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Synthesis of Naphthoquinones by Pd-Catalyzed Heck–Matsuda Arylation of Lapachol

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ABSTRACT

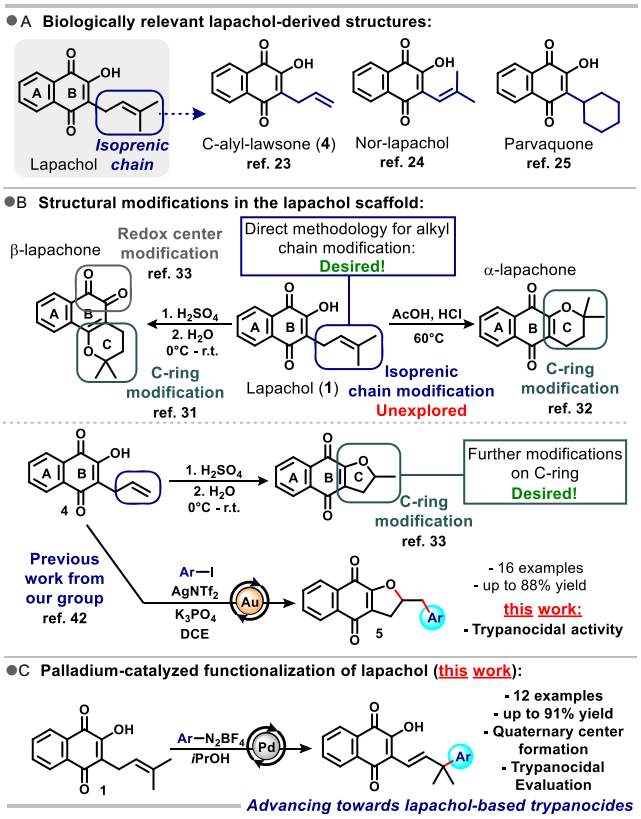
Direct Heck–Matsuda arylation of lapachol provides rapid access to structurally diverse naphthoquinones under homogeneous and heterogeneous palladium catalysis. The methodology features broad substrate scope, gram-scale applicability, and unambiguous structural assignment by single-crystal X-ray diffraction, providing an efficient platform for the diversification of quinones.

1 | Introduction

Quinones constitute a privileged class of redox-active scaffolds at the interface of organic chemistry and biology [1–3]. Their ability to undergo reversible redox cycling enables the modulation of intracellular oxidative stress through the generation of reactive oxygen species (ROS), a mechanism particularly relevant for *Trypanosoma cruzi* (*T. cruzi*), which exhibits a unique and vulnerable redox metabolism [4, 5]. Fine-tuning the electronic properties of quinoidal systems directly influences their redox potential and, consequently, their biological activity and selectivity [6]. Recent advances in medicinal chemistry have therefore emphasized the rational design of structurally modified quinones to optimize pharmacological performance while mitigating toxicity [7–9]. Among naturally occurring quinones, the 1,4-naphthoquinone scaffold stands out as versatile and biologically active [10–12]. Its modular structure enables strategic derivatization at both the quinone core (B-ring) and benzenoid ring (A-ring). These modifications allow systematic modulation of electronic distribution, lipophilicity, and redox behavior, thereby providing an effective platform for the generation of focused molecular libraries aimed at expanding the accessible chemical space around bioactive quinoidal frameworks [13–18].

Lapachol (**1**) is a naturally occurring 1,4-naphthoquinone widely distributed in plants of the genus *Tabebuia* (family Bignoniaceae), commonly known as "Ipê" trees and native to South America [19]. This compound is mainly isolated from the heartwood and bark of these species and has attracted considerable attention due to its broad spectrum of biological activities, including anticancer [20], antimicrobial [21], anti-inflammatory [22], and antiparasitic properties [23]. Structural modification of the lapachol alkyl chain has proven to be an effective strategy for modulating biological activity and expanding the chemical diversity of bioactive naphthoquinones (Scheme 1A).

Among these derivatives, C-allyl-lawsone (**4**), obtained by allylic substitution on the lawsone framework, represents an interesting



SCHEME 1 | Overview.

example in which the introduction of an allyl group significantly enhances biological properties [24]. While the parent compound lawsone exhibits little or no activity against *T. cruzi*, allylated derivatives such as **4** have demonstrated measurable activity in vitro, indicating that relatively small structural changes in the quinone framework can strongly influence antiparasitic potency. Other lapachol-derived structures, such as nor-lapachol and parvaquone, further illustrate the pharmacological relevance of this class of compounds [25, 26].

Related quinones from **1**, such as α- and β-lapachone, have been extensively investigated by our research group through structural modifications of the pyran ring (C-ring) and the quinone redox center (B-ring), with the aim of modulating their biological properties [27–31]. In this context, lapachol often serves as a key precursor for the synthesis of both isomers, enabling further functionalization of the B- and C-rings, providing access to structurally diverse lapachone frameworks [32–34]. These studies have mainly focused on evaluating the activity of such derivatives against *T. cruzi*, the etiological agent of Chagas disease, demonstrating that subtle structural changes can considerably influence antiparasitic activity when the redox center is preserved (Scheme 1B). However, despite the versatility of **1** and **4** as synthetic precursors, methodologies that enable the direct structural modification of these structures while preserving the quinone redox center (B-ring) remain comparatively underexplored. Consequently, the development of strategies that allow the diversification of the quinoidal scaffold without altering its redox-active core represents an attractive approach for expanding the chemical space of bioactive naphthoquinones.

Among the various palladium-catalyzed carbon–carbon bond-forming reactions, the Heck–Matsuda reaction has emerged as a particularly attractive alternative to the classical Mizoroki–Heck coupling due to the high reactivity of aryldiazonium salts under mild conditions [35–37]. Unlike conventional aryl halides, aryldiazonium salts readily undergo oxidative addition to palladium without the need for strongly electron-rich ligands or elevated temperatures, enabling efficient olefin arylation with excellent functional-group tolerance and broad substrate scope [38]. Inspired by these advantages, we envisioned that the direct functionalization of lapachol via Heck–Matsuda coupling could provide rapid access to structurally diverse lapachol-based derivatives. Additionally, **4** was previously transformed into a series of C-ring-functionalized derivatives through gold-catalyzed oxyarylation by our research group in collaboration with Patil's group [39]. In the present study, these previously reported compounds were evaluated against *T. cruzi* to assess their trypanocidal activity (Scheme 1B).

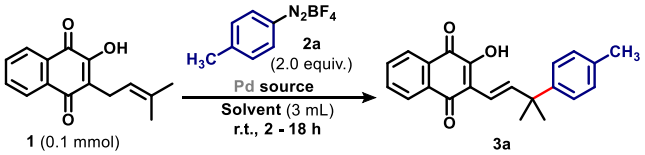
This novel strategy enables the introduction of different aromatic fragments into the isoprenyl side chain, expanding the structural diversity of the resulting compounds while preserving the redox-active quinoidal system. Such modifications are expected to influence the electronic and steric environment of the molecule, potentially impacting its biological activity against *T. cruzi*. In this context, the present work explores the synthesis of new lapachol-derived quinones through Heck–Matsuda reactions and previously reported gold-catalyzed oxyarylation and evaluates their antiparasitic activity to identify promising candidates for the development of new trypanocidal agents.

2 | Results and Discussion

The model reaction for the Heck–Matsuda coupling between lapachol (**1**) and aryldiazonium salt **2a** was systematically investigated, and the results are summarized in Table 1. Initial screening focused on the palladium source and solvent effects under mild conditions (room temperature, 2–18 h). Using $Pd(OAc)_2$ (3 mol%) as the catalyst, no conversion was observed in MeCN, and traces of product were detected with EtOAc (entries 1 and 2), indicating that polar aprotic or weakly coordinating solvents are not suitable for this transformation. Switching alcohol-based solvents led to a marked improvement in reactivity. While MeOH and EtOH afforded moderate yields (37% and 41%, entries 3 and 4), a significant increase was obtained using *i*PrOH, delivering **3a** in 79% yield (entry 5). Further optimization revealed that increasing $Pd(OAc)_2$ loading to 4 mol% in *i*PrOH provided **3a** in an excellent 91% isolated yield (entry 6), identifying these conditions as optimal within the $Pd(OAc)_2$ series. Control experiments confirmed the essential role of palladium, as no reaction occurred in its absence under the best conditions (entry 7). Increasing the catalyst loading to 5 mol% led to diminished efficiency (79%, entry 8), while diminishing the amount of tetrafluoroborate salt **2a** also had a negative impact, resulting in a decreased yield (76%, entry 9).

With the optimized conditions in hand, the generality of the Heck–Matsuda coupling was investigated using a variety of aryldiazonium tetrafluoroborate salts bearing different electronic

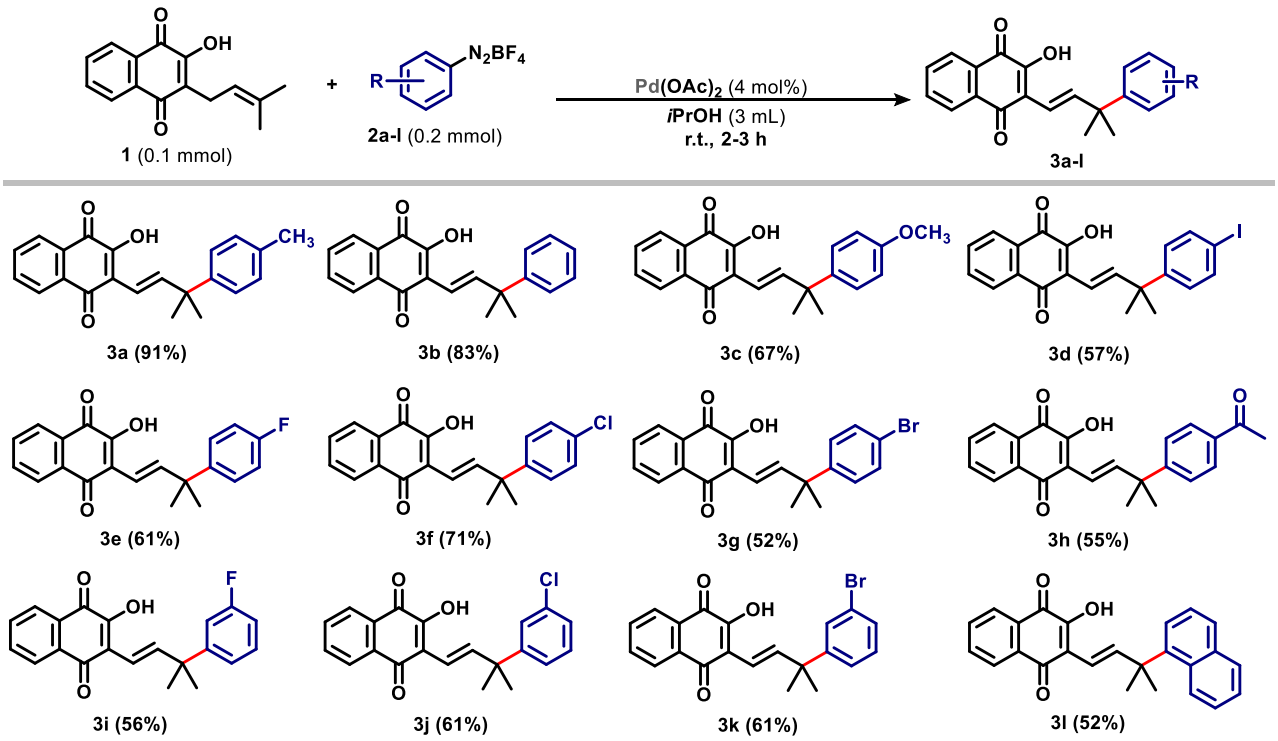
TABLE 1 | Optimization of homogeneous conditions.



Entry	Pd source	Solvent	Yield
1	$Pd(OAc)_2$ (3 mol%)	MeCN	N.R.
2	$Pd(OAc)_2$ (3 mol%)	EtOAc	Traces
3	$Pd(OAc)_2$ (3 mol%)	MeOH	37%
4	$Pd(OAc)_2$ (3 mol%)	EtOH	41%
5	$Pd(OAc)_2$ (3 mol%)	*i*PrOH	79%
6	**$Pd(OAc)_2$ (4 mol%)**	***i*PrOH**	**91%**
7	No $Pd(OAc)_2$	*i*PrOH	N.R.
8	$Pd(OAc)_2$ (5 mol%)	*i*PrOH	79%
9	$Pd(OAc)_2$ (4 mol%)	*i*PrOH	76%[a]

Note: All yields were isolated. Bold values indicate the highest yield achieved.
Abbreviation: N.R., no reaction.
[a]1.5 equivalents of **2a** were used.

and steric profiles (Scheme 2). Overall, the transformation proved to be broadly applicable, affording the desired lapachol derivatives in moderate-to-excellent yields (52%–91%), thus demonstrating the robustness of the methodology under the optimized reaction conditions previously identified. Electron-neutral and weakly electron-donating aryl diazonium salts performed particularly well in this transformation. For instance, the coupling with the *p*-tolyl diazonium salt **2a** furnished product **3a** in excellent yield (91%), consistent with the high reactivity noted during the optimization stage. Similarly, the unsubstituted phenyl derivative **3b** was obtained in a high yield (83%), confirming that electronically unbiased aryl groups are well accommodated under these conditions. The presence of a stronger electron-donating substituent, such as a *p*-methoxy group (**2c**), led to product **3c** in a slightly diminished yield (67%). This moderate decrease may reflect the reduced electrophilicity of the corresponding diazonium species or subtle



SCHEME 2 | Substrate scope for the Heck–Matsuda reaction of **1** with Ar-N_2BF_4 salts. All yields were isolated. All reactions were carried out using **1** (0.1 mmol), **2a–l** (0.2 mmol), catalyst (4.0 mol%), and *i*PrOH (3.0 mL).

electronic effects influencing the migratory insertion step of the Heck–Matsuda catalytic cycle.

A range of halogenated diazonium salts were also compatible with the reaction, highlighting the functional group tolerance of the protocol. Para-substituted iodo, fluoro, chloro, and bromo derivatives delivered products **3d–3g** in yields ranging from 52% to 71%. While the *p*-fluoro and *p*-chloro substrates afforded satisfactory yields (61% and 71%, respectively), heavier halogens such as bromine and iodine resulted in slightly lower yields. This trend may be attributed to increased steric demand and subtle electronic effects associated with larger halogen substituents, which could influence the migratory insertion or β-hydride elimination steps of the catalytic cycle. Importantly, the preservation of the C—X bonds in these products provides valuable synthetic handles for subsequent cross-coupling or diversification reactions. Electron-withdrawing substituents were also tolerated, as illustrated by the *p*-acetyl-substituted derivative **3h**, obtained in 55% yield. The reduced yield in this case may reflect the stronger electron-withdrawing nature of the carbonyl group, which can influence the reactivity or stability of the diazonium salt under the reaction conditions. In addition, other positions of the substituent on the aromatic ring were examined. Meta-substituted fluoro, chloro, and bromo diazonium salts furnished products **3i–3k** in moderate yields (56%–61%), indicating that position effects on the aromatic ring have only a modest influence on the reaction outcome. Finally, the methodology was extended to a more sterically demanding aromatic system. The coupling with a 1-naphthyl diazonium salt provided product **3l** in 52% yield, demonstrating that even extended aromatic systems can participate in the transformation, albeit with somewhat reduced efficiency likely due to increased steric hindrance during the migratory insertion step.

With the objective of advancing a more sustainable and contemporary version of this transformation, we designed a heterogeneous and recyclable catalytic system based on carbon nanotubes functionalized with palladium nanoparticles (PdCNT, Figure 1). This material was prepared using a layer-by-layer assembly strategy, adapted from methodologies previously reported by our group [40, 41]. Attention was then turned to the application of small amounts of PdCNT (0.1 mol%) (Table 2). Under the standard conditions in *i*PrOH, PdCNT showed poor performance, even at higher catalyst loadings (entries 1 and 2). However, solvent effects proved crucial: replacing *i*PrOH with DMSO led to moderate conversion (38%, entry 3), while a DMSO/*i*PrOH (1:1) mixture resulted in a slightly reduced yield (27%, entry 4). In contrast, the use of aqueous media had a pronounced effect. Whereas pure water was ineffective (entry 5), a $CHCl_3/H_2O$ (1:1) solvent system dramatically enhanced catalytic efficiency, affording **3a** in 91% yield (entry 6). This result underscores the beneficial role of mixed aqueous media in facilitating the Heck–Matsuda process, possibly by improving diazonium salt stability and catalyst dispersion. Other solvent combinations, such as $CHCl_3/H_2O$ (3:7), were ineffective (entry 7), and diminishing the amount of **2a** resulted in moderate yields (entry 8). In general, two optimal and complementary sets of conditions were identified: a homogeneous system using $Pd(OAc)_2$ (4 mol%) in *i*PrOH and a heterogeneous system employing PdCNT (0.1 mol%) in $CHCl_3/H_2O$ (1:1), both delivering excellent yields (91%). The latter is particularly attractive from a sustainability perspective due to the low palladium loading

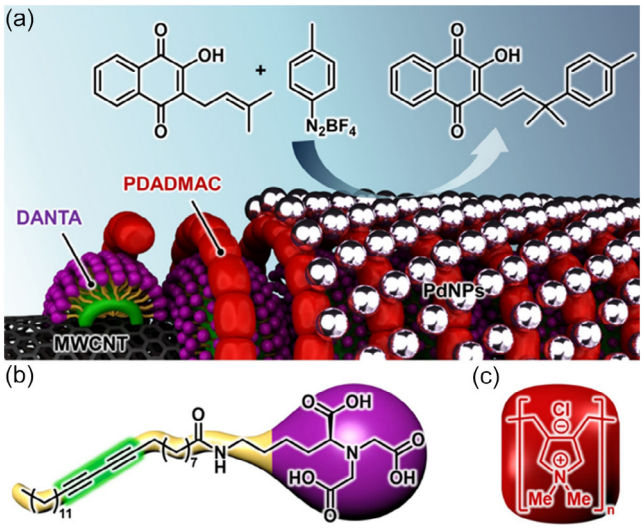


FIGURE 1 | (a) Nanotube-palladium nanohybrid catalyst (PdCNT) design. (b) Structure of diacetylene nitrilotriacetic amphiphile (DANTA). (c) Structure of cationic poly(diallyldimethylammonium chloride) (PDADMAC).

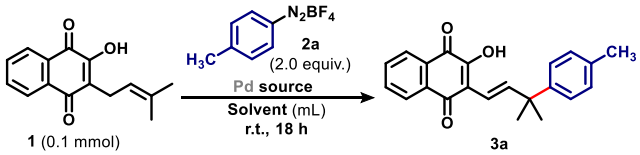
(40-fold decrease in comparison to the homogeneous system) and the use of an aqueous solvent mixture.

To further demonstrate the practical applicability of the methodology, the Heck–Matsuda arylation was performed on a gram scale using the heterogeneous PdCNT nanocatalyst under the optimized reaction conditions (Table 2, entry 6). Gratifyingly, the reaction proceeded efficiently, affording compound **3a** in 84% isolated yield, with a performance comparable to that observed on the small scale, highlighting the robustness and scalability of the heterogeneous catalytic system.

Single-crystal X-ray diffraction analyses of compounds **3a** and **3d** (Figure 2) played a decisive role in the unambiguous structural assignment of the Heck–Matsuda products and in clarifying the regiochemical outcome of the transformation. Given that **1** contains an electron-deficient naphthoquinone core conjugated to an exocyclic olefin, arylation could, in principle, occur at either carbon of the C=C bond during the migratory insertion step, leading to distinct regioisomeric products [42]. The crystallographic structures, depicted with thermal ellipsoids at the 50% probability level, unequivocally demonstrate that the aryl fragment is installed at the terminal carbon of the olefinic moiety, affording a single regioisomer in both cases (Figure 2). Furthermore, the X-ray analyses confirm the exclusive formation of the (*E*)-configured olefin, with the trans relationship between the aryl substituent and the quinoidal framework clearly established in the solid state. This assignment is fully consistent with the large vicinal coupling constant observed in the ^1H NMR spectra ($J \approx 16.5$ Hz). Together, the crystallographic and spectroscopic data provide definitive evidence for both the regioselectivity and stereoselectivity of the Heck–Matsuda arylation, eliminating any ambiguity regarding alternative regioisomeric products or *Z*-configured olefins.

Our group has previously synthesized and reported a number of naphthoquinone derivatives, obtained through gold-catalyzed

TABLE 2 | Optimization of heterogeneous conditions.



Entry	Pd source	Solvent	Yield
1	PdCNT (0.1 mol%)	*i*PrOH (3 mL)	Traces
2	PdCNT (0.1 mol%)	*i*PrOH (1 mL)	Traces
3	PdCNT (0.1 mol%)	DMSO (1 mL)	38%
4	PdCNT (0.1 mol%)	DMSO/*i*PrOH 1:1 (1 mL)	27%
5	PdCNT (0.1 mol%)	H_2O (1 mL)	N.R.
6	**PdCNT (0.1 mol%)**	**$CHCl_3/H_2O$ 1:1 (1 mL)**	**91% (84%)**[b]
7	PdCNT (0.1 mol%)	$CHCl_3/H_2O$ 3:7 (1 mL)	Traces
8	PdCNT (0.1 mol%)	$CHCl_3/H_2O$ 1:1 (1 mL)	71%[a]

Note: All yields were isolated. Bold values indicate the highest yields achieved.
Abbreviation: N.R., no reaction.
[a]1.5 equivalents of **2a** were used.
[b]Gram-scale reaction: **1** (5.0 mmol), **2a** (10 mmol), $CHCl_3/H_2O$ 1:1 (50 mL).

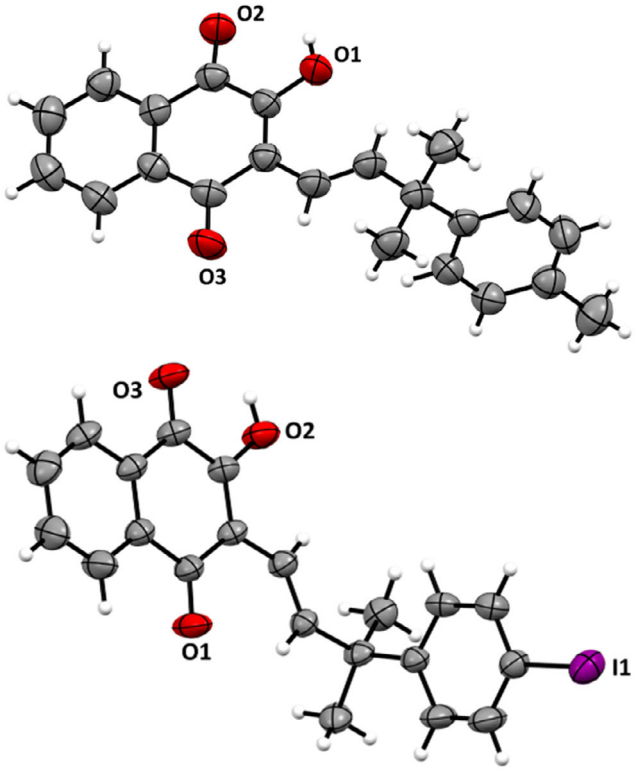


FIGURE 2 | Crystal structures of **3a** and **3d**, with atomic labeling. Nonhydrogen atoms are shown as thermal ellipsoids at the 50% probability level. Carbon atoms are shown in gray, and hydrogen atoms are shown as white spheres. Carbon and hydrogen atoms are not labeled for clarity.

oxyarylation of C-allyl-lawsone (**4**) (see Scheme S1) [39]. In the present study, these compounds were prepared in quantities sufficient to evaluate their biological activity against the trypomastigote forms of *T. cruzi*, the infective stage associated with Chagas disease. The substrate scope of the gold-catalyzed oxyarylation was evaluated using a series of aryl iodides bearing electronically and sterically distinct substituents (Scheme S1).

The biological evaluation of compounds **3a–l** and **5a–p** against bloodstream trypomastigote forms of *T. cruzi* was performed to investigate the influence of structural modifications on antiparasitic activity (see Table S2). Overall, the Heck–Matsuda-derived lapachol analogs **3a–l** displayed little or no activity under the evaluated conditions, indicating that direct arylation of the exocyclic olefin is not a favorable strategy for improving the trypanocidal profile of this scaffold. In contrast, the previously reported oxyarylated derivatives **5a–p**, synthesized according to our earlier procedure [39], exhibited significantly improved biological activity, with several compounds showing promising antiparasitic profiles. These results suggest that conformational restriction through fused dihydrofuran formation is beneficial for biological activity.

3 | Conclusion

The Pd-catalyzed Heck–Matsuda methodology developed herein provides access to a new family of quinonoid compounds with broad substrate scope and good functional group tolerance, enabling systematic structure–activity relationship (SAR) studies. In parallel, we evaluated the trypanocidal activity of dihydrofuran-fused naphthoquinones previously synthesized by our group through gold-catalyzed oxyarylation of alkenes [39]. Biological evaluation against bloodstream trypomastigote forms of *T. cruzi* revealed clear differences between the two molecular series. Whereas the Heck–Matsuda products generally exhibited low-to-moderate activity, the oxyarylated derivatives displayed improved trypanocidal potency, suggesting that structural rigidity and dihydrofuran ring fusion may contribute to the biological properties of quinone-based scaffolds.

SAR analysis further indicated that both electronic and conformational factors may influence the antiparasitic activity of these quinonoid systems. In particular, the enhanced activity observed for oxyarylated derivatives **5b**, **5c**, and **5o** suggests that preserving the quinone redox core while increasing conformational restriction could represent a promising strategy for the design of new trypanocidal agents. Overall, the results presented herein indicate that catalytic diversification of naturally derived quinones may provide access to structurally complex and biologically relevant molecules. Together, the synthetic methodology and biological findings reported in this study may serve as a useful foundation for future optimization of quinone-based compounds against *T. cruzi*. Moreover, as part of our ongoing medicinal chemistry program, the continuous synthesis and biological evaluation of quinonoid compounds over the past two decades have contributed to an expanding SAR knowledge base that may facilitate the identification of new trypanocidal lead compounds.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.