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Stereoselective cobalt-catalyzed halofluoroalkylation of alkynes†

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Stereoselective additions of highly functionalized reagents to available unsaturated hydrocarbons are an attractive synthetic tool due to their high atom economy, modularity, and rapid generation of complexity. We report efficient cobalt-catalyzed (*E*)-halofluoroalkylations of alkynes/alkenes that enable the construction of densely functionalized, stereodefined fluorinated hydrocarbons. The mild conditions (2 mol% cat., 20 °C, acetone/water, 3 h) tolerate various functional groups, *i.e.* halides, alcohols, aldehydes, nitriles, esters, and heteroarenes. This reaction is the first example of a highly stereoselective cobalt-catalyzed halo-fluoroalkylation. Unlike related cobalt-catalyzed reductive couplings and Heck-type reactions, it operates *via* a radical chain mechanism involving terminal halogen atom transfer which obviates the need for a stoichiometric sacrificial reductant.

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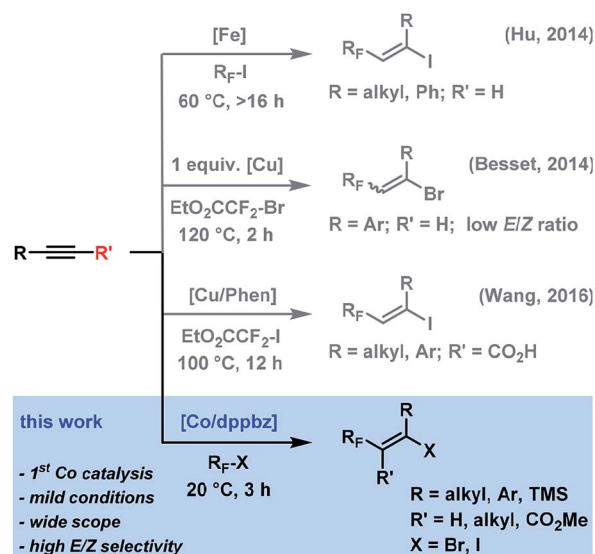
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1 Introduction

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 °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 propiolic 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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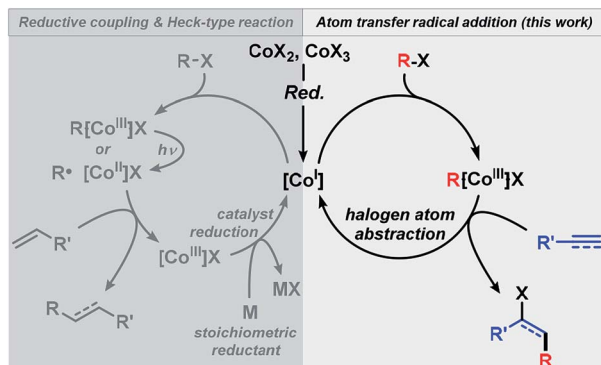
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a significant advancement of the current technology and have considerable use in the synthesis of densely functionalized fluorinated building blocks. To the best of our knowledge, there are no literature reports of ATRA reaction between alkyl halides 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 phenylacetylene (**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 CoBr₂, 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). CoCl₂ and CoCl₂·4H₂O 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 [%]
1	None	87 (63) ^c
2	Without H ₂ O	69
3	MeCN instead of acetone	65
4	Without CoBr ₂ or Zn or dppbz	0
5	dppe 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 ₂ TiCl ₂ instead of CoBr ₂	0 ^d
13	CoCl ₂ instead of CoBr ₂	82 ^d
14	CoCl ₂ ·4H ₂ O instead of CoBr ₂	83 ^d

dppbz

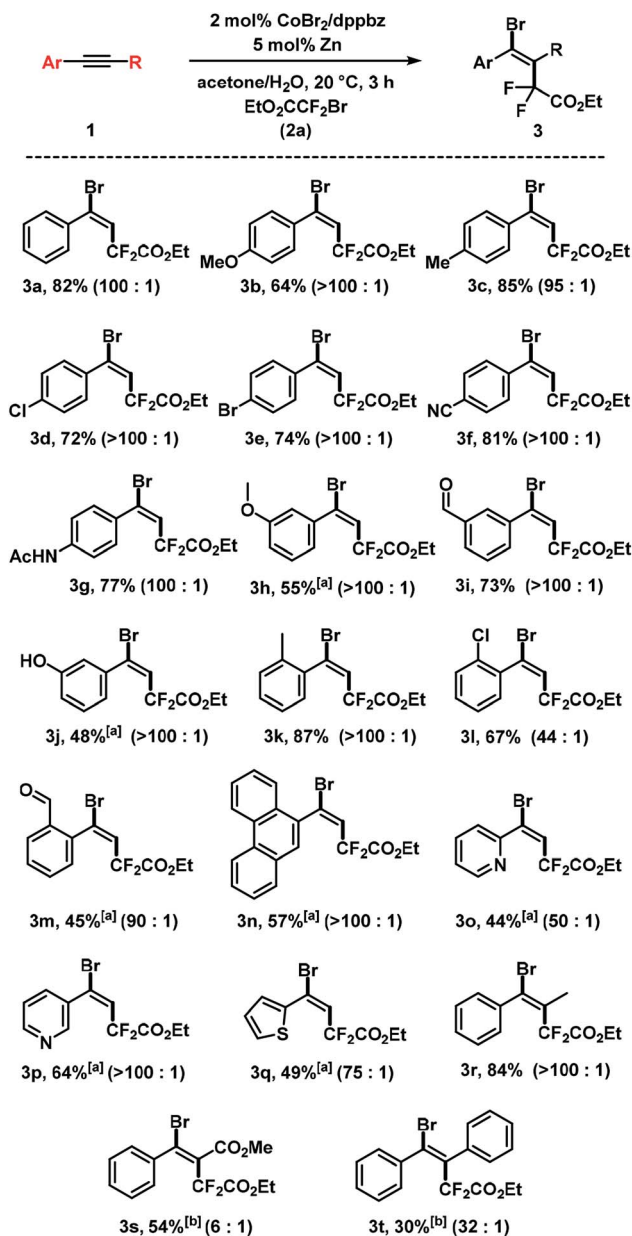
dppe

dppen

bipy

^a Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), CoBr₂ (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% CoBr₂, 1 mol% dppbz, 10 mol% Zn. ^d 5 mol% CoBr₂, 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 halo-fluoroalkylation with different fluoroalkyl halides (Scheme 5). Iododifluoroacetate ICF₂CO₂Et, perfluoroalkyl iodides such as C₄F₉I, C₆F₁₃I and C₈H₁₇I, and the perfluoroalkyl bromide C₈F₁₇Br 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.

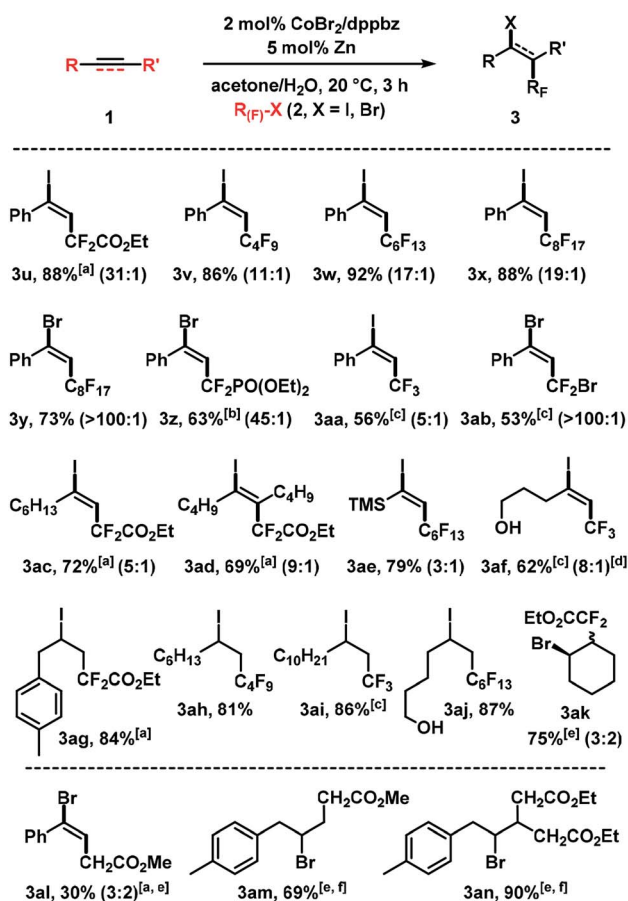
conditions (room temp., 2 mol% catalyst, 3 h). BrCF₂PO(OEt)₂, CF₃I, and CF₂Br₂ afforded slightly lower yields; the reaction with CF₃I exhibited low stereocontrol. Reactions of alkyl-substituted alkynes with fluoroalkyl iodides gave good yields and moderate E/Z selectivities (**3ac–3af**). The reaction conditions were also applied to reactions of (cyclo)alkenes with halo-fluoroacetates (**3ag–3ak**). A method extension to reactions of simple bromoacetates 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

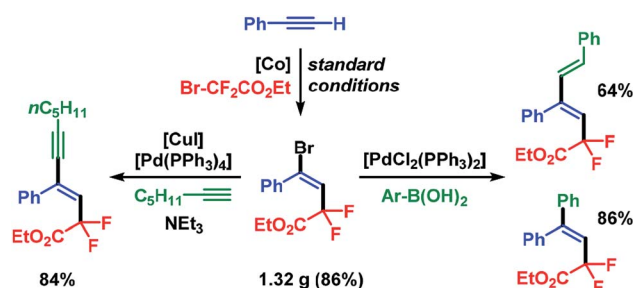
Further attention was devoted to the study of the reaction mechanism. In addition to the initial optimization reactions (Table 1), key mechanistic experiments were conducted. The model reaction between **1a** and **2a** was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The TEMPO–CF₂CO₂Et adduct was observed by mass spectrometry (Scheme 7, eqn (1)). The TEMPO–CF₂CO₂Et 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 EtO₂CCF₂• 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





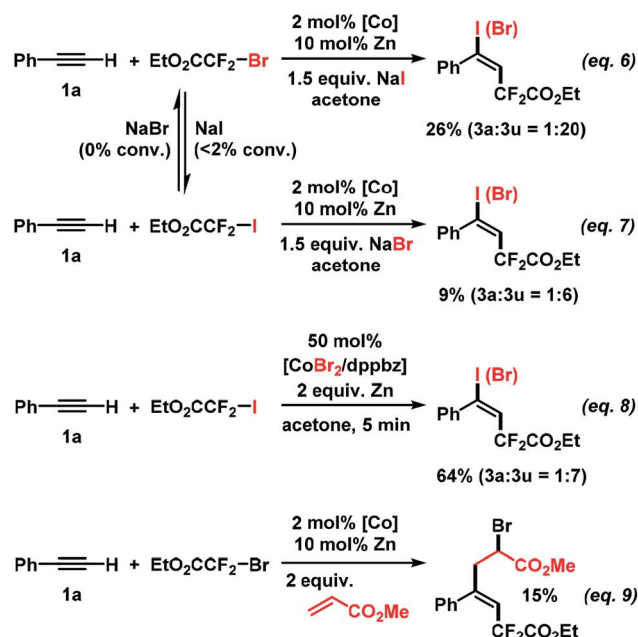
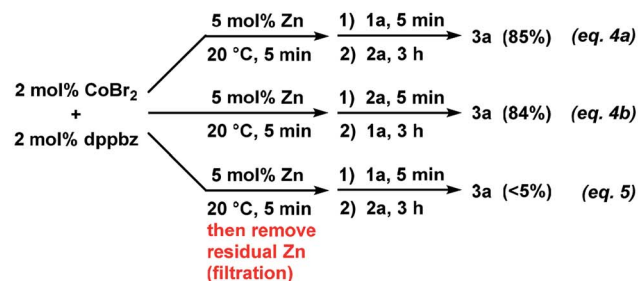
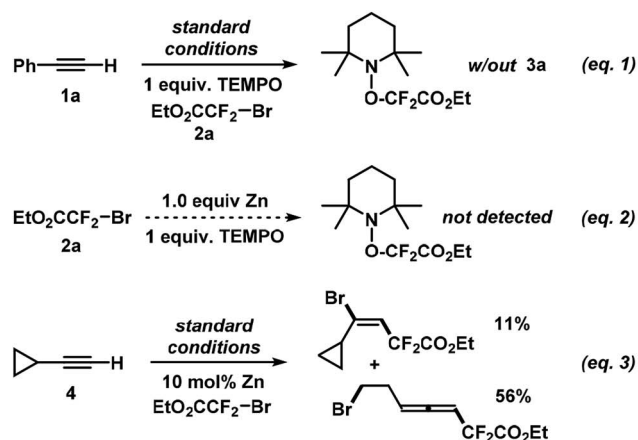
Scheme 5 Cobalt-catalyzed halo-fluoroalkylation of alkynes and alkenes. Standard conditions: **1** (0.3 mmol), **2** (0.45 mmol), CoBr₂ (2 mol%), dppbz (2 mol%), Zn (5 mol%), 0.6 mL acetone/H₂O, 20 °C, 3 h under N₂. Isolated yields given; E/Z ratios in parentheses (by ¹⁹F NMR). ^[a] 20 mol% Zn. ^[b] R_F-Br (1.0 equiv.), 10 mol% Zn. ^[c] R_F-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 EtO₂CCF₂I was converted into EtO₂CCF₂Br using NaBr as additive; only minimal amounts of EtO₂CCF₂Br (<2%) were converted to EtO₂CCF₂I 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% CoBr₂/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 R_FX *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 R_FX 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 stereoelectronic 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-2nd 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 $[\text{Co}^{\text{I}}(\text{dppbz})_2\text{Br}]^+$ 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 2nd 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

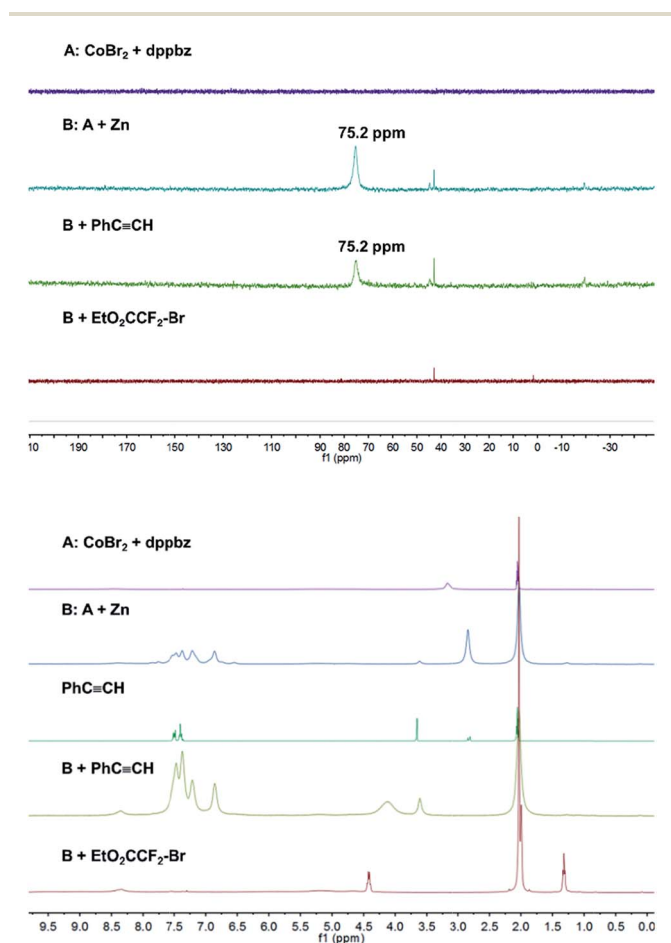


Fig. 1 ^{31}P NMR (top) and ^1H NMR (bottom) monitoring of catalyst formation and reductive electrophile activation.

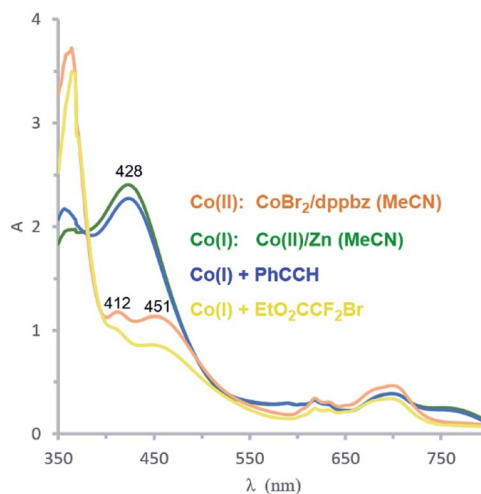


Fig. 2 UV-vis absorption spectra: $\text{CoBr}_2/\text{dppbz}$ (orange); after reduction of Co(II) with Zn to Co(I) (green); Co(I) with 1 equiv. **1a** (blue); Co(I) with 1 equiv. of **2a** (yellow).



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