes:

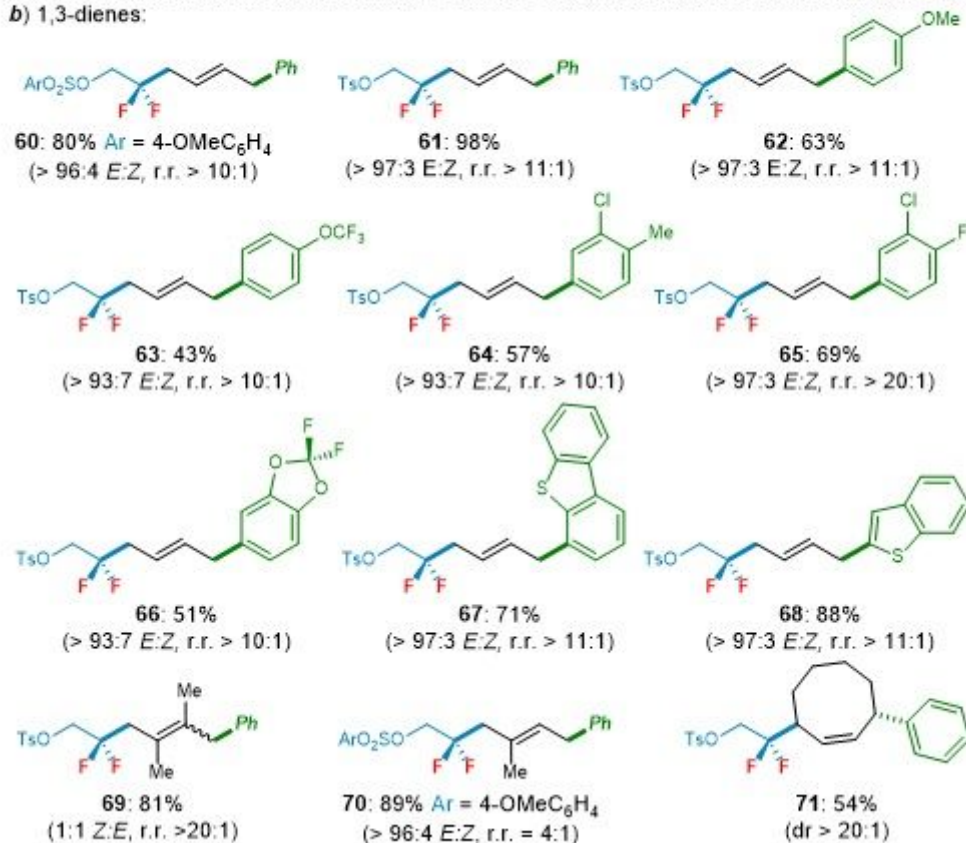


Figure 6

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.

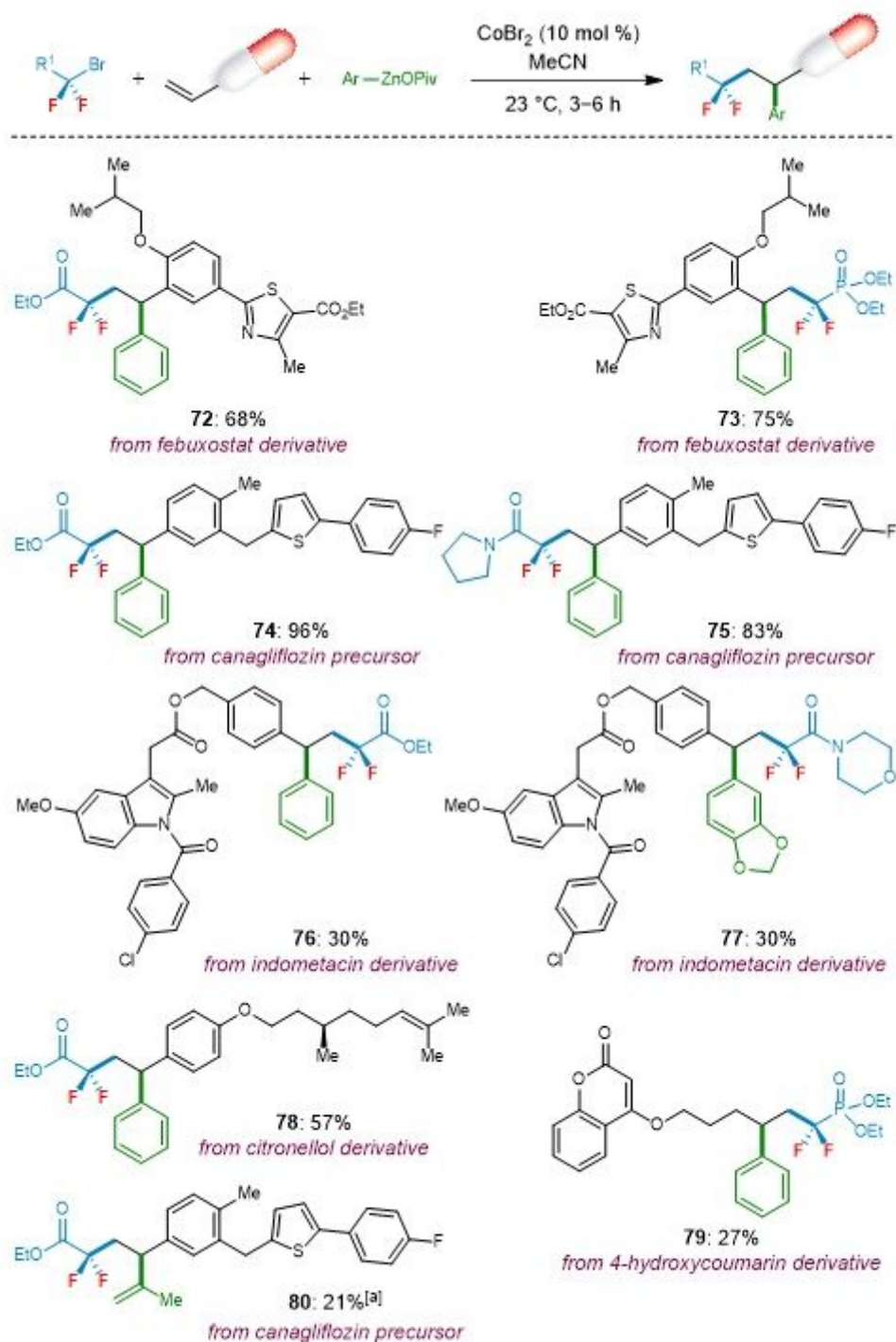
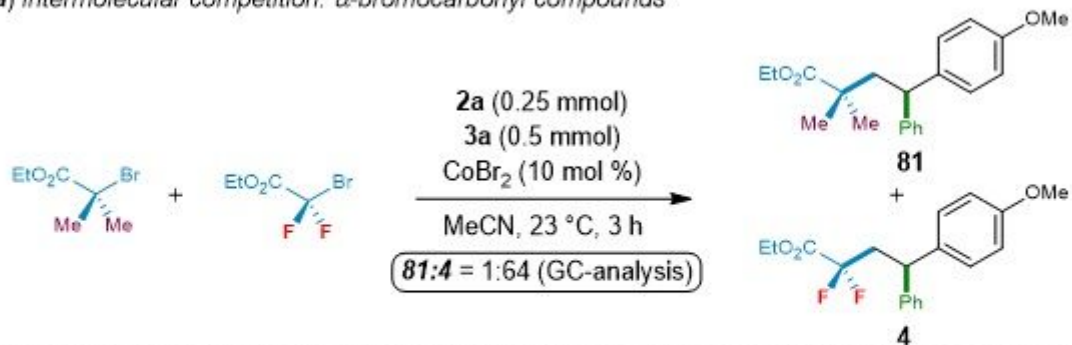


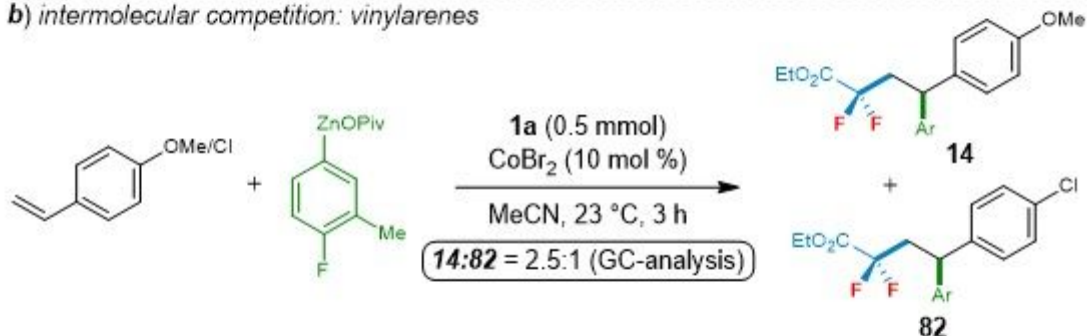
Figure 7

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

a) intermolecular competition: α -bromocarbonyl compounds



b) intermolecular competition: vinylarenes



c) intermolecular competition: arylzinc pivalates

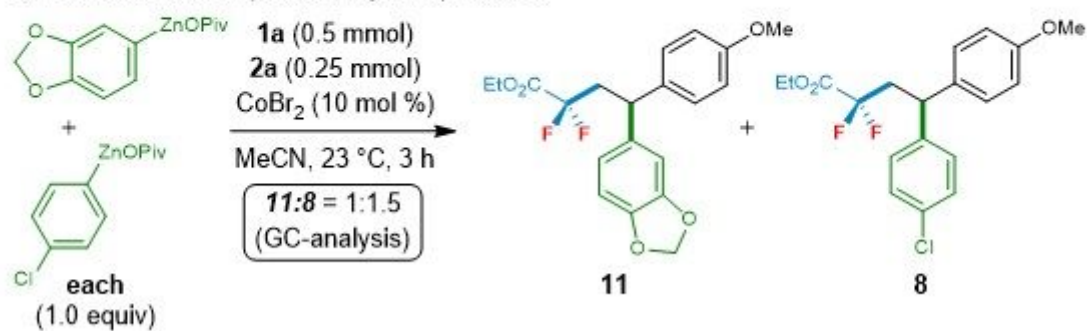
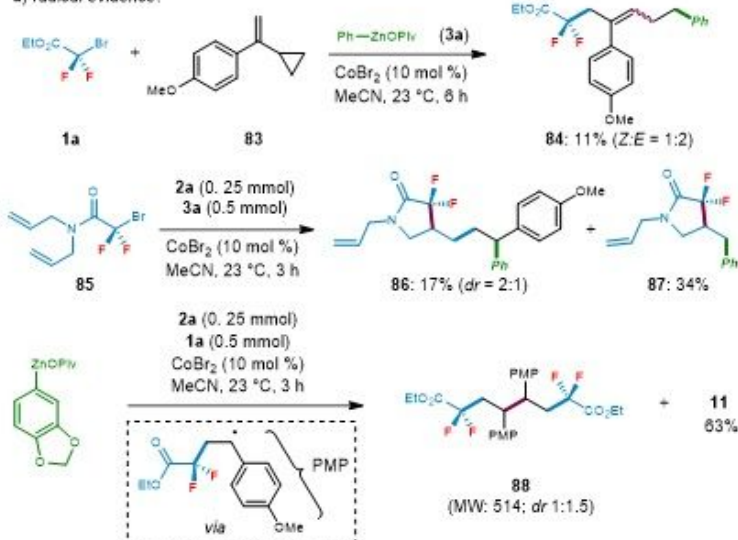


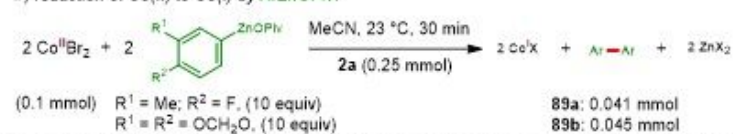
Figure 8

Scheme 8. Competition experiments.

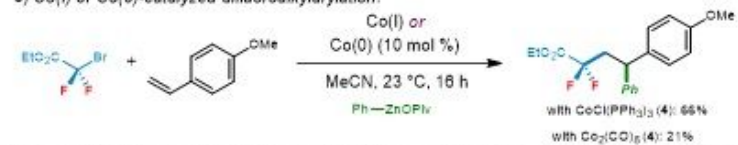
a) radical evidence:



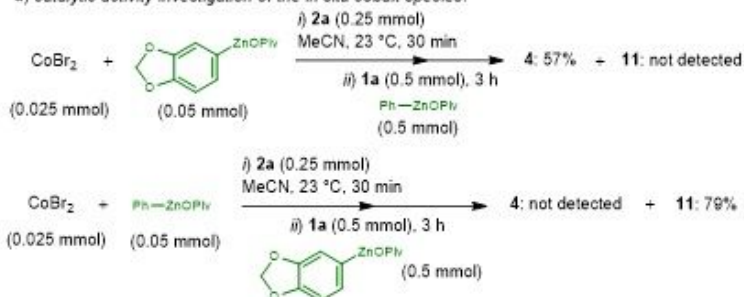
b) reduction of Co(II) to Co(I) by ArZnOPiv:



c) Co(I) or Co(0)-catalyzed difluoroalkylation:



d) catalytic activity investigation of the in situ cobalt species:



e) EPR experiments:

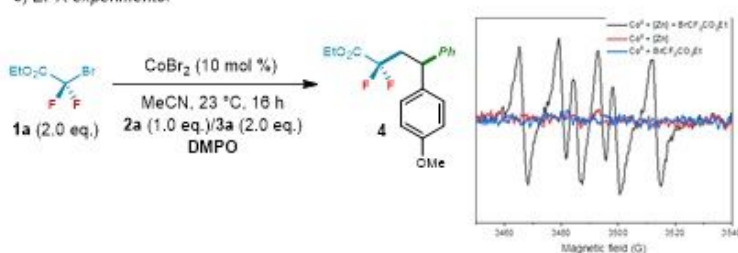


Figure 9

Scheme 9. Mechanistic studies for cobalt-catalyzed cascade difluoroalkylation.

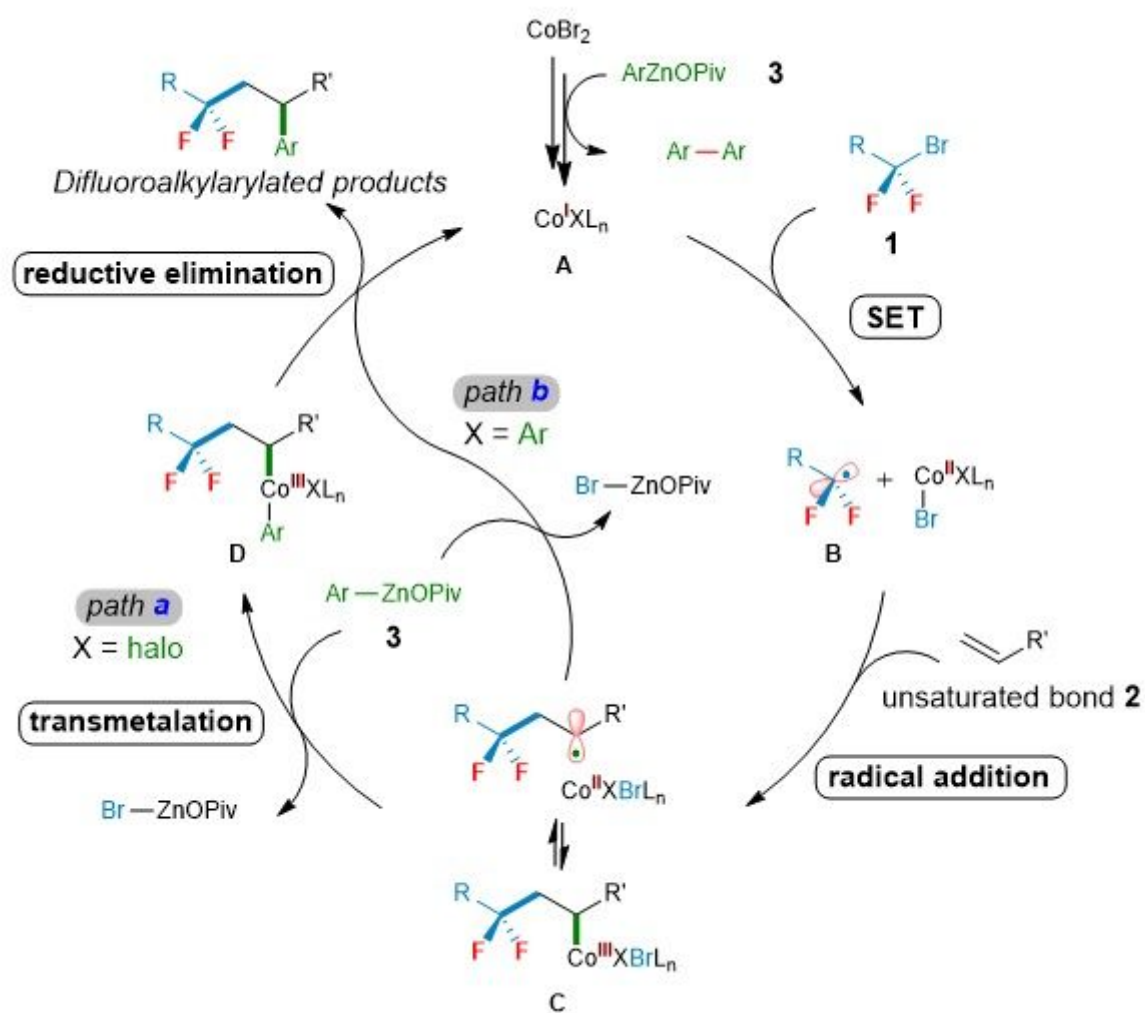
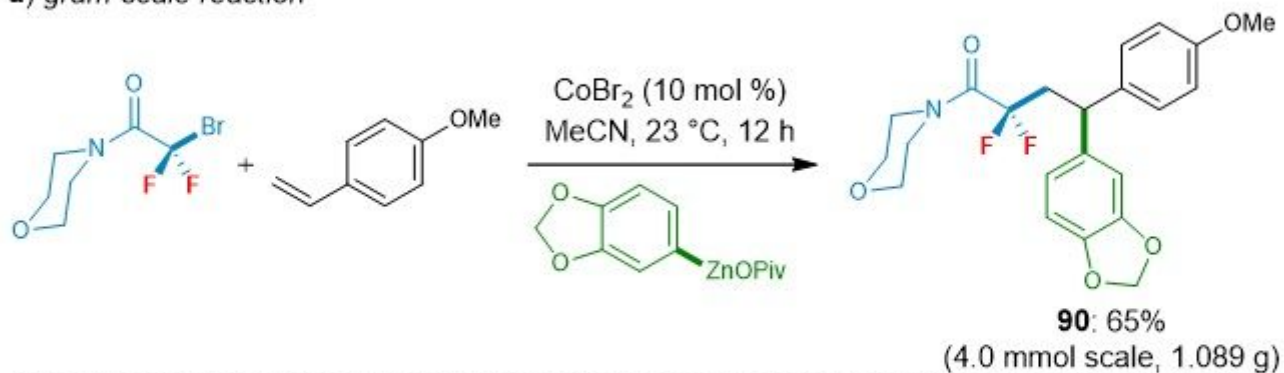


Figure 10

Scheme 10. Proposed catalytic cycle

a) gram-scale reaction



b) modification of difluoroalkylated products

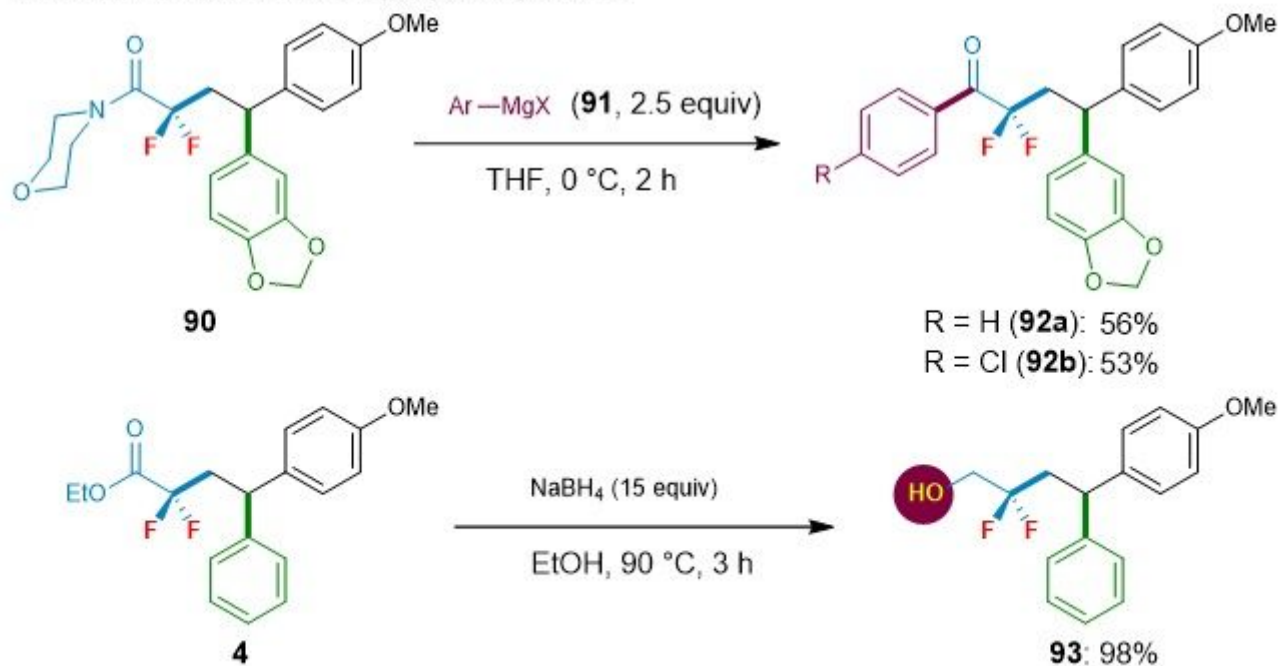


Figure 11

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

Supplementary Files

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