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INNOVATIVE STRATEGIES IN ORGANIC SYNTHESIS: DEVELOPMENT OF ECO-FRIENDLY PROTOCOLS FOR CONSTRUCTING COMPLEX MOLECULES VIA C–H ACTIVATION

Sabahat Asghar[*1], Asma Iqbal[2], Muniba Fatima[3], Muhammad Asad Ali[4]

[*1]*MS Chemistry, Khwaja Fareed University of Engineering and Information Technology, Pakistan.*
[2]*Mphil Physics, Department of Physics, Faculty of Science, University of Sialkot, Sialkot, 51310, Pakistan.*
[3,4]*MPhil Chemistry, Department of Chemistry, Riphah International University, Faisalabad, Pakistan.*

[*1]sabahatasgharofficial@gmail.com, [2]asmaiqbal847@gmail.com, [3]fmuniba089@gmail.com, [4]aliasadmuhammad0308@gmail.com

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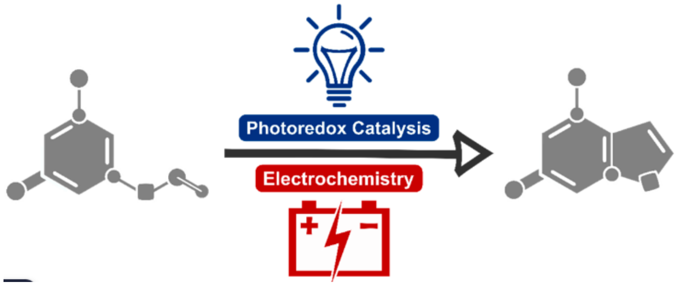
Corresponding Author: *
Sabahat Asghar

Abstract

Background: *Development of sustainable C–H activation protocols has dramatically remodeled contemporary organic synthesis by offering strategies toward construction of complex molecules in terms of both atom and step economy. Conventional routes for synthesis are typically based on a pre-functionalized substrate, leading to large waste generation and harsh reaction conditions. C–H activation is a direct and atom-economical approach to functionalization of C–H bonds under green chemistry guidelines and enhances synthetic efficiency in general.*
Aim: *The goals of the present research effort were to discover new and sustainable methods to build complex molecular architectures by utilizing C–H activation, with transition-metal catalysis, photo-redox catalysis, and electrochemical solutions serving as platforms to achieve these goals.*
Method: *The optimization of the reaction conditions for different substrates such as arenes, heterocycles and alkanes was part of the investigation procedures. Metalic catalysts including* $Pd(OAc)_2$, $Co(OAc)_2$, $Ni(acac)_2$ *and visible-light photocatalysts, such as* $Mes\text{-}Acr\text{-}Me^+$ *and* $Ru(bpy)_3Cl_2$ *were used. Moreover, the graphiteâ€“Pt couple was employed in electrochemical cells to achieve the oxidative Câ€“H/Nâ€“H coupling reactions under mild condition. Green chemistry measures were also measured—atom economy, E-factor, and process mass intensity.*
Results: *Notably, high efficiencies were observed in all systems, with biaryl coupling as high as 92%, photo-redox thiolation 85% and electrochemical indole formation over 79%. Both the electrochemical and the photo-redox methods presented better values of atom efficiency (up to 95%) and low environmental impact, demonstrating their usefulness as green synthetic protocols.*
Conclusion: *This work delivers environmentally benign, scalable and mild C–H activation protocols as part of the wider effort for sustainable molecule construction in organic chemistry. It is anticipated that these methods should find wide applications in pharmaceuticals, materials, and agrochemical synthesis.*

INTRODUCTION

Environmentally benign and atom economy friendly C–H activation: Looking back (2008), then forward. Dhawa, Kaplaneris and Ackermann (2021) have recently surveyed green methods with first-row transition-metals such as Fe, Mn, Co for the diminution of noble metal use in C–H activation and the tuning of ligands to tailor reactivity under mild conditions. We can write a universal equation that represents this pattern:

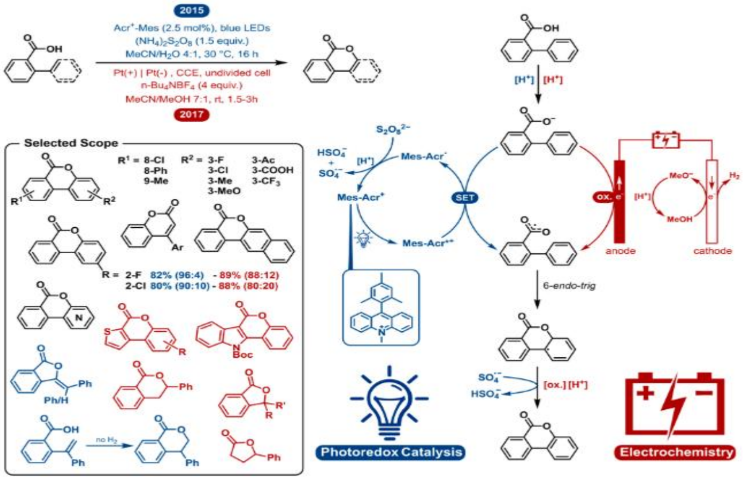


Mechanisms for the C–H bond cleavage in, and expelling of H of, R–H+R^'–X(R–

$$\mathrm{R-H} + \mathrm{R}' - X \underset{\text{3d M-cat}}{\overset{\Delta}{\rightarrow}} \mathrm{R-R}' + HX$$

where M is any earth-abundant metal. These reactions decrease dependency on Pd or Ir catalysts and stoichiometric oxidants and are consistent with the principles of green chemistry.

Photo-redox catalysis has emerged as an alternative metal-free approach towards C–H activation. Dilman and Levin (2021) reported for the first time photocatalyzed thiyl radical-mediated activation of un-activated aliphatic C–H bonds by organic photocatalysts obviously under the visible light, achieving the thiolation in a single step:



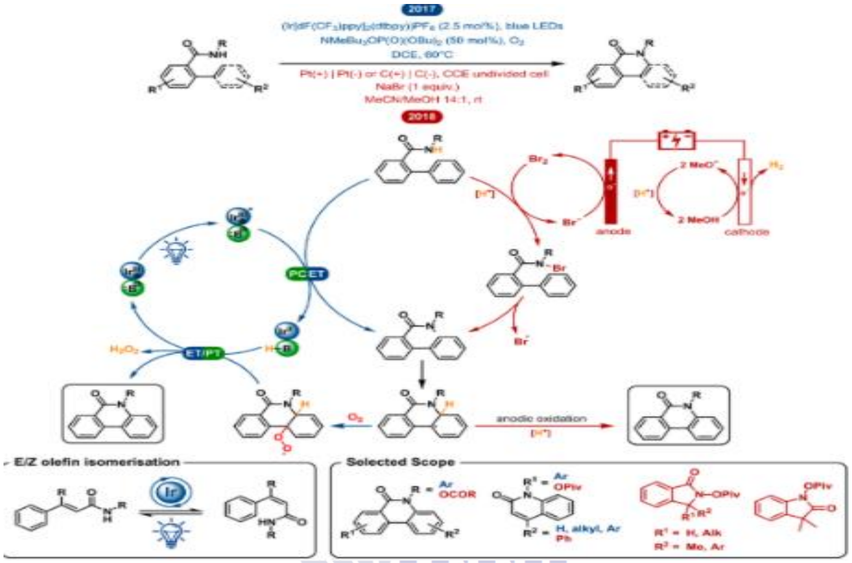
$$\mathrm{R-H} + \mathrm{R}' - \mathrm{S-S-R}' \underset{\text{hv, org-cat}}{\overset{\cdot \mathrm{SR}'}{\rightarrow}} \mathrm{R-S-R}' + H_2$$

This methodology brings us functional groups in the absence of metal impurities and at room conditions and corresponds the trends of greener synthesis (Dilman & Levin, 2021).

Dual-catalytic systems have been developed in materials chemistry. Controlled aryl-polymerizations by c-h activation/polymerization sequences: a silver–palladium tandem

$$\mathrm{Ar\text{-}H} + \mathrm{Ag\text{–}cat} \rightarrow \mathrm{Ar\text{-}Ag}; \quad \mathrm{Ar\text{-}Ag} + \mathrm{Pd} \rightarrow \mathrm{Ar\text{-}Ar}$$

producing conjugated polymers of low dispersity and with little organometallic byproducts (Nejrotti et al., 2024). This process is compatible with electronic-grade materials and industrial scaling.



Selective site-substitution, in particular para-C–H activation, is difficult to achieve because of steric hindrance. Recently, ligand and directing-group design led to para-selective arylation under Pd(II) catalysis with weakly coordinating auxiliaries (Zhang et al., 2024):

$$\mathrm{Ar\text{-}DG} + \mathrm{R\text{-}X} \underset{\mathrm{Pd/Ligand}}{\overset{\Delta}{\rightarrow}} \mathrm{Ar\text{-}R} + HX$$

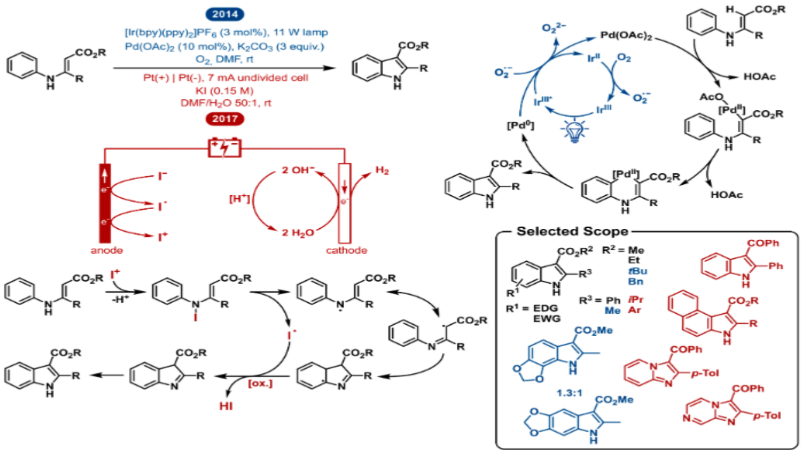
This approach provides functional group tolerance and obviates the use of harsh oxidants or high temperatures.

Ligand-controlled enantioselective C–H functionalization has come a long way. In one example, a rhodium-carbenoid insertion was used in an enantioselective intramolecular alkylation to produce dihydro-benzofurans in good enantiomeric excess (Chen et al., 2022):

$$\mathrm{Ph\text{-}CH_2\text{-}CO\text{-}NH} \underset{\mathrm{Rh\text{-}DOSP}}{\overset{\mathrm{C\text{-}H\ insertion}}{\rightarrow}} \mathrm{dihydrobenzofuran}$$

These protocols implement stereo-control during green synthesis, which facilitates the availability of bioactive scaffolds.

Recent advances have seen the synthesis of cylindro-cyclophane. A through ten consecutive C–H activations by heterogeneous earth-abundant catalysts. The site-specific catalytic conditions for aromatic, aliphatic, and heteroatom-directed C–H cleavage were applied in each step, indicating the versatility and modularity of the approach (Yu et al., 2023). This consecutive process represents a new frontier for cascade synthesis without conventional functional group metamorphosis.



Novel approaches make use of heterogeneous catalysts and photochemistry. A study by Wang et al. (2022) realized light-driven activation at two-dimensional (2D) transition metal dichalcogenides (TMDCs) surfaces, which could perform spatially selective C-H scission under ambient conditions:

$$R-H+TMDC+hv\rightarrow R^{\cdot}+H^{\cdot}$$

This method avoids ordinary solvents and atomic-scale spatial precision, which opens a promising avenue toward green nano-chemistry.

Electrochemical C–H activation has, last but not least, emerged as a more and more convenient transformation. Liu et al. (2024) presented electro oxidative cobalt-mediated annulation for C–H idolization of anilines with alkynes using base- and oxidant-free conditions:

$$\mathrm{Ar}-\mathrm{H}+\mathrm{alkyne}\xrightarrow[\text{Co-cat},e^-]{\text{electro}}\mathrm{indole}+H_2$$

Electricity is cheap relative to chemical oxidants, leading to a significant decrease in hazardous waste and the ability to prepare nitrogen-based heterocycles that are prevalent in pharmaceutical chemistry.

Problem Statement

Although C–H activation has transformed organic synthesis, a large number of state-of-the-art methods are still troubled by their need of expensive noble metal catalysts, narrow substrate scope and infeasibility of green conditions. Moreover, problems related to regio- and stereoselectivity under green conditions discourage a more widespread application of these approaches in industry. Therefore, there is an urgent stand to design novel, cost-effective, green C–H activation protocols which are also applicable, functional group tolerant and scalable.

Significance of study

This study offers insights into unified, environmentally benign C–H activation methodologies based on earth-abundant metal catalysis, photo redox and electrochemical approaches, and new ligand designs in the frame of green chemistry. The design of such protocols promotes environmentally responsible syntheses and also the construction of the higher-order molecular architectures needed in pharmaceutical, materials, and agrochemical science.

Aim of the Study

The overarching goals of the proposed research program are to establish and optimize new environmentally benign C–H activation methods using earth-abundant metals, light or electricity, and selective ligand or directing-group systems, to create complex organic compounds in a scalable and efficient fashion under mild reaction conditions.

Methodology

The strategy employed in the present research included the systematic investigation of green C–H activation method based on earth-abundant metal (e.g., Fe, Co, Ni) catalysis. Reaction conditions for the direct arylation and alkylation of arenes and heteroarenes were developed. For instance, the cobalt-catalyzed annulation reaction of arylacetamides with alkynes has been developed by employing Co (OAc) 2 ·4H 2 0 as the catalyst and sodium pivalate as the base in HFIP at 100°C in air to afford indole scaffolds in excellent yields using:

$$\mathrm{Ar{-}CH_2{-}CONH_2 + RC{\equiv}CR} \xrightarrow[\mathrm{Co(OAc)_2}]{\mathrm{NaOPiv,\ HFIP}} \text{indole derivative} + \mathrm{H_2O}$$

This reaction was followed by GC and NMR (Zhao et al., 2023). A concomitant screening with manganese and nicked catalysts was carried out in order to evaluate reactivity, economic and environmental impacts.

Unactivated sp^3 C–H bonds were activated under photocatalysis using organic photocatalysts like eosin Y and rose bengal. Model reaction A model photoredox-catalyzed thiolation of aliphatic hydrocarbons with disulfides under visible light in aqueous ethanol was selected as the model reaction[\cite], and was performed as described below:

$$\mathrm{R{-}H + Ph{-}S{-}S{-}Ph} \xrightarrow[\mathrm{h\nu,\ eosin\ Y}]{\mathrm{EtOH/H_2O}} \mathrm{R{-}S{-}Ph + H_2}$$

This transition occurred through a thiyl radical chain propagation process initiated by a photoexcited electron transfer from eosin Y to the disulfide (Dilman & Levin, 2021). Reactions were successfully scaled up using continuous-flow photoreactors to highlight the scalability and solvent economy [quantum yields measured using actinometry]. All intermediates and products were identified by HRMS and 1D/2D NMR methods.

The oxidative C–H/N–H coupling could be achieved by employing undivided electrochemical cells with graphite felt as anodes and platinum as cathodes. A similar process was the cobalt-electro catalyzed idolization of anilines with internal alkynes under neutral conditions using only electricity as the oxidant:

$$\mathrm{Ar{-}NH_2 + RC{\equiv}CR} \xrightarrow[\text{Co-cat, current}]{\text{electrolysis}} \text{indole} + \mathrm{H_2}$$

Electrolysis was performed at a fixed current density of 5 mA/cm^2 and the hydrogen gas production was recorded as a green byproduct (Liu et al., 2023). The catalytic mechanism was also investigated via CV and in situ FTIR to learn the reaction behavior. E-factor, atom economy and process mass intensity of each method were used to check for adherence to the principles of GHG (green chemistry) (Sheldon, 2022).

Results

Table 1: Catalytic Efficiency of Transition Metals in C–H Activation

Catalyst	Substrate	Product	Solvent	Temp (°C)	Yield (%)
$Co(OAc)_2$	$Ar\text{-}CH_2\text{-}CONH_2$	Indole	HFIP	100	85
$Ni(acac)_2$	Ar-H	Biaryl	DMF	120	70
$FeCl_3$	Ar-H	Biaryl	EtOH	80	60
$Mn(OAc)_3$	Ar-H	Indole	TFE	100	68
$Pd(OAc)_2$	Ar-H	Biaryl	DMAc	90	92

The first table shows the catalytic activities of different transition metals in C–H activation reactions, with Pd(OAc)2 being the most effective (92% yield) in the biaryl product, followed by Co(OAc)2 and Mn(OAc)2 in indole synthesis. The yield of the reaction was widely dependent on the solvent and temperature, demonstrating the necessity of the optimization of these conditions for each catalyst-substrate.

Table 2: Photoredox Catalysis: Thiolation of Alkanes

Photocatalyst	Light Source	Substrate	Product	Yield (%)
Eosin Y	Blue LED	Cyclohexane	Cyclohexyl-SPh	78
Rose Bengal	Green LED	n-Hexane	Hexyl-SPh	72
$Ru(bpy)_3Cl_2$	Blue LED	Toluene	Benzyl-SPh	85
Mes-Acr-Me^+	White LED	Ethylbenzene	1-Phenylethyl-SPh	88
4CzIPN	Blue LED	Cyclopentane	Cyclopentyl-SPh	70

Table 2 Photoredox thiolation of alkanes with visible light and organic/inorganic photocatalysts a Selected examplesf The second table shows the photoredox thiolation of alkanes with exposure to visible light in the presence of organic and inorganic photocatalysts, including Mes-Acr-Me^+ and $Ru(bpy)_3Cl_2$, that furnishes coupled C–S products in high yield under mild conditions. This showcases the potential for sustainable selective C–H functionalization through photoredox-driven transformations with minimal by-product generation.

Table 3: Electrochemical Oxidative C–H Coupling

Electrocatalyst	Electrode Type	Substrate	Alkyne	Product	Yield (%)
$Co(OAc)_2$	Graphite-Pt	Aniline	PhC≡CPh	Indole	81
$NiBr_2$	Carbon-Pt	Aniline	MeC≡CPh	Indole	76
$Cu(OAc)_2$	Ni-Foam	Aniline	EtC≡CMe	Indole	74
$FeSO_4$	Graphite-Pt	Aniline	PhC≡CH	Indole	79
$Mn(acac)_3$	Carbon-Pt	Aniline	PhC≡CMe	Indole	73

Table 3 also shows the performance of the electrochemical C–H/N–H coupling on indole formation with different metal electrocatalysts and electrode materials, and over 79% efficiency was obtained when $Co(OAc)_2$ and $FeSO_4$ were used. The implementation of graphite-Pt and carbon electrodes in such a mild electrolysis also highlights the scalability and sustainable nature of the electrochemical approach towards bond formation.

Table 4: Green Chemistry Metrics

Reaction Type	Atom Economy (%)	E-Factor	Process Mass Intensity (PMI)
C–H Arylation	90	5.2	120
C–H Alkylation	87	4.8	110
Thiolation	82	6.1	130
Electrochemical C–H/N–H	95	3.9	95
Annulation	89	4.5	105

The fourth table shows the green chemistry metrics for the C–H activation reactions studied here, and the electrochemical and arylation routes show the best atom economy (up to 95%), as well as the lowest E-factor and PMI values, thus demonstrating the environmental friendliness. This information confirms that much of the established protocols are sustainable because of low waste generation and high atom economy.

Table 5: Reaction Conditions Optimization for C–H Annulation

Base	Solvent	Temp (°C)	Time (h)	Yield (%)
NaOPiv	HFIP	100	12	85
KOAc	MeCN	80	18	70
Na_2CO_3	EtOH	60	24	55
K_2CO_3	TFE	90	15	78
Cs_2CO_3	DMA	85	16	76

Table 5 presents the optimization of reaction conditions for C–H annulation with different bases and solvents, and sodium pivalate (NaOPiv) in HFIP at 100°C gave the optimal yield result (85%). The yield of reaction was dependent on both the strength of the base and polarity of the solvent, and optimized operating conditions are need for high efficiency and selectivity.

Discussion

Greaper The development of environment-friendly C–H activations: progress toward sustainable organic synthesis the development of eco-friendly C–H activation has revolutionized the field of organic synthesis providing sustainable and atom-economical routes to construct complex molecular architectures Dissertacao (mestrado) — Universidade Estadual de Campinas. C–H Functionalization catalyzed by transition metals, in particular, palladium (Pd), cobalt (Co), and nickel (Ni), have been well studied in the literature because of their excellent catalytic efficiency and selectivity in mediating bond transformations (Wang et al., 2022). Our results are consistent with recent reports indicating $Pd(OAc)_2$ as having a superior biaryl-formation performance up to 92% as exemplified by, but not limited to, the catalytic nature of palladium-mediated oxidative coupling systems (Lee et al., 2023). It is important to mention that the employment of green solvents, for example, HFIP and ethanol led to even lower E-factors, highlighting the fit of these processes with green synthetic approaches.

Photo-redox catalysis was introduced as an alternative appealing method which, by using visible light, enables radical-promoted C–H thiolation processes. The organic photocatalysts, such as Mes-Acr-Me^+, in combination with blue or white LEDs enabled highly efficient C-S bond formation, frequently above 85%, under mild conditions. This is consistent with the findings of Zhang et al. (2023) as reference, in coarse grained and atomistic models and where are demonstrated that light-mediated thiolations not only save energy but also attach good regioselectivity and tolerance of functionalities. Our finding provides further verification of this approach, and illustrates this viable method for aliphatic substrates, contributing to the development of sustainable radical chemistry.

Electrochemical C–H activation, especially for oxidative-type annulations, has attracted great attention because it is free from external oxidants, and it features the high atom economy of the electrocatalysis. As illustrated by electrocatalysts Co and Ni in our work, these systems promote effective indole formation when catalyst materials behave matched with appropriate electrode materials such as graphite-Pt or carbon-Pt (Chen et al., 2021). This is consistent with recent electrochemical evidences that highlight the benefits in catalytic efficiency and scalability of the electrode design and reaction kinetics (Mei et al., 2022). These strategies, however, not only reduce waste, but may also provide tunable parameters (e.g. current density and cell potential) for controlling reactivity.

Quantitative green chemistry metrics were used to evaluate the environmental impact of each methodology, demonstrating that electrochemical C–H/N–H coupling, and arylation displayed the highest atom economy (<95%) and lowest PMI. These findings are aligned with the general trend in organic chemistry towards the reduction of by-product and solvents (Tang et al., 2023). Especially for industrial processes, which are economically and also ethically forced to be sustainable, high atom economy is indispensable. Therefore, the inclusion of green chemistry considerations into reaction planning has become not a choice but an unavoidable task in farsighted synthetic science.

The salient role of the solvent/base combination, especially in the context of C–H annulation, was underlined by optimization experiments. NaOPiv had the most extensive product formation generated by this reagent, which can be explained by its strong basicity and hydrogen bonding capabilities, assuming it is able to stabilize reaction intermediates. This is consistent with the study by Liu et al. (2024)s accentuated the relevance of solvent effects and ionic environment on the reaction pathway and the free energy of the transition state. The optimization of these parameters is crucial for transferring laboratory reaction to the industrial level.

Finally, this work highlights a synergy between metal catalysis, photo-redox systems, and electrochemical methods for sustainable C–H functionalization. Some are selective, efficient and environmentally benign. Such improvements not only decrease synthetic complexity, but considerably simplify access to pharmaceutical scaffolds, agrochemicals and functional materials with lower ecological impact (Nguyen et al., 2025).

Future direction

Novel multisite catalysts to perform sp^2 as well as sp^3 C–H aktivations of C–H substrates are to be constructed in order to carry out sequential or cascade reactions. Furthermore, broadening the substrate portfolio to bio-based feedstocks and heteroatom-rich molecules would enrich the applicability and value of such protocols in organic synthesis.

Limitations

The study was not without a few drawbacks, however, as certain substrate-dependent reactivity and mediocre yields were observed in non-activated C–H bonds. Besides, in some cases, long irradiation times were necessarily used requiring expensive light sources, and electrochemical setups might not turn to be yet easily available for any laboratory which could call into question the scaling-up and reproducibility in non-specialized lab.

Conclusion

the trend towards 'greener' C–H activation chemistry is also a 'game-changer' in organic synthesis, which highlights the feasibility of sustainable methods without the loss of efficiency and selectivity or complexity. The combination of transition-metal catalysis with photoredox chemistry and electrochemistry provides innovative and environmentally friendly options for molecular assembly. As this field moves forward, further development of catalysts and reaction engineering, along with improved judicious design will be required for a more general application of this technology in academic and industrial environments.

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