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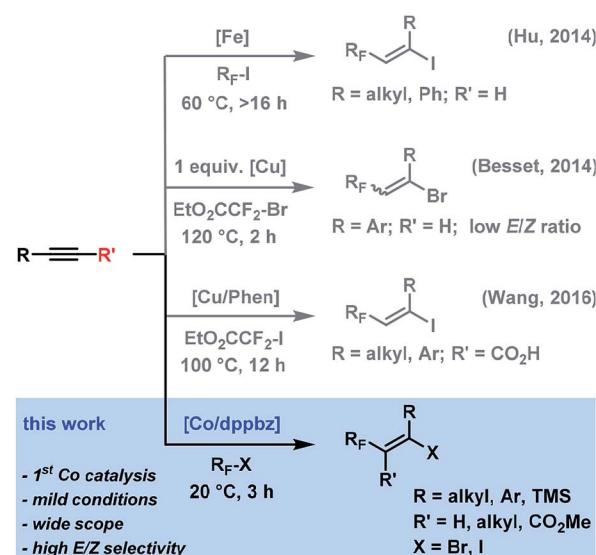
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1 Introduction

Fluorinated hydrocarbons constitute key structural motifs in many bioactive molecules, agrochemicals, and pharmaceuticals due to their high metabolic stability, lipophilicity, and bioavailability compared with the parent compounds.¹ Fluoroalkylation methods of easily accessible precursors have therefore attracted great interest in the past years.^{2,3} While many protocols are substitution processes that require highly pre-functionalized starting materials and produce unwanted by-products, direct additions to unsaturated hydrocarbons exhibit higher modularity and atom-efficiency and provide ample opportunities of regio- and stereocontrol. The addition of halo-fluoroalkanes to alkynes is an especially attractive tool due to the easy availability of the reagents and the great synthetic versatility of the resultant halo-fluoroalkenes. Many methods operate *via* an atom transfer radical addition (ATRA) mechanism in the presence of radical initiators (*e.g.* BET_3 , AIBN, $\text{Na}_2\text{S}_2\text{O}_3$ or light)⁴ that showed narrow substrate scope and poor selectivity. Mechanistically closely related transition metal-mediated halo-fluoroalkylations have been recently reported, but with a narrow focus on iodofluoroalkylations and/or moderate stereo-control (Scheme 1). Hu *et al.* devised an iron-catalyzed addition of perfluoroalkyl iodide to alkynes with moderate to good *E/Z*-selectivities in the presence of Cs_2CO_3 . The radical reaction with alkyl-substituted alkynes required long reaction times at $60\text{ }^\circ\text{C}$ and could not convert perfluoroalkyl bromides.⁵ Besset *et al.* postulated a different

mechanism for the copper-mediated synthesis of difluoromethyl alkenes from $\text{BrCF}_2\text{CO}_2\text{Et}$ and alkynes. However, significantly lower stereoselectivities were obtained and stoichiometric amounts of copper salt were employed.⁶ Very recently, Wang and co-workers reported a copper-catalyzed decarboxylative ATRA reaction between $\text{ICF}_2\text{CO}_2\text{Et}$ and substituted propionic acids.⁷

Despite the developments of novel iron- and copper-catalyzed procedures, the reactions generally utilize expensive fluoroalkyl iodides as starting materials, high catalyst loadings, long reaction times, and high reaction temperatures. An efficient and robust yet highly stereoselective method that operates at mild conditions and low catalyst loadings and that is applicable to various fluoroalkyl halides would constitute



Scheme 1 Metal-mediated halo-fluoroalkylations of alkynes.

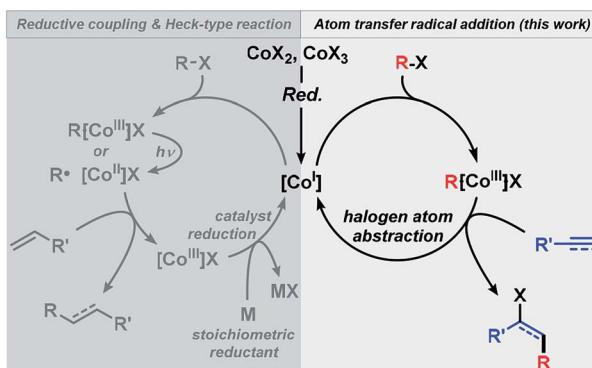
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a significant advancement of the current technology and have considerable use in the synthesis of densely functionalized fluorinated building blocks. To the best of our knowledge, there are no literature reports of ATRA reaction between alkyl halides and alkynes with low-valent cobalt catalysts. Here, we report the cobalt-catalyzed halofluoro-alkylation of alkynes which enables the highly regioselective and stereoselective synthesis of a diverse set of halofluoroalkenes under unprecedentedly mild conditions (Scheme 1).

The utility of alkyl halides in cross-couplings and reductive additions has recently been greatly enhanced by the development of low-valent iron group metal catalysts (Fe, Co, Ni)^{8–10} that engage in facile alkyl-X activation. The high propensity of late 3d transition metals to undergo single-electron transfer (SET) processes often results in the intermediacy of carbon-centered radical species.^{8g,h,9h,10f} The reductive formation of alkyl radicals from alkyl-X electrophiles is thermodynamically favoured when the formal electron septet-carbon is stabilized by heteroatoms, conjugation, hyperconjugation, or inductive effects. Efficient cobalt catalysts have been reported for several reductive coupling reactions between alkyl halides and Michael-type acceptors as well as for Heck-type reactions between alkyl halides and alkenes.¹¹ These processes mostly follow the same mechanistic scenarios involving (i) initial formation of a low-valent Co(i) species from a Co(ii,iii) precursor in the presence of a reductant; (ii) reductive cleavage of the alkyl halide to give an alkyl radical R[·] and a Co(ii) complex (by SET activation or homolysis of R-Co(iii)), (iii) addition of R[·] to the olefin and formation of an organocobalt species that is subject to disproportionation (Heck-type reaction) or hydrolysis (reductive coupling) to release the Co(iii) complex, (iv) regeneration of the Co(i) catalyst with a stoichiometric reductant (Scheme 2, left). We surmised that an ATRA reaction between alkyl halides and alkynes could follow a similar mechanism using low-valent Co catalysts but would require only catalytic amounts of a reductant (Scheme 2, right). Cobalt-catalyzed Heck-type and reductive coupling reactions were realized in the presence of stoichiometric reductants such as Zn, Mn, and Grignard reagents¹¹ which effect the Co(iii) → Co(i) reduction. Cobalt-catalyzed ATRA reactions of alkynes with alkyl halides have not been reported.



Scheme 2 Generalized mechanistic dichotomy of radical addition reactions under low-valent cobalt catalysis.

2 Results and discussion

2.1 Discovery of a cobalt-catalyzed ATRA reaction

We commenced our investigations with the reaction of phenyl-acetylene (**1a**) and ethyl bromodifluoroacetate (**2a**). Variations of reaction conditions, solvents, and catalysts led to an optimized procedure that utilized a three-component catalyst comprising of CoBr_2 , dppbz (1,2-bis(diphenylphosphino)benzene) and zinc in acetone/water at 20 °C to furnish the synthesis of the desired adduct ethyl 4-bromo-2,2-difluoro-4-phenylbut-3-enoate (**3a**) in 83% yield (87% GC yield, Table 1, entry 1). Significantly lower yields were obtained when replacing dppbz with other bidentate phosphines or 2,2'-bipyridine (entries 5–8). Other transition metals were inactive (entries 9–12). CoCl_2 and $\text{CoCl}_2 \cdot 4\text{H}_2\text{O}$ exhibited similar activity (entries 13, 14).

2.2 Substrate scope

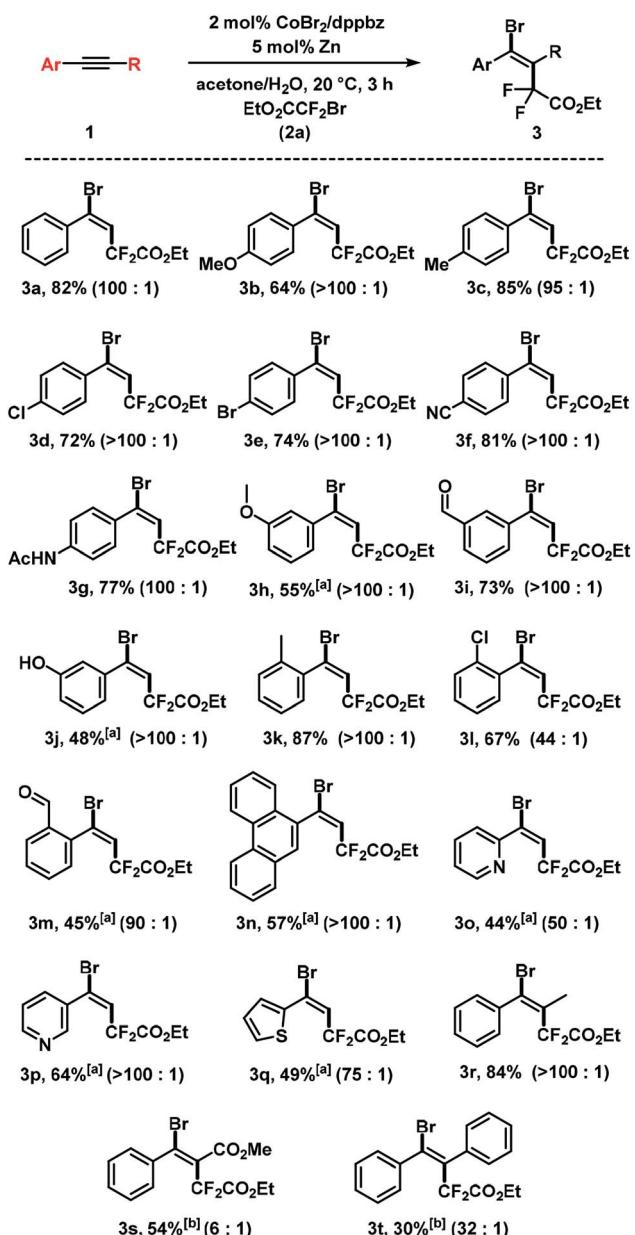
The substrate scope of reactions between terminal and internal aryl acetylenes and **2a** (Scheme 3). Many substitution patterns were tolerated (*ortho*, *meta*, *para*, electron-withdrawing, electron-donating substituents). The reaction displayed remarkable compatibility with functional groups including aldehydes, halides, nitriles, amides, hydroxyl, pyridines, thiophenes. All products were obtained with perfect regiocontrol and high *E/Z* diastereo-selectivity (>50/1). However, alkyl-substituted terminal alkynes fared poorer (Scheme 4). Reactions of **2a** with 1-heptyne

Table 1 Selected optimization experiments^a

Entry	Deviations from conditions above	3a ^b [%]	2 mol% CoBr_2 /dppbz 5 mol% Zn acetone/H ₂ O, 20 °C, 3 h $\text{EtO}_2\text{CCF}_2\text{Br}$ (2a)	
			Ph	3a
1	None	87 (63) ^c		
2	Without H_2O	69		
3	MeCN instead of acetone	65		
4	Without CoBr_2 or Zn or dppbz	0		
5	dppbz instead of dppbz	29 ^d		
6	dppen instead of dppbz	31 ^d		
7	dppf instead of dppbz	0 ^d		
8	bipy instead of dppbz	0 ^d		
9	FeBr_2 instead of CoBr_2	0 ^d		
10	NiCl_2 instead of CoBr_2	0 ^d		
11	CrCl_3 instead of CoBr_2	0 ^d		
12	Cp_2TiCl_2 instead of CoBr_2	0 ^d		
13	CoCl_2 instead of CoBr_2	82 ^d		
14	$\text{CoCl}_2 \cdot 4\text{H}_2\text{O}$ instead of CoBr_2	83 ^d		

^a Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), CoBr_2 (2 mol%), dppbz (2 mol%), Zn (5 mol%), 0.6 mL acetone/H₂O, 20 °C, 3 h. ^b GC yield vs. internal *n*-dodecane. ^c 1 mol% CoBr_2 , 1 mol% dppbz, 10 mol% Zn. ^d 5 mol% CoBr_2 , 5 mol% dppbz, 20 mol% Zn.

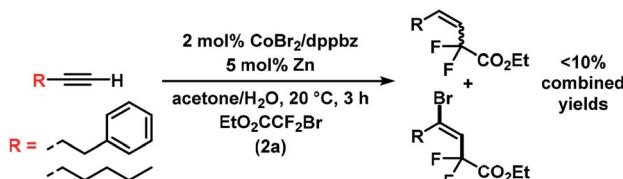




Scheme 3 Cobalt-catalyzed bromo-carboxydifluoromethylation of alkynes. Standard conditions: 1 (0.3 mmol), 2a (0.45 mmol), CoBr₂ (2 mol%), dppbz (2 mol%) and Zn (5 mol%), 0.6 mL acetone/H₂O, 20 °C, 3 h under N₂. Isolated yields are given; E/Z ratios in parentheses (by ¹⁹F NMR). ^[a] 20 mol% Zn. ^[b] 40 mol% Zn, 8 h.

and 4-phenyl-1-butyne, respectively, afforded mixtures of bromo-difluoro-alkylation and hydrodifluoroalkylation products in low yields.

We then examined the cobalt-catalyzed halofluoroalkylation with different fluoroalkyl halides (Scheme 5). Iododifluoroacetate $\text{ICF}_2\text{CO}_2\text{Et}$, perfluoroalkyl iodides such as $\text{C}_4\text{F}_9\text{I}$, $\text{C}_6\text{F}_{13}\text{I}$ and $\text{C}_8\text{H}_{17}\text{I}$, and the perfluoroalkyl bromide $\text{C}_8\text{F}_{17}\text{Br}$ were competent electrophiles which afforded the desired adducts in good to excellent yields. The fluoroalkyl bromides gave generally better E/Z selectivities than the iodides. While this trend is in full agreement with the literature, it can now be harnessed at much milder



Scheme 4 Reactions with alkyl-substituted terminal alkynes.

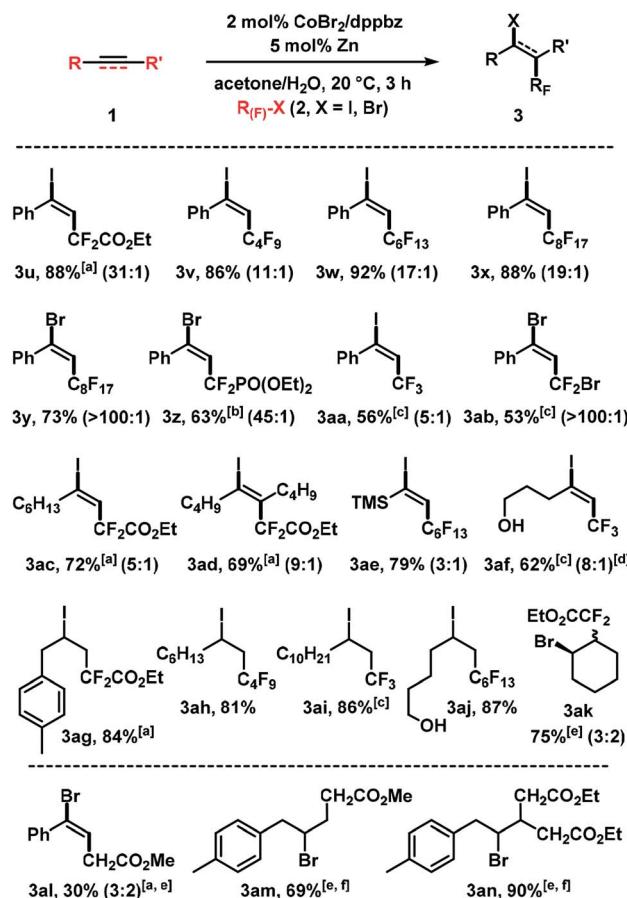
conditions (room temp., 2 mol% catalyst, 3 h). $\text{BrCF}_2\text{PO}(\text{OEt})_2$, CF_3I , and CF_2Br_2 afforded slightly lower yields; the reaction with CF_3I exhibited low stereocontrol. Reactions of alkyl-substituted alkynes with fluoroalkyl iodides gave good yields and moderate E/Z selectivities (3ac–3af). The reaction conditions were also applied to reactions of (cyclo)alkenes with halofluoroacetates (3ag–3ak). A method extension to reactions of simple bromoacettes with alkenes gave the desired adducts 3al–3an.

The synthetic utility of the stereoselective cobalt-catalyzed halo-fluoroalkylation protocol was demonstrated in a gram-scale setup which delivered pure ethyl (E)-4-bromo-2,2-difluoro-4-phenyl-but-3-enoate (3a) in 86% isolated yield (1.32 g) after 3 h. Substitution of the Br substituent in 3a by Sonogashira and Suzuki cross-coupling reactions, respectively, afforded the fluorinated alkenes in very good yields and with complete retention of stereochemistry (Scheme 6).

2.3 Mechanistic studies

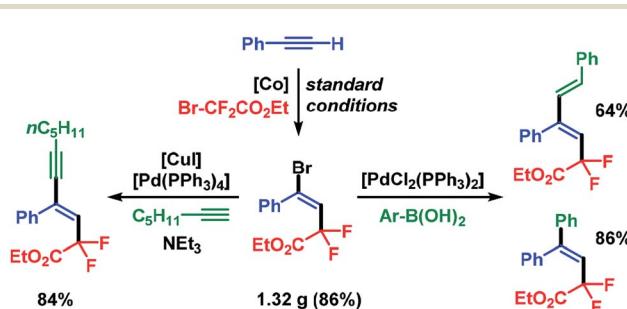
Further attention was devoted to the study of the reaction mechanism. In addition to the initial optimization reactions (Table 1), key mechanistic experiments were conducted. The model reaction between 1a and 2a was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The TEMPO– $\text{CF}_2\text{CO}_2\text{Et}$ adduct was observed by mass spectrometry (Scheme 7, eqn (1)). The TEMPO– $\text{CF}_2\text{CO}_2\text{Et}$ adduct was not detected when treating 2a with equimolar Zn which supports the notion that the SET reduction of the alkyl halide is induced by the cobalt catalyst (Scheme 7, eqn (2)). Upon employment of cyclo-propylacetylene (4), the vinylcyclopropane product was formed in 11% yield while ring-opening to the 7-bromohepta-3,4-dienoate (56%) was the major pathway. This is in full agreement with the intermediacy of an internal vinyl radical formed by radical addition of $\text{EtO}_2\text{CCF}_2^{\cdot}$ to the alkyne (Scheme 7, eqn (3)). Identical rates and yields were observed in reactions where 1a and 2a were successively added to the catalyst solution. The reverse order of addition (2a, then 1a) gave an identical result. Importantly, no product was formed when prior to the addition of 1a and 2a – the catalyst suspension (CoBr₂, dppbz, Zn) was filtered (to remove residual zinc) or when the supernatant solution was decanted into a new reaction vessel (eqn (4)). These experiments suggest that the initially formed Co(i) species alone cannot catalyze the reaction but requires the presence of zinc, at least for the first turnover of the catalytic mechanism. Zn is employed only in catalytic amounts (5 mol%, i.e. 2.5 equiv. per Co)! The addition of sodium iodide and sodium bromide, respectively, shed light on the nature of the operating halogen transfer. 1a and 2a reacted with added NaI





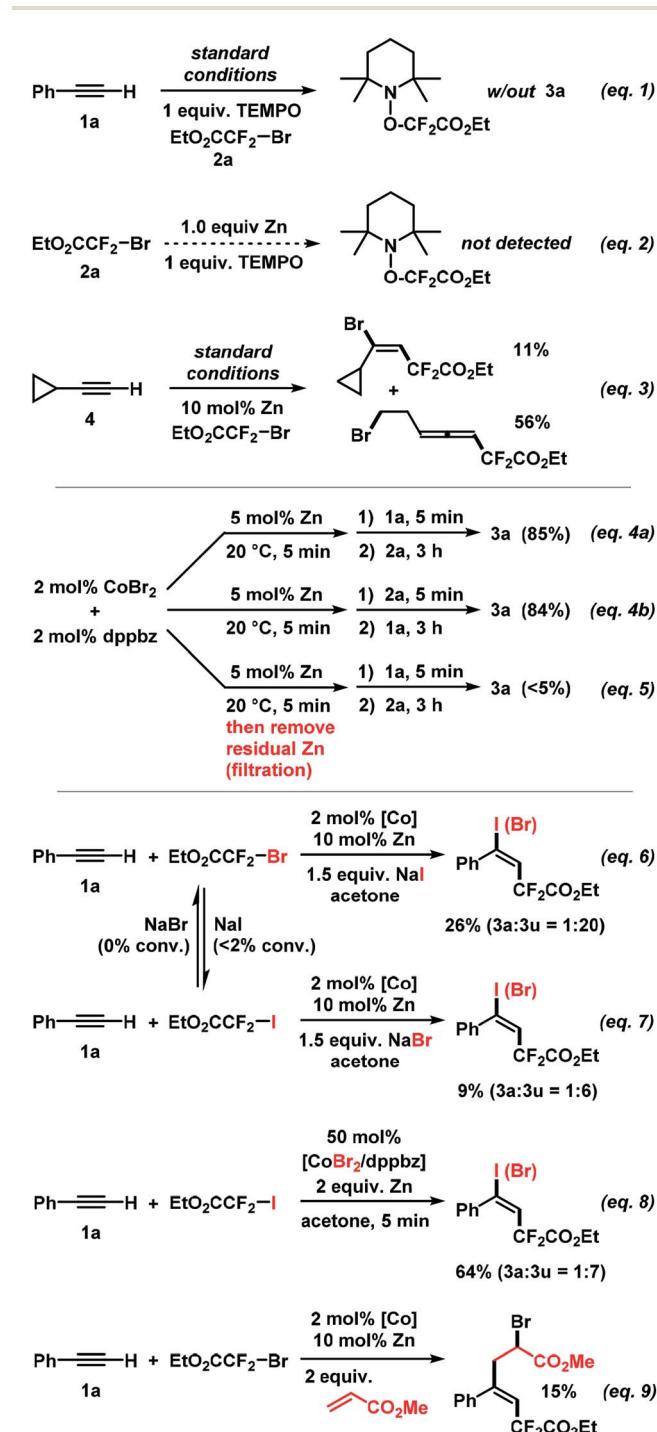
Scheme 5 Cobalt-catalyzed halo-fluoroalkylation of alkynes and alkenes. Standard conditions: 1 (0.3 mmol), 2 (0.45 mmol), CoBr_2 (2 mol%), dppbz (2 mol%), Zn (5 mol%), 0.6 mL acetone/ H_2O , 20 °C, 3 h under N_2 . Isolated yields given; E/Z ratios in parentheses (by ^{19}F NMR). ^[a] 20 mol% Zn. ^[b] $\text{R}_\text{F}-\text{Br}$ (1.0 equiv.), 10 mol% Zn. ^[c] $\text{R}_\text{F}-\text{X}$ (3.0 equiv.), 10 mol% Zn. ^[d] E/Z ratio of isolated products. ^[e] 10 mol% Zn. ^[f] 6 h.

(1.5 equiv.) to give the iodo adduct **3u** as major product (**3a** : **3u** = 1 : 20, Scheme 7, eqn (6)). With NaBr added, the reaction between **1a** and **2b** gave **3a** and **3u** in a 1 : 6 ratio (Scheme 7, eqn (7)). Control experiments documented that no $\text{EtO}_2\text{CCF}_2\text{I}$ was converted into $\text{EtO}_2\text{CCF}_2\text{Br}$ using NaBr as additive; only minimal amounts of $\text{EtO}_2\text{CCF}_2\text{Br}$ (<2%) were converted to $\text{EtO}_2\text{CCF}_2\text{I}$ with NaI as additive under the same conditions. A similar outcome was observed when the standard reaction was



Scheme 6 Post-ATRA transformations by cross-coupling reactions.

performed with 50 mol% $\text{CoBr}_2/\text{dppbz}$ (**3a** : **3u** = 1 : 7, Scheme 7, eqn (8)). These experiments document that the halogen atom X in the product does not originate from the electrophilic $\text{R}_\text{F}-\text{X}$ via a direct radical chain transfer but is transferred from the cobalt catalyst. This is a fine but important distinction from previously reported ATRA reactions that all involved halogen transfer from $\text{R}_\text{F}-\text{X}$ to the vinyl radical. This has great implications for catalyst design and reaction development as the thermodynamics and kinetics of the halogen atom transfer step are



Scheme 7 Key mechanistic experiments.



no longer depending on the nature of the employed substrates but can be finely tuned through the stereochemical properties of the catalyst. We further believe that halogen atom transfer to a vinyl radical intermediate (rather than a vinyl cation) is operative: (i) the addition of water (as a nucleophile) resulted in no product bearing oxo functions; (ii) the presence of methyl acrylate as a radical acceptor led to the formation of the heptene-1,7-dioate *via* radical insertion of the acrylate (eqn (9)). A cationic intermediate would not add to this Michael acceptor.

Catalyst formation and substrate additions were monitored by ^{31}P NMR and ^1H NMR spectroscopy (Fig. 1). The reduction of the (NMR silent) $\text{CoBr}_2/\text{dppbz}$ mixture with Zn resulted in a Co(i) species with a ^{31}P resonance at 75.2 ppm. The ^1H NMR spectrum of this low-spin Co(i) complex gave signals 7–8 ppm. No changes were observed in ^{31}P and ^1H NMR spectra when phenyl acetylene (**1a**) was added to Co(i) which suggests the absence of significant alkyne–catalyst coordination. On the other hand, complete disappearance of the ^{31}P (75.2 ppm) and ^1H (7–8 ppm) signals was observed upon addition of $\text{EtO}_2\text{CCF}_2\text{Br}$ (**2a**). This is a direct consequence of the reductive activation of **2a** which leads to a paramagnetic Co(II,III) species and the carbon-centered radical.¹² These results are consistent with the UV-vis spectra (Fig. 2). Reduction of Co(II) with Zn (and removal of residual Zn) resulted in an intense absorption of the

Co(i) complex at 428 nm (green curve). Addition of **1a** to this solution gave no change of the absorption in this region (blue curve), whereas the addition of **2a** to Co(i) led to immediate colour change and the appearance of two weak bands at 412 and 451 nm (yellow curve).

The standard reaction between **1a** and **2a** went to completion within 90 min (with 2 mol% catalyst) and 12 min (4 mol% catalyst), respectively. Analysis of the initial rates (0.5–8 min, 1–4 mol% catalyst) displayed a near- 2^{nd} order behavior of the catalyst concentration. We postulate the following reaction mechanism (Scheme 8). Complexation of dppbz with CoBr_2 leads to the formation of $[\text{Co}^{\text{II}}(\text{dppbz})_2\text{Br}]^+$ as observed by the soft and inert mass spectrometric technique for sensitive organometallics LIFDI-MS (liquid injection field desorption ionization mass spectrometry). Reduction of the Co(II) complex with equimolar Zn generates the catalytically active $[\text{Co}^{\text{I}}(\text{dppbz})_2\text{Br}]$.^{12d} Exposure to oxygen/air gives $[\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}(\text{O}_2)]$ (LIFDI-MS). $[\text{Co}^{\text{I}}(\text{dppbz})_2\text{Br}]$ effects the reductive single-electron activation of $\text{R}_\text{F}\text{Br}$ to give a $[\text{R}_\text{F}\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$ species (LIFDI-MS)¹² which is presumably a direct result of rapid combination of the intermediate Co(II) complex and free radical R_F^\cdot .¹⁴ We have demonstrated that in the absence of residual zinc $[\text{R}_\text{F}\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$ is not a catalyst (*vide supra*). Therefore, we propose – in contrast to the light-induced Co–R homolysis^{11g,13} – the reduction of $[\text{R}_\text{F}\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$ by Zn in the first catalytic turnover to form the unstable complex $[\text{R}_\text{F}\text{Co}^{\text{II}}(\text{dppbz})_2\text{Br}]$. Dissociation of the fluoroalkyl radical R_F^\cdot regenerates $[\text{Co}^{\text{I}}(\text{dppbz})_2\text{Br}]^{12h-j}$ which can undergo another reductive activation of $\text{R}_\text{F}\text{X}$ to give $[\text{R}_\text{F}\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$. The catalytic amounts of Zn present in the reaction dictate that another mechanism operates from the 2^{nd} turnover on, most likely an ATRA reaction involving halogen atom transfer from the cobalt complex $[\text{R}_\text{F}\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$. Accordingly, the addition of R_F^\cdot to the alkyne results in the formation of a vinyl radical intermediate which undergoes rapid halogen atom abstraction from $[\text{Co}^{\text{III}}(\text{dppbz})_2\text{Br}]^+$ to form the catalytically active Co(i) complex and R_F^\cdot .¹⁵ The high *E*-selectivity of the radical addition is

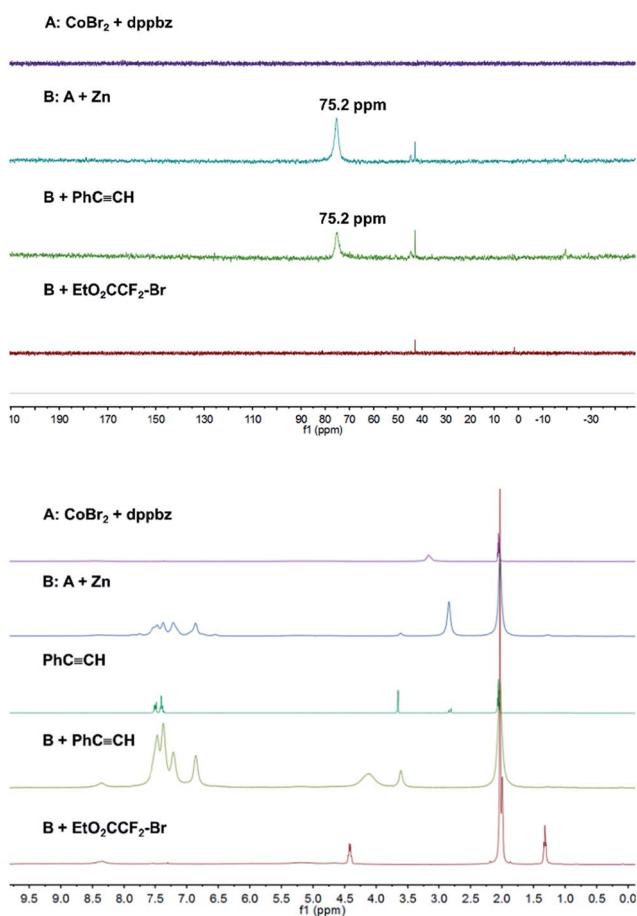


Fig. 1 ^{31}P NMR (top) and ^1H NMR (bottom) monitoring of catalyst formation and reductive electrophile activation.

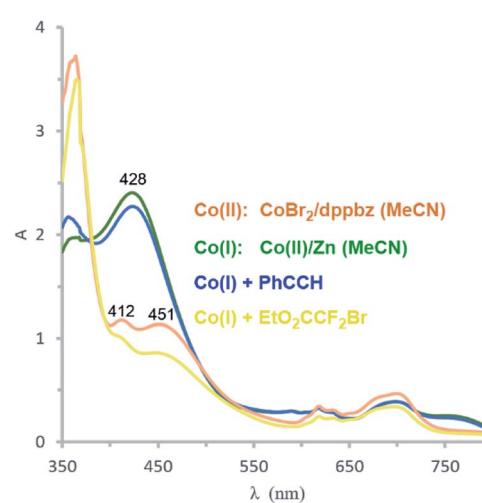
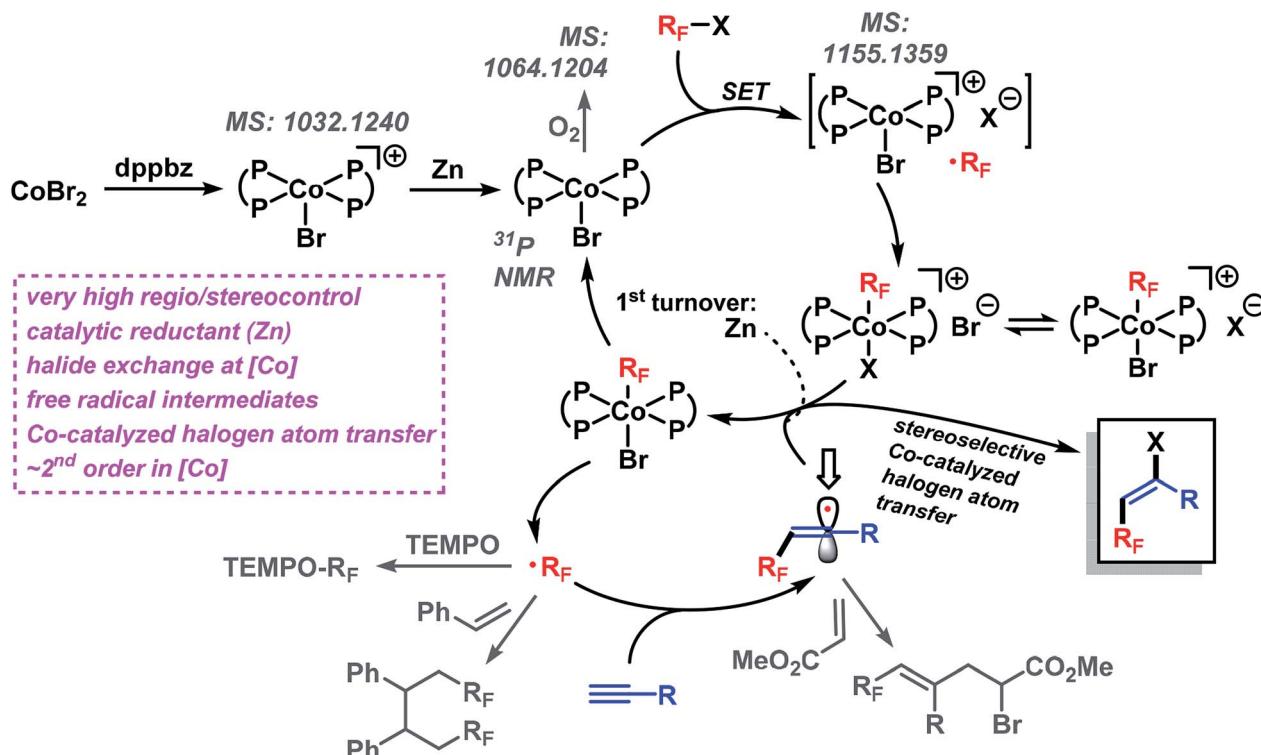


Fig. 2 UV-vis absorption spectra: $\text{CoBr}_2/\text{dppbz}$ (orange); after reduction of Co(II) with Zn to Co(i) (green); Co(i) with 1 equiv. **1a** (blue); Co(i) with 1 equiv. of **2a** (yellow).





Scheme 8 Proposed reaction mechanism.

a direct consequence of the steric hindrance by the R_F group in the vinyl radical.¹⁶ The higher *E/Z* stereoselectivity of the bro-moalkylation over the iodoalkylation reactions can be explained by the shorter Co-Br bond (vs. Co-I) in the key catalytic Co(III) species which effects an enhanced facial differentiation of the vinyl radical. The facile operation of this halogen atom transfer step with the intermediate vinyl radical is the key to the realization of an overall process that is catalytic in both metals, Co and Zn.

3 Conclusions

We have developed a convenient cobalt-catalyzed halofluoroalkylation that exhibits wide substrate scope including terminal and internal alkynes, alkenes, and various fluoroalkyl and alkyl bromides and iodides. The protocol enables the highly regio-selective and stereoselective synthesis of densely functionalized halogenated (*E*)-alkenes under very mild reaction conditions (2 mol% catalyst, 5 mol% Zn, acetone/water, 20 °C, 3 h). Contrary to literature reports, mechanistic studies documented for the first time that the halogen atom transfer is a cobalt-mediated process. The $R_F\text{Co}^{\text{III}}\text{X}$ complex is the key catalytic intermediate which generates the free $R_F\cdot$ radical and mediates the halogen atom transfer to the terminal vinyl radical. This mechanistic deviation from substrate control to catalyst control may provide the basis for the development of related halogen atom transfer reactions through catalyst design. Further, this ATRA reaction operates without a stoichiometric reductant for the regeneration of the low-valent Co(I) catalyst.

The high functional group tolerance and mild reaction conditions make this protocol highly attractive in the context of complex molecule synthesis with potential utility for medicinal chemistry endeavours.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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