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Communication

Catalytic Synthesis of Cyclopropenium Cations with Rh-Carbynoids

Hang-Fei Tu, Aliénor Jeandin, and Marcos G. Suero*

Cite This: J. Am. Chem. Soc. 2022, 144, 16737−16743
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ABSTRACT: Herein, we report the first catalytic one-step synthesis of cyclopropenium cations (CPCs) with readily available alkynes and hypervalent iodine reagents as carbyne sources. Key to the process is the catalytic generation of a novel Rh-carbynoid that formally transfers monovalent cationic carbynes (:$^{+}$C-R) to alkynes via an oxidative [2+1] cycloaddition. Our process is able to synthesize a new type of CPC substituted with an ester group that underpins the regioselective attack of a broad range of carbon and heteroatomic nucleophiles, thus providing a new platform for the synthesis of valuable cyclopropenes difficult or not possible to make by current methodologies.

Cyclopropenium cations (CPCs), discovered by Prof. Ronald Breslow in the late 1950s,[1−3] are the smallest member of the Hückel aromatic systems. These aromatic cations with two π-electrons delocalized over three 2p orbitals are known to have considerable thermodynamic stability and molecular strain (Figure 1A). The highly stable tris-

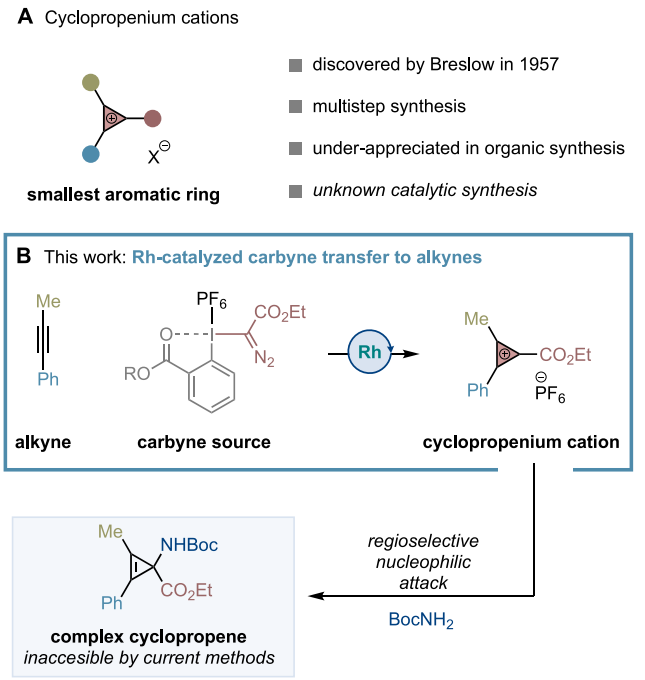


Figure 1. Catalytic synthesis of cyclopropenium cations.

(dialkylamino)CPC derivatives have recently found applications as electrophotocatalysts,[4] gene delivery agents,[5] catholytes for nonaqueous redox batteries,[6] or liquid crystals.[7] However, CPCs have been largely underappreciated in organic synthesis, despite their potential as three-carbon building blocks in the construction of complex architectures.

One of the main reasons is that the majority of synthetic strategies toward CPCs, developed between the 1950s and 1980s, rely on multistep sequences and show limitations in efficiency. Those methods require the synthesis of cyclopropene derivatives that lead to the CPC upon (pseudo)halide, nitrile, carbonyl, or hydride abstraction with strong Lewis/Brønsted acids.[1,3,8] Alternative approaches based on functionalizations of alkynes with chlorocarbenes generated from chlorodiazirines under UV light irradiation[9] or with a cationic metal-carbyne $[(\eta^5\text{-}C_5H_5)(CO)_2Mn{\equiv}CPh]^+$ show very limited scope (only two examples are described in the latter case).[10] In addition to this, nonsymmetrical CPCs are likely to react with poor regioselectivity in nucleophilic events. In fact, pioneering work by Padwa showed that reactions between CPCs and Grignard reagents provided mixtures of regioisomers.[11]

Herein, we would like to disclose the invention of a one-step Rh-catalyzed process for the preparing of CPCs that combines readily available alkynes and hypervalent iodine reagents as formal cationic carbyne sources (Figure 1B).[12] The process showed a broad scope of a new class of CPCs substituted with an ester group that, upon treatment with a diverse range of nucleophiles, provided access to valuable and elusive classes of cyclopropene derivatives.[13]

Our research group is focused on the development of a carbyne transfer platform in organic synthesis using tailored hypervalent iodine reagents[14] as carbyne synthons.[15] The catalytic activation with dirhodium carboxylate catalysts[16] provides access to Rh-carbynoids (***int*-1**) (Figure 2),[15b,d] a novel class of Rh-carbene species substituted with an ester group and a hypervalent iodine moiety as outstanding nucleofuge.[17] Such species have the ability to emulate the carbene/carbocation behavior of a monovalent cationic carbyne (:$^{+}$C−

Received: July 22, 2022
Published: September 8, 2022

https://doi.org/10.1021/jacs.2c07769
J. Am. Chem. Soc. 2022, 144, 16737−16743

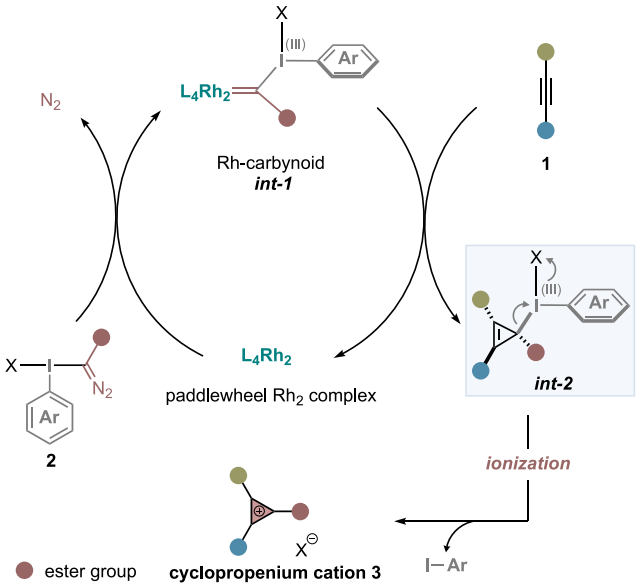


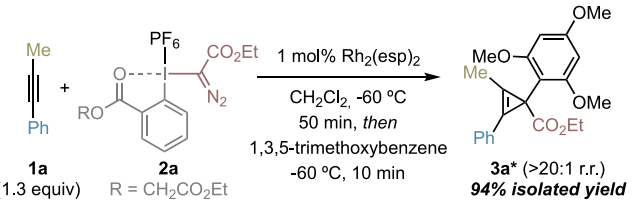
Figure 2. Mechanistic hypothesis.

R) and provide a transient cyclopropyl-$I^{(III)}$ intermediate upon alkene cyclopropanation. Recently, we questioned whether we could exploit our Rh-catalyzed carbyne transfer platform for the discovery and development of the first one-step and catalytic synthesis of cyclopropenium cations (Figure 2). We hypothesized that the catalytically generated Rh-carbynoid (***int*-1**) could intercept alkynes and provide cyclopropenyl-$I^{(III)}$ intermediates (***int*-2**) that, upon an ionization process that occurs with the departure of the $I^{(III)}$ leaving group, would lead to a new class of CPC substituted with an ester group.[18]

With this mechanistic proposal in mind, we evaluated the feasibility of this idea using 1-phenyl-1-propyne, a broad range of commercial Rh_2 catalysts, and diazomethyl-based hypervalent iodine reagents **2** (see Supporting Information for full optimization studies). Taking into account the possible instability and reactivity of the desired CPC, we employed 1,3,5-trimethoxybenzene as external nucleophile to quantify the efficiency of the transformation. To our delight, after extensive optimization studies, we were able to find that pseudocyclic reagent **2a** and the Du Bois catalyst[19] $Rh_2(esp)_2$ (1 mol %) led to cyclopropene **3a*** with excellent efficiency (94% yield, >20:1 r.r.) (Table 1). The only regioisomer observed comes from the selective attack of the nucleophile to the cyclopropenium carbon atom substituted with the ester group.

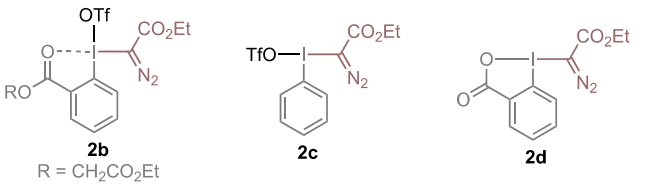
During the optimization of the reaction, we observed that other sterically demanding catalysts worked well (Table 1, entry 1); however, $Rh_2(OAc)_4$ or the more electrophilic $Rh_2(TFA)_4$ was not competent (entries 2, 3). The nature of the hypervalent iodine reagent played also a key role in the efficiency of the transformation. The use of triflate as counterion provided a moderate yield of **3a*** (entry 4). However, although full consumption of linear reagent **2c** was observed, no conversion to the desired product was detected (entry 5). On the other hand, cyclic reagent **2d** was inert to catalytic diazo activation with $Rh_2(esp)_2$ (entry 5). Only upon addition of $Zn(OTf)_2$ as the additive, a well-known activator of cyclic $I^{(III)}$ reagents,[14] was a moderate yield of **3a*** observed (entry 6). We also found that higher reaction temperatures could give product **3a*** but with lower efficiency (entry 7).

Table 1. Optimization Studies[a,b]



entry	deviation of reaction conditions	yield[b] **3a***, %
1	$Rh_2(OPiv)_4$ instead of $Rh_2(esp)_2$	93
2	$Rh_2(OAc)_4$ instead of $Rh_2(esp)_2$	4
3	$Rh_2(TFA)_4$ instead of $Rh_2(esp)_2$	0
4	**2b** instead of **2a**	50
5	**2c,d** instead of **2a**	0
6	**2d** used with $Zn(OTf)_2$ instead of **2a**	60[c]
7	reaction carried out at −50 °C	81

[a]Reactions performed with alkyne **1a** (0.2 mmol, 2.0 equiv), reagents **2** (0.1 mmol, 1 equiv), Rh catalyst (1 mol %), and 1,3,5-trimethoxybenzene (4 equiv) in CH_2Cl_2 (0.067 M). [b]Yields are reported on the basis of ^1H NMR analysis using CH_2Br_2 as the internal standard. [c]0.5 equiv of $Zn(OTf)_2$ was used.



During the optimization process, we observed that the addition of **2a** to **1a** and $Rh_2(esp)_2$ at −60 °C provided the formation of a slurry, which quickly turned into a clear solution after the addition of 1,3,5-trimethoxybenzene. We believed that this observation suggested the potential formation of either intermediate ***int*-2** or CPC **3a**. Initial experiments performed to isolate the intermediate at room temperature were unsuccessful; however, slow addition of dry hexane at −60 °C and quick filtration provided a white solid, which was subjected to spectroscopic analysis using mono- and bidimensional nuclear magnetic resonance (^1H, ^{13}C, ^{19}F, ^{31}P, ^1H–^{13}C NMR, CD_3NO_2 as solvent), IR, and HRMS. The three deshielded signals at 171.5, 166.7, and 156.0 ppm observed in the ^{13}C NMR spectra clearly referred to the cyclopropenium carbon atoms, thus confirming the formation of **3a** (86% yield) (Table 2). **3a** could be stored at −20 °C under argon for at least 1 month without detectable decomposition and can be handled at room temperature without the need of a glovebox.

Encouraged by the results, we next aimed to develop the scope of our catalytic protocol for the synthesis of CPCs **3** by examining a wide range of alkynes (Table 2). In case the CPC was difficult to isolate, it was transformed to the corresponding cyclopropene **3*** with 1,3,5-trimethoxybenzene. We were delighted to observe that our process worked well for alkynes with aryl rings substituted with synthetically useful functionalities such as halogens (**3b**–**e**, **3l**–**n**), acetoxy (**3f**), phenyl (**3g**), CF_3 (**3h**), ester (**3i**), alkene (**3j**), and methyl (**3k**) in *para*, *meta*, and *ortho* positions as well as naphthalene (**3o**,**p**) and heterocycle cores (**3q***).

Alternative primary alkyl groups such as ethyl (**3r**), *sec*-butyl (**3s**), chloroalkyls (**3t***, **3u**), benzyl (**3v***), and alkyl groups functionalized with protected amines (**3w***) or alcohols (**3x***, **3y**) were well tolerated. Secondary alkyl substituents like

https://doi.org/10.1021/jacs.2c07769
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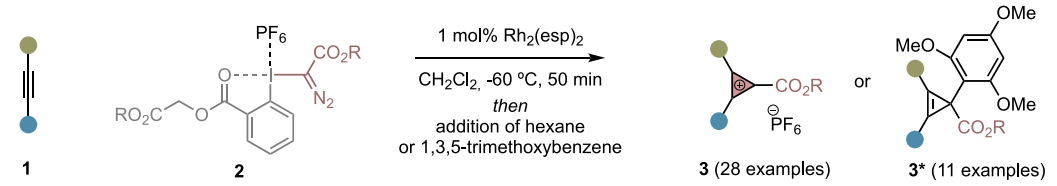
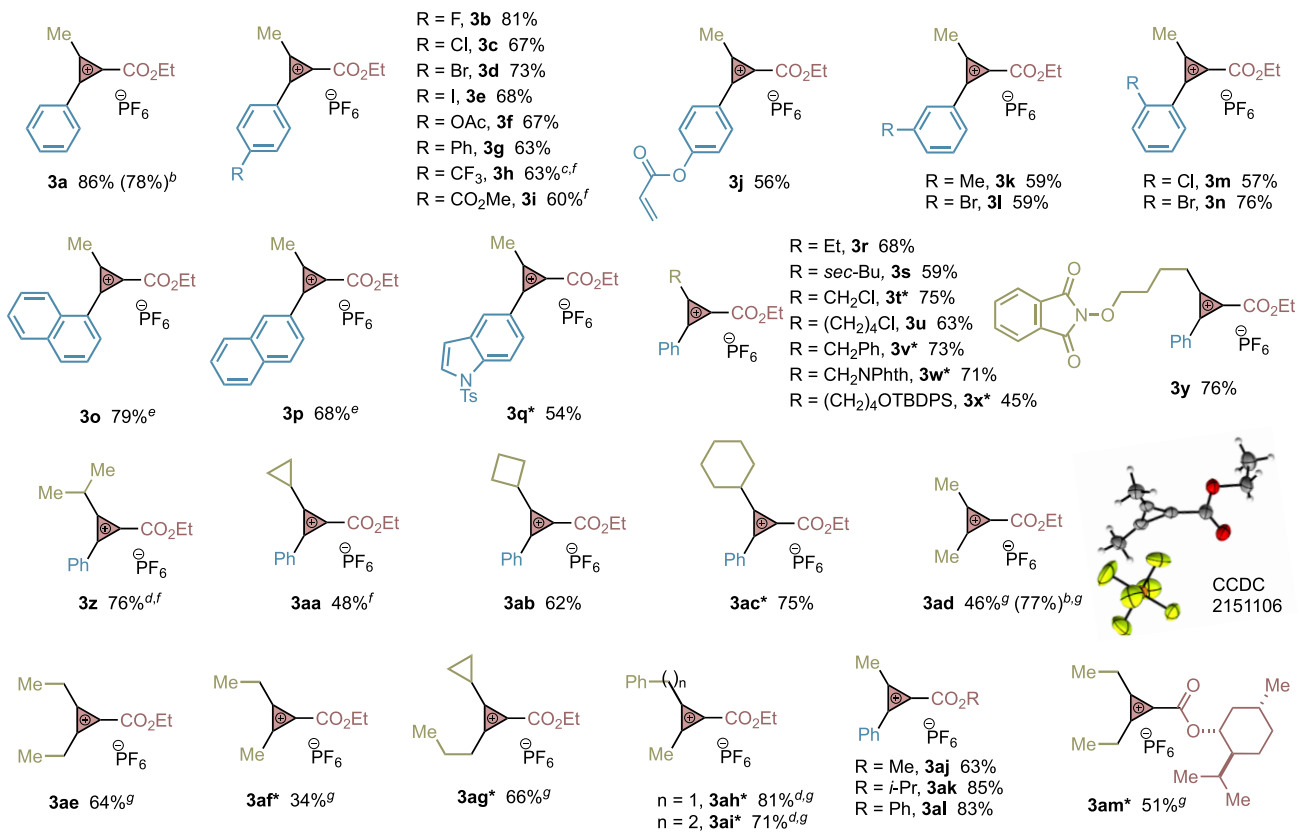
Table 2. Scope of the Catalytic Synthesis of Cyclopropenium Cations 3[a]





[a]Performed with alkyne **1** (0.26 mmol, 1.3 equiv), hypervalent iodine reagents **2** (0.2 mmol, 1.0 equiv), CH_2Cl_2, −60 °C, 50 min, 1,3,5-trimethoxybenzene (0.8 mmol, 4.0 equiv) was added for the synthesis of **3***. [b]Yield of the reaction to give 1.08 g of **3a** and 1.10 g of **3ad**. [c]1.5 mol % catalyst. [d]2 mol % catalyst. [e]Reaction carried out at −63 °C. [f]1.5 equiv of alkyne. [g]2.0 equiv of alkyne.

isopropyl required an increment on the catalyst loading (2 mol %) and alkyne (1.5 equiv) (**3z**); however, cyclic derivatives such as cyclopropyl (**3aa**), cyclobutyl (**3ab**), and cyclohexyl (**3ac***) worked well under the standard conditions. Alkynes substituted with tertiary groups like *tert*-butyl or trimethylsilyl provided traces of the desired CPCs. On the other hand, while alkynes substituted with two alkyl groups were well tolerated (**3ad**−**ai***), diphenylacetylene was unreactive and terminal alkynes such as phenylacetylene provided mixtures of products difficult to identify.[20] We also demonstrated that alternative ester substituents at the hypervalent iodine reagents were possible (**3aj**−**al**, **3am***). Finally, it is worth highlighting that CPC **3a** and **3ad** were prepared in >1 g without compromising the efficiency of the process.

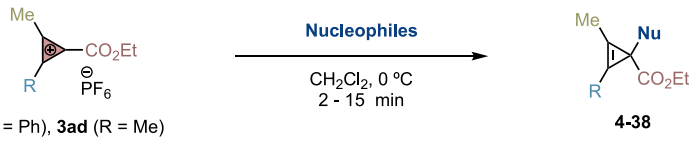
We next turned our attention to evaluate the reactivity of our cyclopropenium cations with a broad range of carbon and heteroatomic nucleophiles aiming to develop a novel synthetic route to cyclopropenes (Table 3). These highly strained, three-membered unsaturated carbocycles are well known for their unique potential as versatile building blocks in organic synthesis that can undergo nucleophilic or electrophilic additions, substitutions, rearrangements, cycloadditions, and ring-opening reactions, delivering pharmaceutical-relevant scaffolds like cyclopropanes or complex structures,[21] but also as biorthogonal reagents for chemical biology applications.[22]

Considering that the nucleophilic attack of 1,3,5-trimethoxybenzene to **3a** proceeds with outstanding regioselectivity, we hoped that alternative nucleophiles could behave analogously. We were delighted to observe that a variety of commercial or readily available aryl, alkyl, vinyl, and alkynyl Grignard reagents provided instantaneous access to cyclopropenes **4**−**19** as single regioisomers and in high efficiency with simple reaction conditions (CH_2Cl_2, 0 °C, 2−15 min). Moreover, alternative nucleophiles such as boronic acid (**20**), organozinc (**21**), organosilicon (**22**, **23**), carbonyl (**24**, **25**) and isocyanide nucleophiles (**26**) performed well, and in many cases, no chromatographic column was needed to obtain the corresponding cyclopropene product.

It is worth highlighting that our methodology with cyclopropenium cations provides a new approach to the synthesis of complex cyclopropenes[23] and solutions to challenges observed in metal-catalyzed carbene transfer with diazo acetates to

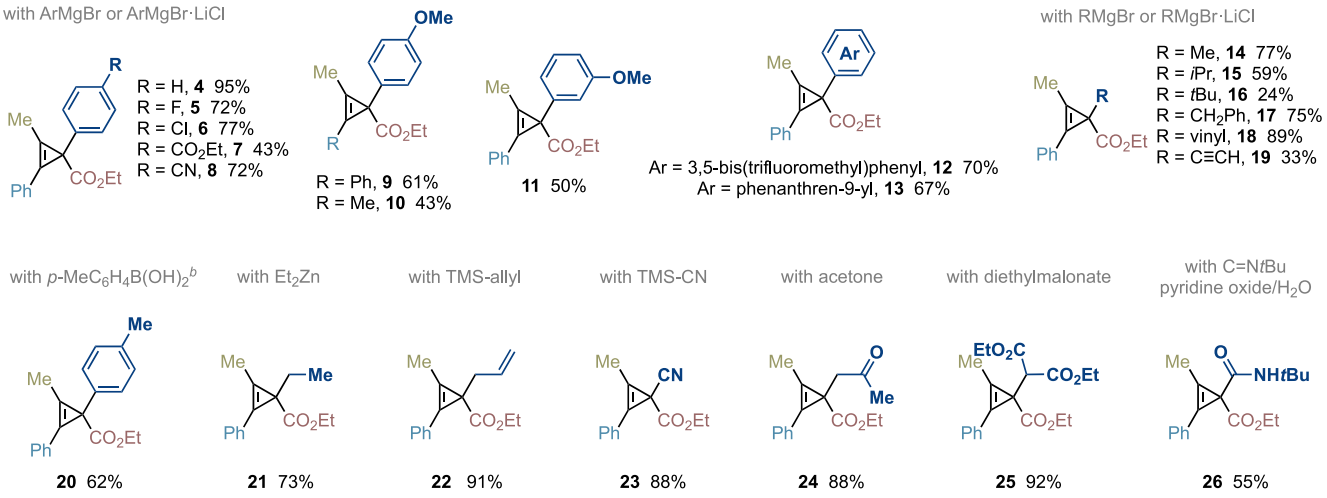
https://doi.org/10.1021/jacs.2c07769
J. Am. Chem. Soc. 2022, 144, 16737−16743

Table 3. Synthesis of Tri- and Tetrasubstituted Cyclopropenes by Nucleophilic Attack[a]

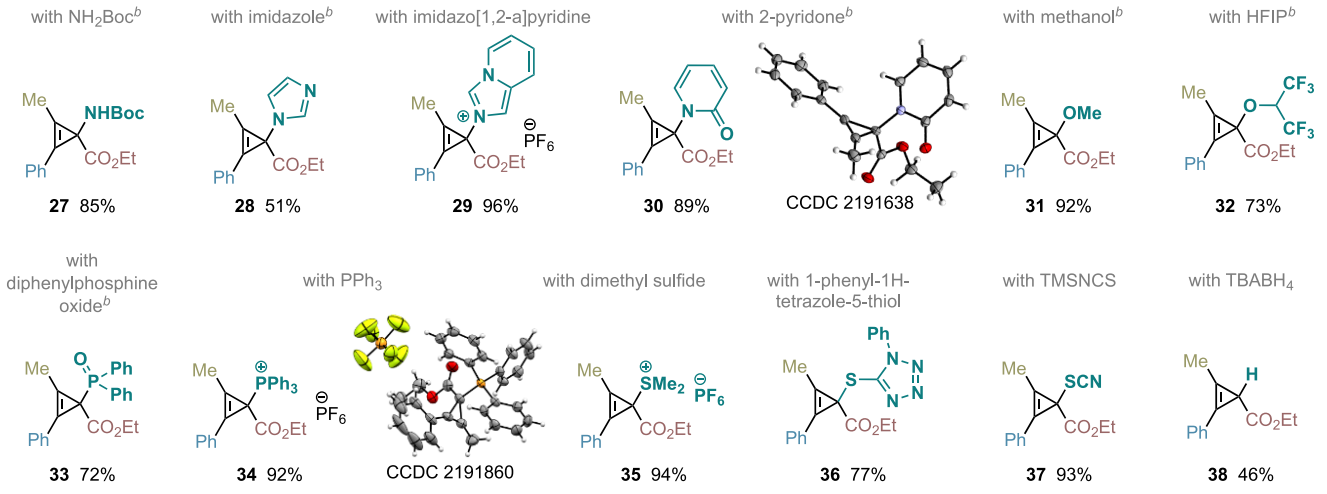


3a (R = Ph), 3ad (R = Me) 4-38

A *carbon nucleophiles*



B *heteroatomic nucleophiles*



[a]Performed with **3** (0.1 mmol), carbon or heteroatomic nucleophiles (0.15−0.2 mmol), CH_2Cl_2, 0 °C, 2−15 min. [b]Cs_2CO_3 (0.1 mmol) was added as base. Yields are reported on the basis of isolated pure product.

internal alkynes. Catalytically generated metal-carbenes substituted with alkyl or allyl groups undergo faster β-hydride migration[24] or intramolecular cyclopropanation,[25] respectively, before the intermolecular cyclopropenation of the internal alkyne takes place.

The remarkable promiscuity observed of our CPCs to react with carbon nucleophiles encouraged us to question whether heteroatomic nucleophiles could work. If successful, such reactions would provide access to a type of tetrasubstituted cyclopropenes not possible to make by any reaction currently available, because of the lack of heteroatom-substituted diazoacetates or alternative carbene sources.[26] We were delighted to observe that a selection of commercial nitrogen, oxygen, phosphorus, and sulfur nucleophiles provided cyclopropenes **27**−**37** with high efficiency. In addition, a reaction carried out with tetrabutylammonium borohydride provided trisubstituted cyclopropene derivative **38** by the regioselective hydride attack to **3a**.[27,28]

Notably, all kinds of heteroatomic nucleophiles underwent regioselective attack to the cyclopropenium carbon atom substituted with the ester group. The reactions provide access to a plethora of novel cyclopropene derivatives with unknown reactivity, which promise applications in reaction discovery and in the construction of complex skeletons.[21]

Finally, in order to provide an explanation of the outstanding and intriguing regiocontrol observed in the nucleophilic addition to CPCs **3**, we calculated the geometry optimization and LUMO map using SPARTAN 20 at the ωb97xd/6-31G(d)

https://doi.org/10.1021/jacs.2c07769
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level. In Figure 3, it can clearly be appreciated that the carbon atom substituted with the ester group has the highest LUMO

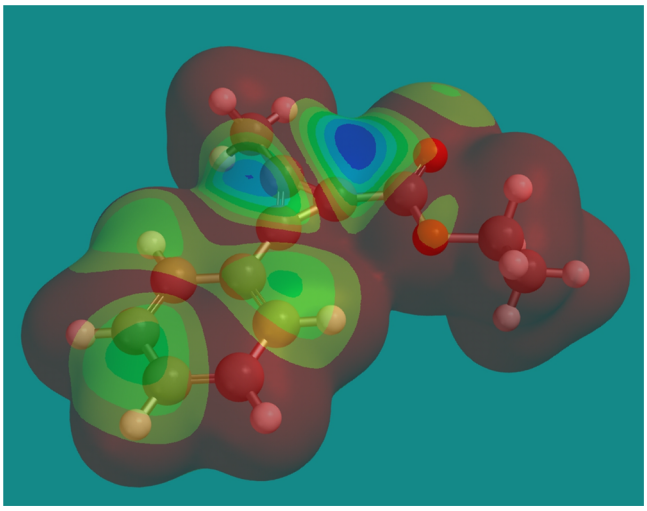

Figure 3. LUMO map of **3a** (method: ωB97X-D, basis set: 6-31G(D)).

coefficient among the cyclopropenium carbon sites, thus suggesting that nucleophilic attack occurs under orbital control.

In summary, we have discovered and developed the first catalytic synthesis of cyclopropenium cations based on the formal transfer of monovalent cationic carbynes ($:^{+}C-R$) to readily available alkynes from a catalytically generated Rh-carbynoid. This type of group transfer process is uncommon for metal-carbyne complexes, which mainly evolve via [2+2] cycloadditions with alkynes.[29,10] Our process accesses previously unknown ester-substituted CPCs, which can be handled outside of a glovebox, from a broad range of internal aryl- and alkyl-substituted alkynes. The synthetic utility of our CPCs has been demonstrated by the regioselective attack of a broad range of carbon and heteroatomic nucleophiles that provided valuable cyclopropenes. Several of those compounds cannot be made by current approaches due to the lack of appropriate diazoacetate reagents as carbene sources or limitations in current methodologies. Current studies are focused on exploiting novel cyclopropenium reactivity for asymmetric synthesis and other applications.[30]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07769.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2151106, 2191637−2191638, and 2191860 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Marcos G. Suero − *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain;* orcid.org/0000-0001-9796-7768; Email: mgsuero@iciq.es

Authors

Hang-Fei Tu − *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain;* orcid.org/0000-0001-7910-2189

Aliénor Jeandin − *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Departament de Química Analítica i Química Orgánica, Universitat Rovira i Virgili, 43007 Tarragona, Spain;* orcid.org/0000-0001-8851-1232

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c07769

Notes

The authors declare the following competing financial interest(s): A patent application has been filed through the Fundaci Institut Catal D'Investigaci Qumica (ICIQ) based on the results presented here.

■ ACKNOWLEDGMENTS

European Research Council (ERC-CoG 2019, 865554), Agencia Estatal de Investigación (AEI) of the Ministerio de Ciencia e Innovación (EUR2019-103814, PID2019-104101GB-I00, Severo Ochoa Excellence Accreditation 2020−2023 -CEX2019-000925-S), ICIQ Foundation, and the CERCA Programme (Generalitat de Catalunya) are gratefully acknowledged for financial support. We thank the European Union for a Marie Skłodowska-Curie Individual Fellowship (101032589).

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https://doi.org/10.1021/jacs.2c07769
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