Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202201928
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Ru(II)-Catalyzed Hydroarylation of in situ Generated 3,3,3-Trifluoro-1-propyne by C–H Bond Activation: A Facile and Practical Access to β-Trifluoromethylstyrenes

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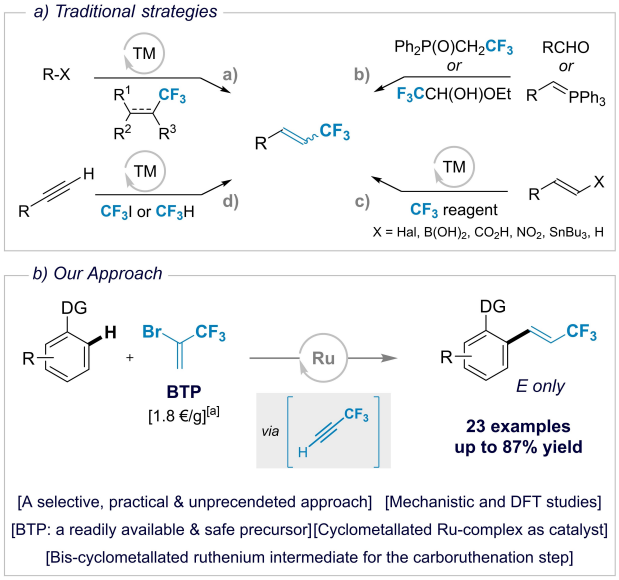
Dedicated to Professor Christian Bruneau for his outstanding contribution to catalysis.

Abstract: In this study, a practical and straightforward synthesis of β-(*E*)-trifluoromethylstyrenes by ruthenium-catalyzed C–H bond activation was developed. The readily available and inexpensive 2-bromo-3,3,3-trifluoropropene (BTP), a non-ozone depleting reagent, was used as a reservoir of 3,3,3-trifluoropropyne. With this approach, the monofunctionalization of a panel of heteroarenes was possible in a safe and scalable manner (23 examples, up to 87% yield). Mechanistic investigations and density functional theory (DFT) calculations were also conducted to get a better understanding of the mechanism of this transformation. These studies suggested that 1) a cyclometallated ruthenium complex enabled the transformation, 2) this complex exhibited high efficiency in this transformation compared to the commercially available $[RuCl_2(p\text{-cymene})]_2$ and 3) the mechanism proceeded through a bis-cyclometallated ruthenium intermediate for the carboruthenation step.

Introduction

Due to the prevalence of fluorinated molecules in material sciences, drug discovery, pharmaceutical and agrochemical industries,[1] there is an increasing demand for innovation in this important and fast-growing research area. Therefore, the design and the development of new technologies to access fluorinated scaffolds aroused the interest of the scientific community and major advances significantly have reshaped this field of research.[2] Indeed, the molecules embedded with a fluorine atom or a fluorinated moiety showed unique behaviors and properties thanks to the features of the fluorine atom.[3] Among them, trifluoromethylated derivatives are major compounds with the Fluoxetine (Prozac®) as a flagship.[1,2] In particular, the vinyltrifluoromethylated residue is found in several compounds of interest: Trifluridine, Bifenthrin and Panomifene, being typical examples. In comparison with the synthesis of trifluoromethylated arenes, the access to β-trifluoromethylstyrene derivatives was less studied. Synthetic pathways generally used for the preparation of these molecules include 1) cross coupling reactions of (hetero)arenes with suitable trifluoromethylated coupling partners (Scheme 1a),[4] 2) olefination reactions (Scheme 1b),[5] 3) the trifluoromethylation of (pre-functionalized) styrene derivatives (Scheme 1c),[6] and 4) the hydrotrifluoromethylation of terminal alkynes (Scheme 1d).[7] Although efficient, the lack of selectivity observed in some cases (*E/Z* mixture) combined with the need to use either pre-functionalized substrates or expensive trifluoromethylating reagents as coupling partners seriously hampered their widespread applications to the synthesis of β-trifluoromethylated alkenes.



Scheme 1. Context of the work. [a] from Apollo Scientific. TM = Transition Metal.

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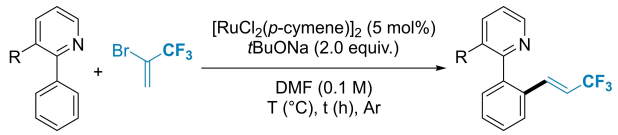
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202201928

With a view to develop an efficient, practical, and selective methodology as a sustainable alternative of the existing routes to β-trifluoromethylstyrenes, an ideal scenario would be the selective C–H vinyltrifluoromethylation of arenes with a readily and inexpensive fluorinated source. Worth mentioning that the direct and formal introduction of a vinyltrifluoromethylated residue by transition metal catalyzed C–H bond activation to afford β-trifluoromethylstyrenes remains an unmet goal, probably due to the challenges related to the use of the corresponding coupling partners (e.g. low boiling points of the 3,3,3-trifluoropropene (−18 °C) and the 3,3,3-trifluoropropyne (−48 °C)). This strongly contrasts with the numerous reports dealing with the synthesis of non-fluorinated styrene derivatives via olefination[8] and hydroarylation[9] reactions of arenes by transition metal catalyzed C–H bond activation. Indeed, over the years, transition metal catalyzed C–H bond activation became an indisputable synthetic tool in organic chemistry for building molecular complexity with wide applications in academia and industry.[10] Therefore the quest for more efficient catalytic systems is of prime importance and recently, the use of cyclometallated metal complexes as catalytically active species (especially derived from ruthenium-based precursors) has emerged as an appealing new trend.[11,12] Hence, we aim at designing the first synthetic route to β-trifluoromethylstyrenes from non-prefunctionalized arenes by transition metal-catalyzed C–H bond activation taking benefit from the unique feature of ruthenium catalysts. With these considerations in mind, we questioned whether we could reach that synthetic goal by the in situ generation of 3,3,3-trifluoropropyne, which would then undergo a directed ruthenium-catalyzed hydroarylation reaction in a one-pot process.[13] The cost and the limited availability of gaseous reagents such as the 3,3,3-trifluoropropene and the hazardous 3,3,3-trifluoropropyne have prompted our interest in finding a synthetic appealing reagent as a formal source of the trifluoromethylvinyl moiety. Therefore, we turned our attention to the inexpensive, readily available and non-ozone depleting 2-bromo-3,3,3-trifluoropropene (BTP), well known to be an efficient coupling partner in cross-coupling reactions and more recently in palladium catalyzed C–H bond activation.[14] Moreover, BTP has been already used for the in situ generation of the 3,3,3-trifluoropropyne upon basic conditions, making this reagent an ideal candidate for the targeted transformation.[15] Herein, we report a robust and original methodology for the synthesis of β-trifluoromethylstyrenes by a directed ruthenium-catalyzed hydroarylation of the in situ generated 3,3,3-trifluoropropyne from BTP upon basic conditions. A fully detailed mechanistic studies along with DFT calculations were conducted to get a better understanding of the reaction.

Results and Discussion

We embarked in this study with the 2-phenylpyridine as the model substrate (Table 1). Using 5 mol% of $[RuCl_2(p\text{-cymene})]_2$ in the presence of BTP and sodium *tert*-butoxide, the functionalization of the 2-phenylpyridine was achieved at 100 °C for 24 h. A mixture of mono- and di-functionalized products was observed in 37% and 4% ^{19}F NMR yields, respectively, with a total control of the selectivity towards the *E* isomer (Table 1, entry 1). To circumvent the difunctionalization side reaction, we hypothesized that using a more sterically hindered directing group might prevent the second *ortho* ruthenation step to occur.[12j,16] With these considerations in mind, the reaction was carried out on the 3-trifluoromethyl-2-phenylpyridine and the 3-methyl-2-phenylpyridine (Table 1, entries 2 and 3). Pleasingly, in both cases, the mono-functionalized product was exclusively obtained, the 3-methylpyridine being the most efficient directing group in this transformation (Table 1, entry 3). The reaction was robust since when the reaction was conducted under air or in the presence of 5 equivalents of water, the expected product was observed in only a slightly lower yield (Table 1, entries 4 and 5). Control experiments revealed that the presence of a catalyst or a base was crucial for the success of the reaction (Table 1, entries 6 and 7). Finally, it turned out that the temperature and the reaction time were key parameters (Table 1, entries 8–11), and when the reaction was conducted at 90 °C for 16 h, the desired product was isolated in 62% yield (Table 1, entry 11).

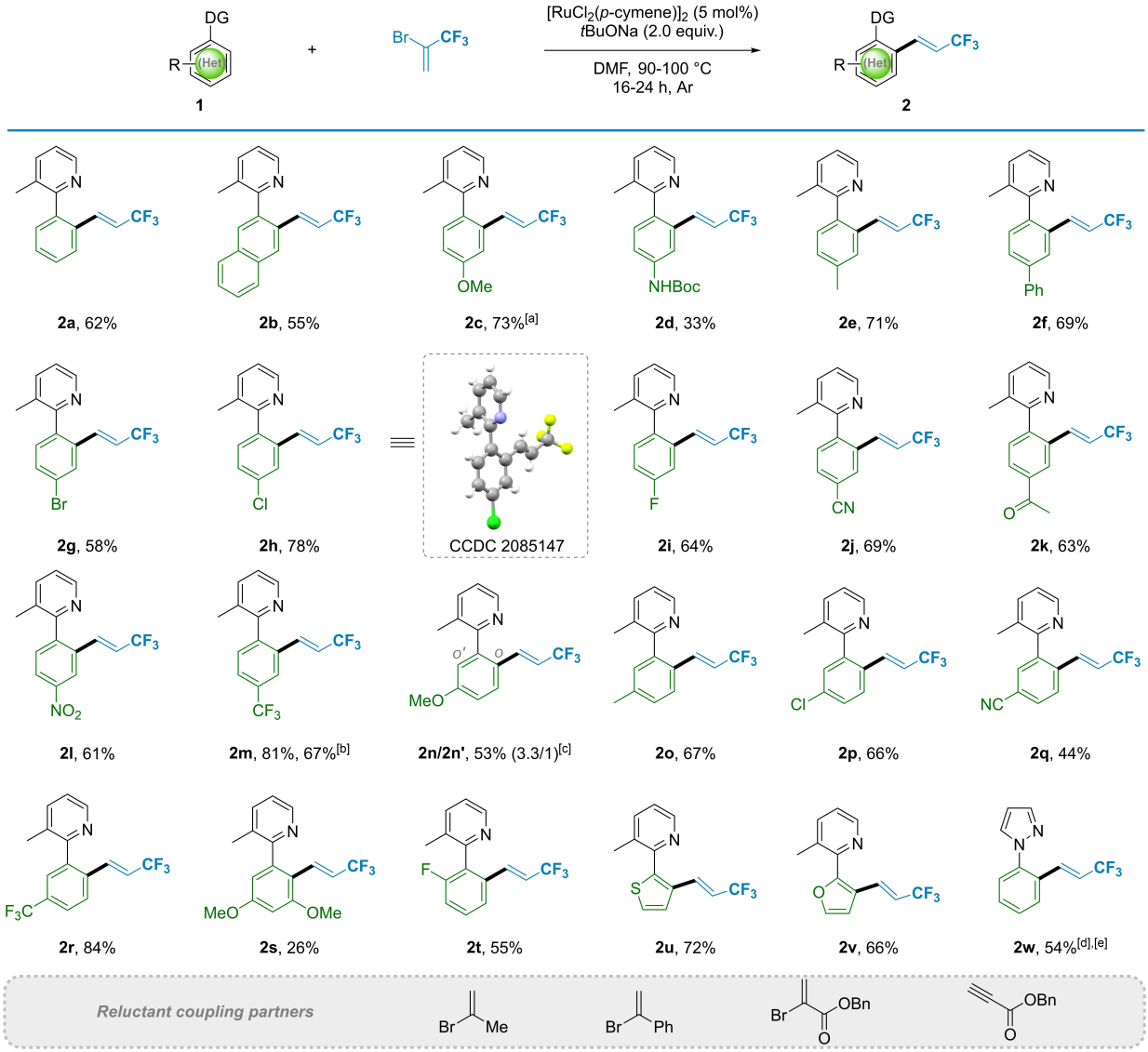
Table 1. Optimization studies. Reaction conditions: (Hetero)arene (0.3 mmol, 1.0 equiv.), BTP (5.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), *t*BuONa (2.0 equiv.), DMF (0.1 M), T (°C), time (h), Ar.



Entry	R	T [°C]	t [h]	Yield [%][a]
1	H	100	24	37 + 4[b]
2	CF_3	100	24	49
3	CH_3	100	24	66 (42)[c]
4[d]	CH_3	100	24	61
5[e]	CH_3	100	24	59
6[f]	CH_3	100	24	NR
7[g]	CH_3	100	24	NR
8	CH_3	90	24	71
9	CH_3	80	24	43
10	CH_3	25	24	NR
11	CH_3	90	16	76 (62)[c]

[a] Yields determined by ^{19}F NMR using α,α,α-trifluoroacetophenone as an internal standard. [b] Difunctionalized compound. [c] Isolated yield. [d] Under an air atmosphere. [e] The reaction was carried out in the presence of 5 equivalent of H_2O. [f] No catalyst. [g] No base. NR: No Reaction.

With these optimized reaction conditions in hand, we explored the substrate scope and a panel of 3-methyl-2-phenylpyridine derivatives diversely substituted on the aryl part was functionalized (22 examples, Scheme 2). Worth mentioning that for less reactive substrates, a slight increase of the reaction temperature and time (100 °C, 24 h) improved the yield of the desired products.[16] When the 3-methyl-2-phenylpyridine **1a** and the 3-methyl-2-naphthylpyridine **1b** were used as substrates, the expected products **2a** and **2b** were isolated in 62% and 55% yields, respectively. Several derivatives substituted at the *para* position were then studied. Compounds bearing electron-donating groups and halogens (**2c**–**2i**) were isolated in good yields (up to 78% yield), except in case of the *N*-Boc protected amine **2d**.

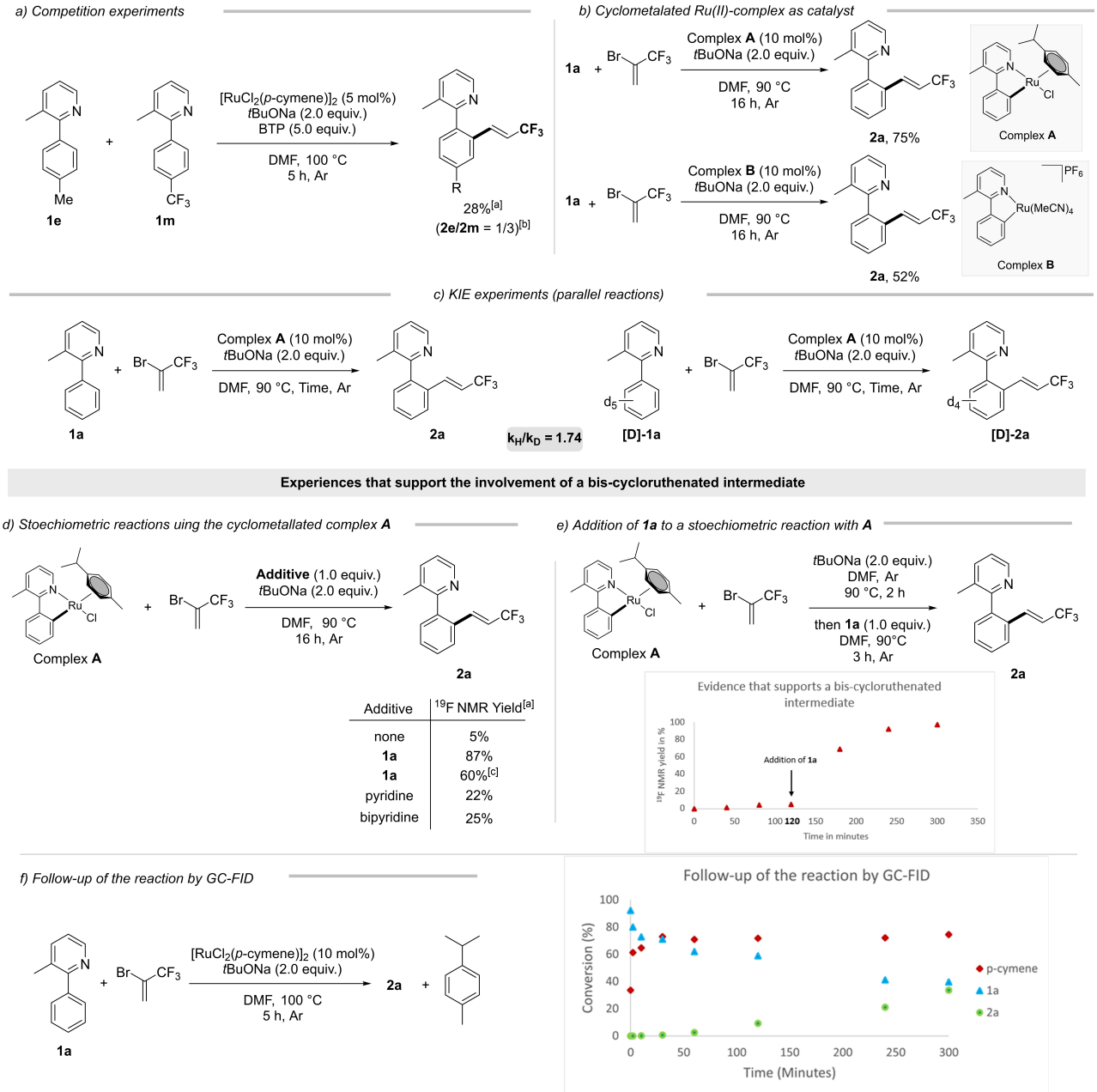


Scheme 2. Scope of the reaction. Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), BTP (5.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), *t*BuONa (2.0 equiv.), DMF (0.1 M), 90–100 °C, 16–24 h, Ar. Isolated yields were given. For more details, see the Supporting Information. [a] **2c** was isolated with an inseparable impurity. [b] Reaction performed on a 4.2 mmol scale (1 g of **1m**). [c] A 3.7/1 ratio for the products **2n/2n'** was determined by ^{19}F NMR on the crude mixture and the products **2n/2n'** were isolated as an inseparable mixture in a 3.3/1 ratio (*o*/*o'*) as determined by ^{19}F NMR. [d] A 10/1 ratio (mono/di) for the product **2w** was determined by ^{19}F NMR on the crude mixture and **2w** was isolated as a mixture with the product resulting from the difunctionalization in a 10/1 ratio (mono/di) as determined by ^{19}F NMR. [e] The reaction was carried out on a 0.2 mmol scale.

Gratifyingly, a X-ray analysis of **2h** was collected, which ascertained the selective formation of the *E* isomer at the *ortho* position of the directing group.[16] Other *para*-substituted arenes with electron-withdrawing groups (**1j**–**1m**) were also investigated and the corresponding compounds were obtained in high yields (**2j**–**2m**). In case of the trifluoromethylated derivative **1m**, the reaction was easily scaled up to a one-gram scale, yielding **2m** in 67% yield. In the same vein, derivatives bearing arenes substituted at the *meta* position with electron-donating groups (**1n, 1o**), halogen (**1p**) and electron-withdrawing ones (**1q, 1r**) were functionalized on the less sterically hindered position, except in case of **1n** for which both positions were functionalized leading to a mixture of **2n/2n'** with 53% isolated yield in a 3.3:1 ratio. In addition, the reaction was tolerant with difunctionalized compound **1s** and went smoothly with the *ortho* substituted derivative **1t**. In general, the transformation turned out to be functional group tolerant (cyano, ketone, nitro, carbamate), which demonstrated further its synthetic potential. Pleasingly, heteroarene derivatives (thiophene and furan) were suitable substrates and **2u** and **2v** were isolated in 72% and 66%, respectively. The reaction was not restricted to the 3-methyl-2-phenylpyridine derivatives as the phenylpyrazole (**1w**) was successfully functionalized in 54% yield. However, **2w** was obtained as a 10:1 mixture of mono- and di-functionalized products. Note that no reaction occurred when replacing the BTP by the 2-bromopropene, the α-bromostyrene, the benzyl 2-bromo-2-propenoate and the

phenylmethyl 2-propynoate, showing the unique behavior of the in situ generated 3,3,3-trifluoropropyne as a coupling partner in this reaction. In addition, when other directing groups were investigated, no expected product was obtained.[16]

To get better insights on the reaction mechanism, we carried out several experiments. At first, an intermolecular competition experiment between **1e** and **1m** was conducted under standard reaction conditions (Scheme 3a), and a mixture of products **2e** and **2m** was observed after 5 h with 28% ^{19}F NMR yield in a 1/3 ratio. These results suggested that electron-deficient substrates reacted slightly preferentially, probably due to an enhance acidity of the proton.[16] Then, based on the recent works from Ackermann,[12a,b,h,i] Larrosa,[12d,e,f] and others who independently reported cyclometallated ruthenium(II) metallacycles as key species, we wondered if it will be also the case in this transformation. Therefore, the complex **A** and the arene-free ruthenacycle **B** were synthetized and used as catalysts in the reaction (Scheme 3b).[12f,16,17] Pleasingly, in both cases, **2a** was successfully obtained, the cyclometallated catalyst **A** being the most efficient one. In addition to these findings, under standard reaction conditions, the decoordination of *p*-cymene from the complex **A** was also observed by ^{1}H NMR and free *p*-cymene was also detected by GC-FID along with the consumption of **1a** and the generation of **2a**.[12i,j,16] All these results strongly supported that a

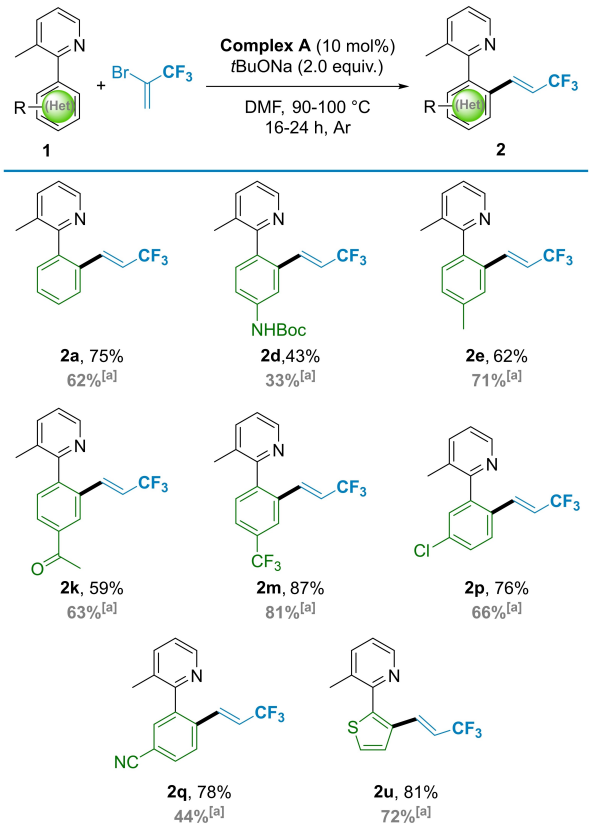


Scheme 3. Mechanistic studies. For more details, see the Supporting Information. [a] Yields were determined by ^{19}F NMR using the α,α,α-trifluoroacetophenone as the internal standard. [b] Ratio was determined by ^{19}F NMR using the α,α,α-trifluoroacetophenone as the internal standard. [c] Reaction carried out using the complex **B** instead of the complex **A**.

p-cymene-free cyclometallated ruthenium (II) complex was the catalytically active species in the process. Besides, a scrambling experiment was carried out using the cyclometallated ruthenium complex **A**, showing no proton-deuterium exchange.[16] Then, a kinetic isotopic effect (KIE) of 1.74 was determined with parallel experiments starting either from **1a** or [D]-**1a** (Scheme 3c).[16] These experiments suggested that the C–H bond activation step was irreversible and probably the rate determining step.[16,18]

Based on recent contributions by key players in the field,[12] we hypothesized the in situ generation of a bis-cyclometallated ruthenium species. Therefore, stoichiometric experiments using the cyclometallated ruthenium complex **A** were conducted. When this latter was reacted with BTP and *t*BuONa (Scheme 3d), traces of **2a** were observed, which excluded the involvement of the ruthenacycle **A** as a key intermediate in the hydroarylation reaction. Pleasingly, the addition of 3-methyl-2-phenylpyridine **1a** (1 equivalent) afforded the expected product **2a** in 87% ^{19}F NMR yield. Similarly, **2a** was observed in 60% ^{19}F NMR yield with a stoichiometric amount of the complex **B**.[16] These observations suggested the formation of a bis-cyclometallated ruthenium-intermediate in the course of the process. Then, experiments with pyridine or bipyridine were conducted. In both cases, **2a** was observed in low yields (22% and 25% ^{19}F NMR yields, respectively), which suggested that the reactivity did not stemmed from a L-type ligand effect from the pyridine part of **1a** but rather from the involvement of a second metallacycle intermediate in agreement with the observations from the group of Larrosa.[12d,e,f] To further ascertain the formation of this bis-ruthenacycle complex, we performed an additional experiment. In the presence *t*BuONa, the complex **A** was first treated with BTP for two hours at 90 °C and no reaction occurred (Scheme 3e). Then, **1a** was added and the reaction was carried out for additional three hours. Pleasingly, the formation of the product **2a** was observed reaching 97% ^{19}F NMR yield. Finally, when we studied the reaction by GC-FID (Scheme 3f), an interesting phenomenon was observed. Indeed, during the first 40 minutes, while **1a** was consumed and free *p*-cymene was generated, **2a** was not detected. This incubation time might support the formation of a bis-ruthenacycle intermediate, necessary for the hydroarylation reaction to proceed. All these results suggested that a bis-cyclometallated ruthenium complex was a plausible key intermediate in this process, probably involved in the carboruthenation step with the 3,3,3-trifluoropropyne as supported by the DFT studies (see Figure 2, see below).

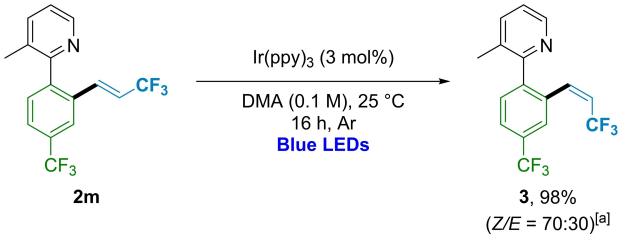
Next, we became interested in the use of the air-stable cyclometallated ruthenacycle **A** as catalyst in order to evaluate its efficiency in this hydroarylation reaction compared to our standard reaction conditions (8 examples, up to 87% yield, Scheme 4). Gratifyingly, the complex **A** generally exhibited a superior reactivity compared to the $[RuCl_2(p\text{-cymene})]_2$ precursor as the desired products were either obtained with higher yields (e.g. **2a**, **2p**, **2q** and **2u**) or similar ones (eg. **2k** and **2m**). For instance, **2q** was isolated in 78% yield with these modified reaction conditions (vs. 44%, see Scheme 2), illustrating further the unique reactivity of this cyclometallated ruthenium(II)-complex as catalyst. Worth mentioning that the product **2a**, which would result from the direct functionalization of the catalyst, has never been detected, confirming the role of the complex **A** as catalyst.



Scheme 4. Scope using the complex **A** as catalyst. On 0.3 mmol scale. [a] Under standard reaction conditions.

To further demonstrate the synthetic value of our methodology, the *E* to *Z* isomerization of the compound **2m** was achieved and the corresponding product **3** with **2m** were isolated as a separable mixture of diastereoisomers in a 98% total yield (Scheme 5).[19]

Then, DFT calculations[20] for the in situ generation of the 3,3,3-trifluoropropyne from BTP under basic conditions were performed at the ωB97X-D/6-31++G(d,p)-SDD IEF-PCM level of theory. They first gave evidence that the involvement of an alkyne intermediate was a reasonable assumption in agreement with literature data.[15] Indeed, as displayed in Figure 1, its



Scheme 5. Post-functionalization reaction. Reaction on 0.3 mmol scale. [a] The *Z*/*E* ratio was determined by ^{19}F NMR on the crude mixture.

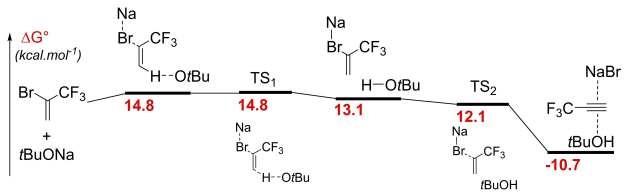


Figure 1. Calculated pathway for the creation of the alkyne intermediate.

formation is highly exergonic (from more than 10 kcal mol^{-1} in terms of standard Gibbs energy) and is associated to a moderate overall activation barrier (about 14 kcal mol^{-1}), while occurring through a standard E1cB mechanism (first step: proton abstraction, second step: bromine elimination[21]).

Extensive DFT calculations (using the dispersion-corrected range-separated hybrid ωB97X-D functional) were then carried out[20] to investigate the catalytic process of this redox-neutral transformation. To this aim, a particular care has been paid to solvation states, to the competition between various ligand coordinations, and to the different conformations each of them can adopt. This study resulted in identifying 46 relevant stationary points on the energy surface, as represented in Figures S1–S4.[16] They are thoroughly discussed in the Supporting Information, and unraveled the following key salient features: 1) the formation of the bis-ruthenacycle is energetically favored in comparison with the monocyclometallated ruthenacycle, 2) the bis-ruthenacycle complex is an important intermediate in the catalytic cycle, and 3) the hydroarylation step likely occurs after the formation of the bis-ruthenacycle.

The Figure 2 depicts the lowest Gibbs energy profile that we have identified, where only key-intermediates are represented for the sake of simplicity.[16] After the formation of the monocyclometallated ruthenium complex **A** by C–H bond activation, a fast ligand exchange between Cl and O*t*Bu occurred (the activation barrier equals 4.3 kcal mol^{-1}) providing **D** (Figure 2). Then, after decoordination of *p*-cymene, the arene-free ruthenacycle **I2trans'** was formed in the presence of **1 a** and the in situ generated 3,3,3-trifluoropropyne. Assisted by the presence of O*t*Bu in the coordination sphere of the metal, the C–H ruthenation on the second substrate occurred, which was the rate determining step with an activation barrier of 17.5 kcal mol^{-1} in term of standard Gibbs energy. Hence, the bis-cyclometallated ruthenium(II) complex **K2trans** was obtained along with the elimination of *t*BuOH. Coordination of the DMF further stabilized the complex **K2trans** by about 3.7 kcal mol^{-1} to afford the intermediate **L2trans**. Then, the insertion of alkyne proceeded, leading preferentially to **M2trans1** with an activation barrier equal to 13.8 kcal mol^{-1}.

In agreement with the literature data,[12] and consistently supported by the above experiments and the DFT studies, we suggested the following mechanism for this redox-neutral process, as depicted in the Scheme 6. At first, formation of the monocyclometallated ruthenium complex **A** occurs by C–H bond activation. Then, in the presence of **1 a**, the in situ generated 3,3,3-trifluoropropyne from BTP and *t*BuONa in DMF, the arene-free ruthenacycle **I2trans'** is generated after decoordination of the *p*-cymene.[16] The latter leads to the irreversible formation of the bis-cyclometallated Ru(II) complex **K2trans** as a key intermediate after a second C–H activation event by means of an inner sphere base-assisted CMD mechanism. After coordination of DMF (**L2trans**) and subsequent carboruthenation the species **M2trans1** is afforded, which selectively provides, after protonation and ligand exchange, the expected β-(*E*)-trifluoromethylstyrene **2 a** and regenerates the monocyclometallated species **I2trans'**.

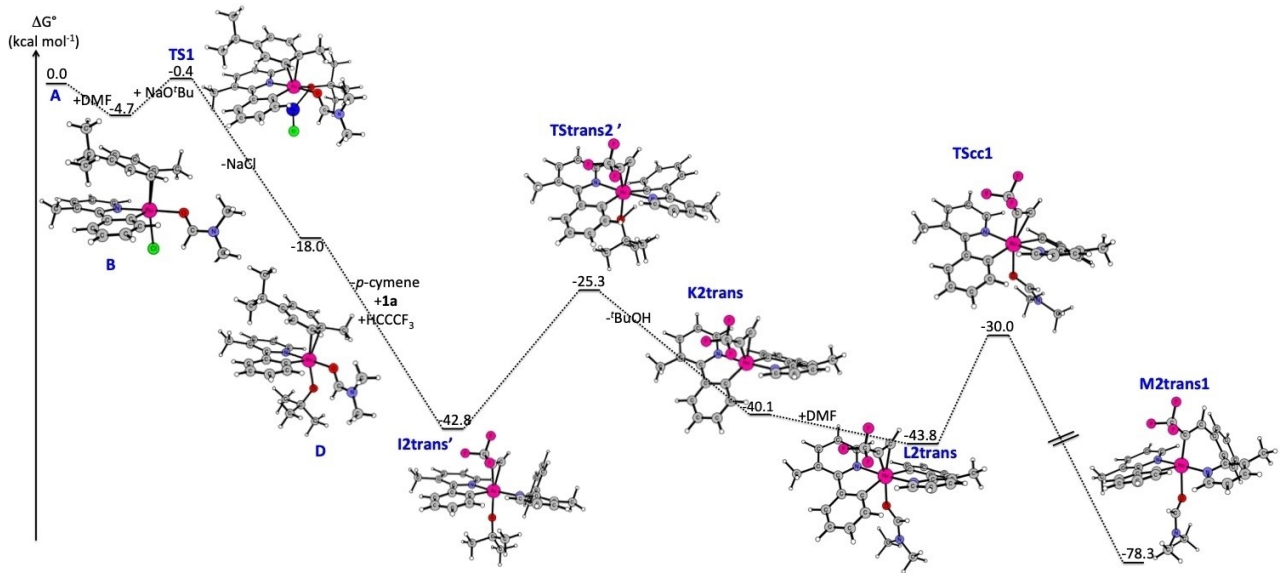
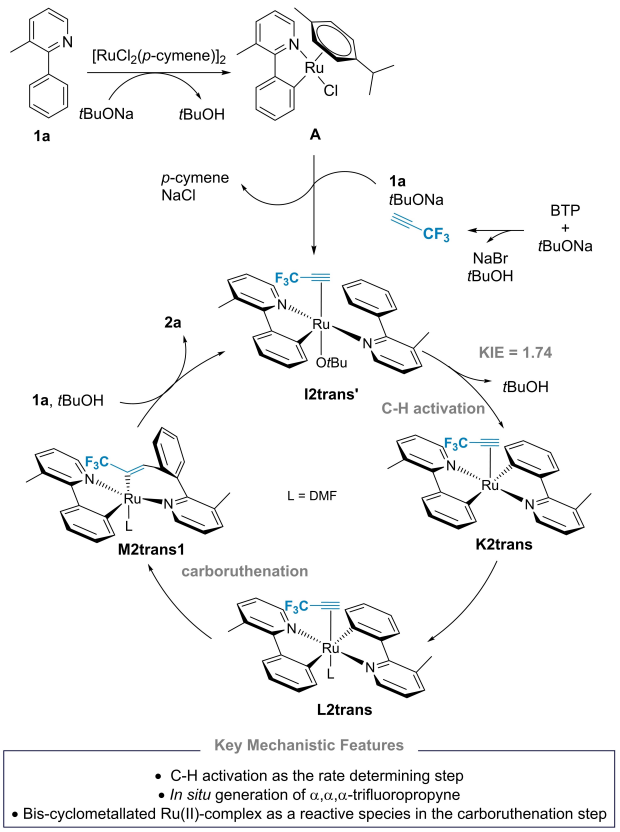


Figure 2. Proposed synthetic pathway from DFT calculations. Standard Gibbs energies in kcal mol^{-1}. Color code: H in white, C in grey, N in soft blue, O in red, Cl in green, Na in dark blue, Ru and F in pink.



Scheme 6. Proposed catalytic cycle.

Conclusion

In summary, we have developed an unprecedented approach for the synthesis of β-trifluoromethylstyrene derivatives via a directed ruthenium-catalyzed hydroarylation process by C–H bond activation. Using the BTP as a readily available, inexpensive and practical precursor of 3,3,3-trifluoropropyne under basic reaction conditions, a broad range of β-trifluoromethylstyrene derivatives was selectively obtained as *E* isomers from non-prefunctionalized substrates (23 examples, up to 87% yield). The reaction was selective for mono- *vs* bis-functionalized products thanks to the astute choice of the 3-methylpyridine as a directing group. Pleasingly, the protocol turned out to be robust (air and moisture tolerant) and functional group tolerant (carbamate, nitro, cyano and ketone), a real asset for late-stage functionalization of complex molecules. This method provides a straightforward synthetic route to original molecular scaffolds, expanding the portfolio of tools to build up these important trifluoromethylated molecules. Detailed mechanistic studies, supported by DFT calculations, provided a better understanding of the reaction mechanism. A metallacycle ruthenium(II)-complex was identified as the catalytically active species and a bis-ruthenacycle was involved as the reactive species in the carboruthenation step. The use of the cyclometallated complex as the catalytically active species in C–H activation reactions offers new perspectives and further investigations are currently ongoing in our group. Finally, this study also demonstrates how we can use a cost-effective and non-ozone depleting reagent to access high-value-added fluorinated scaffolds by means of a sustainable strategy.

Acknowledgements

This work has been partially supported by University of Rouen Normandy, INSA Rouen Normandy, the Centre National de la Recherche Scientifique (CNRS), European Regional Development Fund (ERDF), Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2 C, the graduate school for research XL–Chem (ANR-18-EURE-0020 XL CHEM), and by Region Normandie. M.V. and T.B. thank the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 758710). The authors would like also to gratefully acknowledge the Centre Régional Informatique et d'Applications Numériques de Normandie (CRIANN) for computing resources.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: β-trifluoromethylstyrenes · C–H activation · cyclometallated ruthenium(II)-complex · homogeneous catalysis · synthetic methodology

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[16] See the Supporting Information for more details. Deposition Numbers 2085147 (**2h**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
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Manuscript received: June 22, 2022
Accepted manuscript online: June 23, 2022
Version of record online: August 3, 2022