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RESEARCH ARTICLE

SuFEx-Functionalized Quinones via Ruthenium-Catalyzed C–H Alkenylation: A Potential Building Block for Bioactivity Valorization

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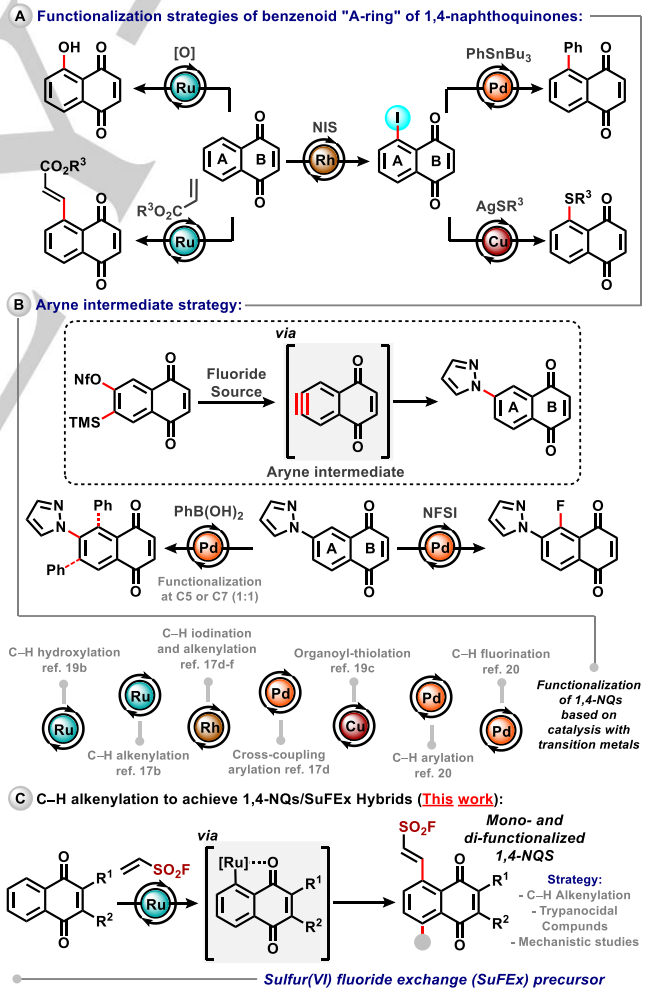
Abstract: Herein, we describe the Ru-catalyzed C–H alkenylation of 1,4-naphthoquinones (1,4-NQs), resulting in 1,4-naphthoquinoidal/SuFEx hybrids with moderate to good yields. This method provides a novel route for direct access to ethenesulfonyl-fluorinated quinone structures. We conducted mechanistic studies to gain an in-depth understanding of the elementary steps of the reaction. Additionally, we evaluated the prototypes against trypomastigote forms of *T. cruzi*, leading to the identification of compounds with potent trypanocidal activity.

Introduction

Quinones are omnipresent motifs found in a wide range of living organisms,[1] existing in nature as fundamental structures that play key roles as organic redox molecules involved in energy transduction and storage in biological systems.[2] Quinones are also fundamental in proton-coupled electron transfer processes, such as photosynthesis[3] and animal respiration.[4] In the human body, quinones are vital for sustaining life, acting in blood coagulation and bone formation.[5] It is considered one of the main groups of secondary plant metabolites, exhibiting a myriad of biological activities,[6] especially as antiparasitic[7] and anticancer agents.[8] Apart from being sourced naturally through plant-based extraction,[9] quinones can also be obtained by classical synthetic routes via oxidation of petroleum based chemicals[10] and biomass feedstock.[11]

Click reactions are considered a ubiquitous breakthrough in modern science, embodying a synthesis philosophy designed to inspire the development of operationally simple, modular, and orthogonal methodologies.[12] Since its creation in 2001 by Sharpless and Meldal,[13] this concept permeated various scientific fields, revolutionizing research, and societal applications. It culminated in the 2022 Nobel Prize, awarded to Sharpless, Meldal, and Bertozzi for their contributions to click and biorthogonal chemistry methodologies.[14] Within this philosophy, sulfur(VI) fluoride exchange (SuFEx) is coined as a new generation of powerful click reactions, enabling the synthesis of hypervalent sulfur compound under metal-free conditions.[15] Since its creation in 2014, SuFEx has been considered a new embodiment of ideal click chemistry, particularly in the modular formation of S(VI)–O, S(VI)–C, and S(VI)–F bonds.[16]



Scheme 1. Benzenoid "A" ring C–H activation portfolio and alkenylation/SuFEx reaction design.

Our research groups have been relentlessly pursuing new and powerful methodologies for the direct functionalization and

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valorization of naphthoquinoidal motifs. We focus on synthetic approaches based on organometallic catalysis, most commonly C–H activation reactions[17] and first generation CuAAc (copper-catalyzed azide–alkyne cycloaddition) click reactions.[18] During this time, different methods have been used in the direct functionalization of quinoidal structures, producing valuable medicinal and technological prototypes.[19] This has led to a diverse portfolio of benzenoid "A" ring functionalizations, as illustrated in Schemes 1A and 1B.[20]

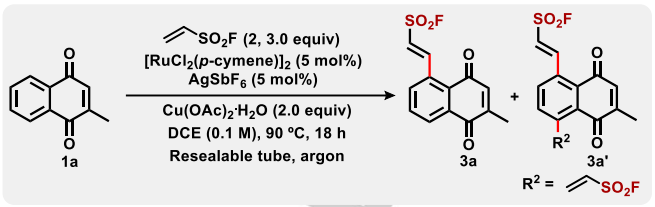
Chagas disease is a serious and neglected health problem, especially in Latin America.[21] Current etiological treatments still rely on drugs developed in the late 1960s, such as benznidazole and nifurtimox,[22] highlighting the urgent need for the identification of new potential structures with trypanocidal activity. Inspired by these successful strategies and aiming to exploit the powerful second-generation click reactions such as SuFEx, we present a new C–H alkenylation protocol for the synthesis of 1,4-naphthoquinone-based SuFEx hybrids (Scheme 1C). This work introduces new potent trypanocidal prototypes to the collection of drugs being studied against the *Trypanosoma cruzi* (*T. Cruzi*) parasite, expanding the scope of potential candidates Chagas disease therapy.

Results and Discussion

Optimization: Our initial attempt involved utilizing a pre-established methodology developed by our team for the olefination of the benzenoid ring of naphthoquinones via ruthenium catalysis,[17b] using ethenesulfonyl fluoride as the olefin source and 1,4-naphthoquinone **1a** as the model substrate (Table 1). To our delight, the catalysis proceeded smoothly, generating derivative **3a** in 60% yield, and the di-functionalized compound **3a'** in 26% yield, resulting in a combined 86% total yield (Entry 1, no variation). Fine tuning was then performed to enhance reaction robustness. Running the reaction with no copper source at 110 ºC resulted in a 31% yield with no formation of the di-functionalized derivative (Entry 2). Varying the amounts of $Cu(OAc)_2.H_2O$ (1.5 and 3.0 equiv.) resulted in lower yields of both products (Entries 3 and 4). Additionally, using 2 mol% of $[RuCl_2(p\text{-cymene})]_2$ led to worse reaction performance (Entry 5). When the reaction was carried out at 110 °C, a 42% yield of **3a** was obtained, with no formation of the di-functionalized adduct (Entry 6). Finally, using 2 equivalents of CH_2CHSO_2F resulted in most of the di-functionalized product **3a'** over the mono-analog (Entry 7, Table 1). When reaction was carried at 110 °C, 42% yield of **3a** was obtained, and no di-functionalized adduct was observed (entry 6). Finally, using 2 equivalents of CH_2CHSO_2F resulted in a majority of di-functionalized product **3a'** over the mono-analog (entry 7, Table 1).

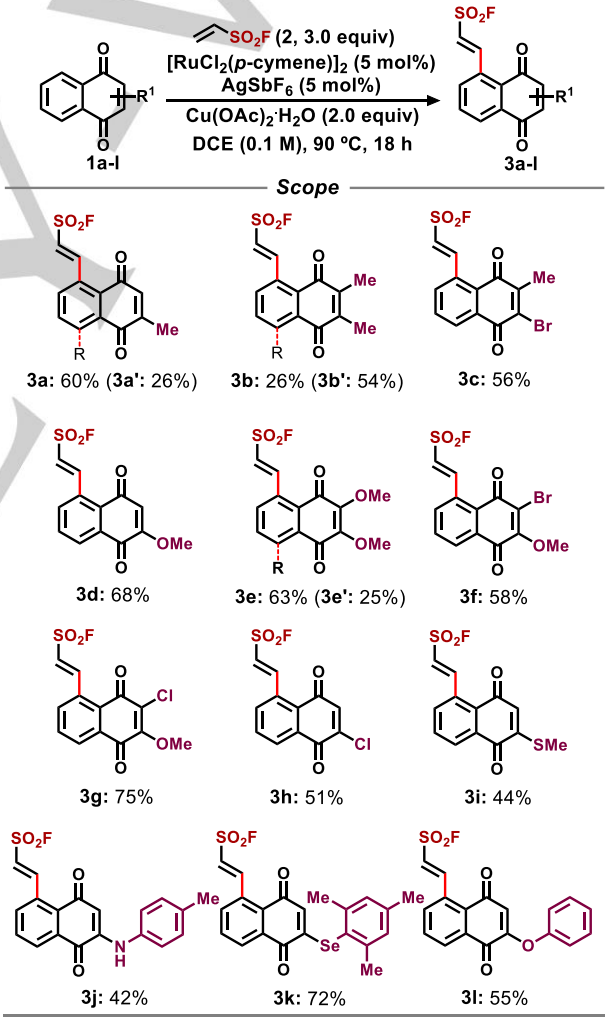
Scope: Compounds containing methyl groups were synthesized to investigate the reaction scope (Scheme 2). Applying the optimal conditions to the mono-methylated compound **1a** afforded derivative **3a** in 60% yield, along with the di-olefinated quinone **3a'** in 26% yield. For the di-methylated compound **1b**, the major product was the di-olefinated derivative **3b'** (54% yield), with the mono-olefinated product **3b** as the minor product (26% yield). Insertion of a bromine atom in the di-carbonylic ring led to a shift in reaction selectivity, resulting in the brominated derivative **3c** as the sole product with a 56% yield.

Table 1. Deviations from the standard conditions.[17b]



Entry	Deviations from the standard conditions	Yield (%)[a]
1	No variation	60/26
2	No $Cu(OAc)_2{\cdot}H_2O$, 110 °C	31/NO
3	$Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv.)	35/NO
4	$Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv.)	21/62
5	$[RuCl_2(p\text{-cymene})]_2$ (2 mol%)	11/NO
6	110 °C	42/NO
7	2 equivalents of CH_2CHSO_2F	9/24

Reaction conditions: **1a** (0.2 mmol), **2** (3.0 equiv) catalyst (5 mol%), $AgSbF_6$ (5 mol%, 0.05 equiv), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv), DCE (2.0 mL), 90 ºC, 18h. [a]Isolated Yields. NO = Not observed.



Scheme 2. Substrate scope for C–H alkenylation of 1,4-naphthoquinones with SuFEx-based reactants. All yields were obtained. All reactions were carried out using **1a-l** (0.2 mmol), **2** (0.8 mmol), catalyst (5.0 mol%), $AgSbF_6$ (5.0 mol%, 0.05 equiv), $Cu(OAc)_2.H_2O$ (2.0 equiv), and DCE (2.0 mL); 90 °C, 18 h. Reported yields pertain to isolated products, with yields of di-functionalized products shown in parentheses.

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Next, the mono-methoxylated substrate **1d** resulted in derivative **3d** in 68% yield, with the *cis* diasteroisomer detected in a 20:1 ratio (see the Supporting Information file for details). Surprisingly, no di-olefinated product was observed in this reaction. For the di-methoxylated compound **1e**, both mono- and di-olefinated products were obtained, with derivative **3e** at 63% and derivative **3e'** at 25% yield, totaling 89% yield. This indicates that a more electron donating group favors the reaction towards the mono-olefinated derivative. With the insertion of halogen atoms in the di-carbonylic ring (compounds **1f** and **1g**), the reaction regioselectivity remained oriented by the methoxy group, affording **3f** and **3g** in 58% and 75% yields, respectively. No di-olefinated compounds were observed in either case.

We exchanged the methoxy for other portions containing atoms with free electron pairs. Reaction with compound **1h**, containing a chlorine atom, provided derivative **3h** in 51% yield. In turn, the sulfur-containing substrate **1i** afforded only the mono-olefinated product **3i** in 44% yield. Insertion of an aniline moiety (compound **1j**) resulted in a moderated yield of 42% for compound **3j**. Interestingly, when using the selenium-containing substrate **1k**, an increase in yield was observed, with derivative **3k** being synthesized in 72% yield. Finally, compound **1l**, which has a phenoxy substituent, afforded derivative **3l** with a 55% yield. No di-olefinated derivatives were detected when using substrates **1h-l** (Scheme 2).

Suitable crystals for X-ray crystallographic analysis were obtained by vapor diffusion of petroleum ether into dichloromethane solutions of the compounds. The structures of the naphthoquinones **3a**, **3b'**, **3d**, **3e**, **3e'**, **3f**, **3i**, and **3j** were successfully solved, supporting the product identities previously determined by NMR and HRMS analyses. Mercury representations of the asymmetric unit of the compounds are shown in Figure 1.[23]

Proposed reaction mechanism: To investigate the alkenylation reaction profile of **1a**, catalyzed by $[RuCl_2(p\text{-cymene})]_2$, resulting in product **3a**, we conducted a detailed computational investigation using density functional theory (DFT) calculations and compared data from literature.[24] We performed geometry optimizations and harmonic vibrational frequencies at the PBE0-D3(BJ)/bs1+CPCM(DCE) level of theory (bs1 = def2-TZVP for Ru, def2-SVP for other elements; DCE = 1,2-dichloroethane), followed by single-point calculations at the PBE0-D3(BJ)/def2-TZVPP+CPCM(DCE) level, as shown in Scheme 3. Further details about these calculations are provided in the Experimental Section.

The reaction pathway is initiated by the coordination of the mono-methylated compound **1a** to $[Ru(OAc)(p\text{-cymene})]^+$ (**A'**, see Scheme 3) through the carbonyl oxygen, resulting in the formation of intermediate **A**. This structure has the appropriate conformation to undergo C–H activation through a six-membered ring transition state (**TS1**), with an energy barrier of $\Delta G^{\ddagger}$ = +15.3 kcal.mol^{-1}, affording intermediate **B** (ΔG = +1.1 kcal.mol^{-1}). Subsequently, the endergonic coordination of the ethenesulfonyl fluoride **2** into **B** leads to intermediate **C** (ΔG = +6.4 kcal.mol^{-1}), which then transforms into intermediate **D** (ΔG = +4.5 kcal.mol^{-1}) *via* migratory insertion. This step proceeds through a transition state (**TS2**) with an energy barrier of $\Delta G^{\ddagger}$ = +11.4 kcal.mol^{-1}. Within intermediate **D**, a Ru–C(phenyl) distance of 2.452 Å was observed, which is nearly 1.35 Å shorter than the sum of the van der Waals radii for Ru (2.10 Å)[25] and C (1.70 Å).[26] Following a conformational change and the detachment of this interaction, the seven-membered ruthenacycle, intermediate **E** (ΔG = –2.2 kcal.mol^{-1}) is formed. Finally, **E** undergoes *β*-hydride elimination, resulting in the ruthenium hydride intermediate **F** (ΔG = +1.0 kcal.mol^{-1}) with a modest energy barrier of $\Delta G^{\ddagger}$ = +5.3 kcal.mol^{-1}. The desired product **3a** is formed after its release from intermediate **F**, leading to the regeneration of the active catalytic species. The DFT calculations support the proposed catalytic cycle for the C–H alkenylation of the mono-methylated 1,4-naphthoquinone **1a**, as shown in Scheme 4.

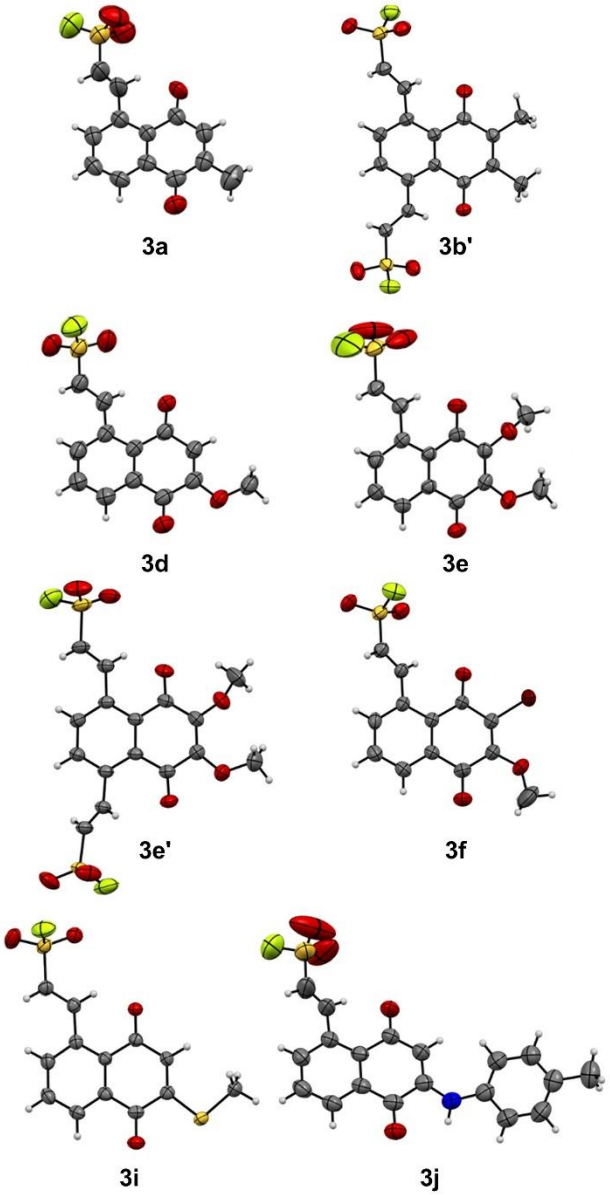

Figure 1. Mercury projections of **3a**, **3d**, **3e**, **3e'**, **3f** and **3j** with displacement ellipsoids at the 50% probability level. Hydrogen atoms have been suppressed for better visualization.

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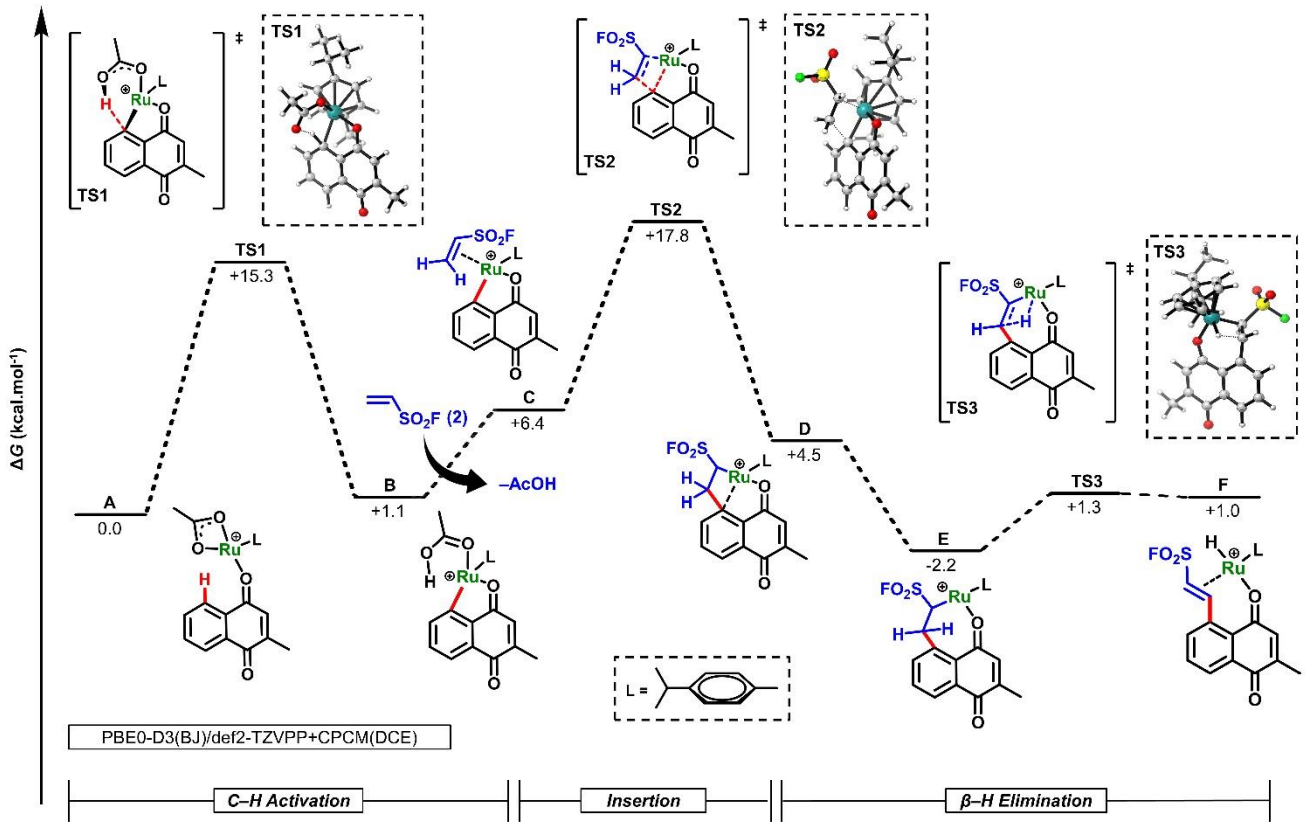
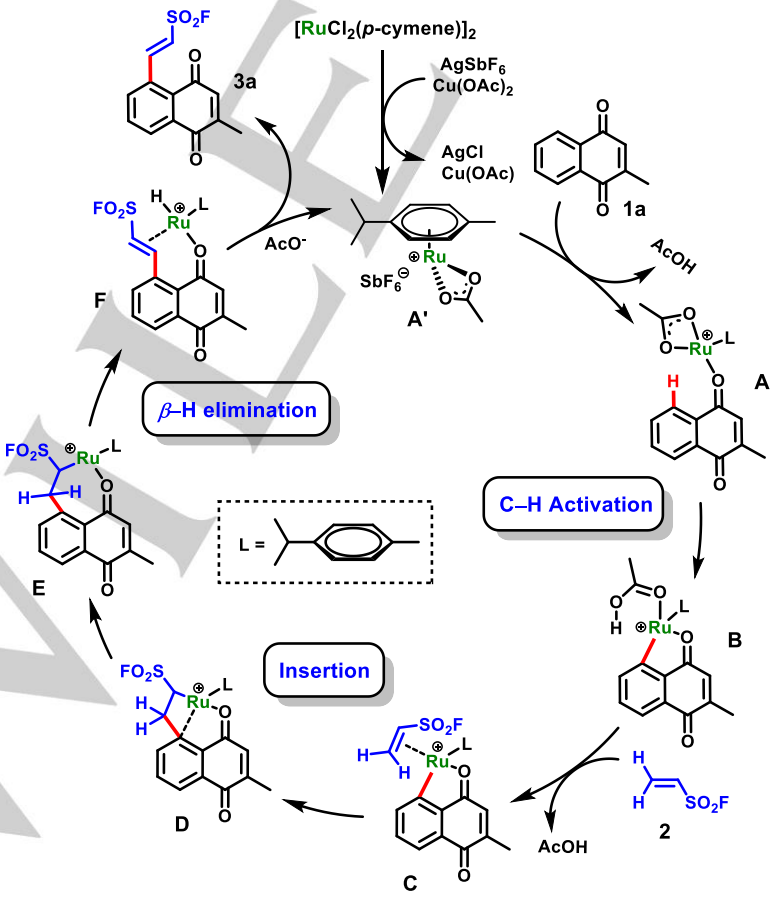


Scheme 3. Computed Gibbs free energies in kcal·mol^{-1} for the C–H alkenylation of the mono-methylated 1,4-naphthoquinone **1a**. Energies are at the PBE0-D3(BJ)/def2-TZVPP+CPCM(DCE) level of theory, from optimized structures at PBE0-D3(BJ)/bs1+CPCM(DCE). See text for more details.



Scheme 4. Proposed catalytic cycle.

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Biological assays: For more than a decade, our collaborative network has been evaluating the trypanocidal activity of quinones as part of a Medicinal Chemistry program to find promising candidates against *T. cruzi*.[27] Our efforts are aimed at the discovery of efficient prototypes to combat the parasite, given that only two drugs are currently available in the therapeutic arsenal to combat the etiological agent of Chagas disease. Herein, we evaluated 14 compounds (Table 2) against the bloodstream trypomastigote forms of *T. cruzi*, successfully identifying three compounds that demonstrated activity against the parasite. Our strategy has proved effective, particularly with compounds **3e**, **3e'** and **3h**, which contain dimethoxy and chlorine substituents, respectively. These compounds highly exhibited activity, with IC_{50} values of 19.0, 14.9 and 15.3 µM. Notably, the di-methoxylated/olefinated products **3e** and **3e'**, along with the chlorinated compound **3h**, were found to be almost seven times more active than the standard treatment drug benznidazole (Bz, IC_{50} = 103.6 µM).

Moderate activity in the range of 130.3-184.6 µM was observed for compounds **3c**, **3f** and **3g**, which feature halogen atoms alongside variations of methyl and methoxy groups in the di-carbonylic B-ring. Low activity was observed for the mono-methoxylated compound **3d** (IC_{50} = 278.4 µM), in contrast with the moderate activity presented by the methoxylated-halogenated compounds **3f** and **3g**. Compounds **3a**, **3a'**, **3b'**, **3k** and **3i** present IC_{50} values in the range of 278.4–630.0 µM. Notably, compounds **3b** and **3j** was found to be inactive against the parasite (IC_{50} > 1000 µM), while **3l** (IC_{50} = 98.4 µM) demonstrated activity similar to that of Bz. Three more active SuFEx-containing quinones were selected and their cytotoxicity evaluated in mammalian cells. Compounds **3e**, **3e'**, and **3h** exhibited LC_{50} values of less than 16.0 µM and selectivity index values close to 1.0. These results suggest that the compounds require further refinement to achieve a more effective biological profile, aiming to maximize their efficacy against the parasite while minimizing cytotoxic effects.

Table 2. Biological assays.

Compounds	IC_{50}/24 h[a] (µM)	Compounds	IC_{50}/24 h[a] (µM)
3a	442.5 ± 55.2	**3f**	184.6 ± 22.0
3a'	331.7 ± 40.1	**3g**	133.9 ± 26.2
3b	>1000	**3h**	15.3 ± 0.7
3b'	313.0 ± 24.0	**3i**	630.0 ± 72.6
3c	130.3 ± 19.0	**3j**	>1000
3d	278.4 ± 39.7	**3k**	404.4 ± 88.2
3e	19.0 ± 3.7	**3l**	98.4 ± 8.7
3e'	14.9 ± 2.3	**Bz**	103.6 ± 0.6

[a]Mean ± SD of at least three independent experiments, 5% of blood at 4 °C. Bz = Benznidazole.

Conclusion

The quest for new trypanocidal scaffolds is crucial for the discovery of novel agents to combat Chagas disease, especially given that the current therapeutic options are limited to just two nitrogen heterocycles: nifurtimox and benznidazole. Our findings underscore the potential of A-ring substituted naphthoquinones as effective trypanocidal compounds. This is further supported by our development of a robust strategy for the straightforward functionalization of the benzenoid A-ring *via* catalytic processes. In this work, we successfully developed an efficient Ru-catalyzed C–H alkenylation of 1,4-NQs, leading to the formation of 1,4-naphthoquinoidal/SuFEx hybrids. Several of these compounds are active against the parasite that causes Chagas disease, with the catalytic process supported by a detailed reaction mechanism investigation based on DFT studies. Further derivatization of SuFEx hybrids is being carried out with the aim of exploring new derivatives with trypanocidal activity.

Experimental Section

Ruthenium(II) Catalysed C–H Alkenylation procedure: A 5.0 mL resealable vessel was charged with the corresponding 1,4-naphthoquinone (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.0 mg, 5 mol%), $AgSbF_6$ (68.5 mg, 5.0 mol%, 0.05 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (80 mg, 0.4 mmol, 2.0 equiv.). The vessel was rubber sealed, and inert nitrogen atmosphere was achieved via Schlenk technique. Ethenesulfonyl fluoride (66.8 µL, 0.8 mmol, 3.0 equiv.) and DCE (2.0 mL) were added via syringe. The vessel was cap sealed, and reaction was kept under stirring for 18 hours at 90 ºC. Next, then the reaction was filtered on celite pad and washed with AcOEt (3 x 5 mL), concentrated under reduced pressure, and purified by silica gel column chromatography to afford the desired products.

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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. Spectra of ^{1}H, ^{13}C, ^{19}F NMR,

HRMS, X-ray crystallography, computational and biological data have been included in the supplementary material.

Keywords: C–H activation • Quinones • Ruthenium • SuFEx • Chagas disease

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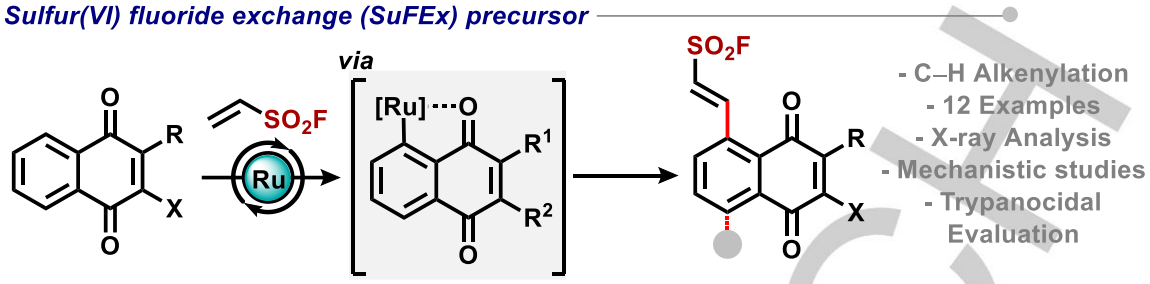

A ruthenium-catalyzed C–H alkenylation of the benzenoid “A-ring” of 1,4-naphthoquinones applying ethenesulfonyl fluoride as the olefin source to afford naphthoquinoidal/SuFEx hybrids has been described. The new methodology enabled the synthesis of new trypanocidal prototypes with relevant activity. DFT mechanistic studies were performed to better understand the reaction mechanism of these transformations.