Tetrahedron Letters 114 (2023) 154272

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of substituted benzoates using a rhodium-mediated Hopf cyclization of 1,3-dien-5-ynes accessed from 2-pyrones

Kristen E. Gardner, Richmond Sarpong *

Department of Chemistry, University of California, Berkeley, CA 94720, United States

ARTICLE INFO

Article history:
Received 23 October 2022
Revised 17 November 2022
Accepted 21 November 2022
Available online 25 November 2022

Keywords:
2-Pyrones
Hopf cyclization
1,3-Dien-5-ynes
Cycloaromatization
Benzoates

ABSTRACT

The synthesis of substituted benzoates from 1,3-dien-5-ynes that are readily accessed from 2-pyrones is described. Highlighted is a 2-pyrone remodeling strategy in which a 3-alkynyl-2-pyrone is selectively opened in a 1,6-fashion using sodium cyanide to provide dienynes that upon treatment with sub-stoichiometric amounts of $[Rh(CO)_2Cl]_2$ at elevated temperature furnish the desired benzoate.

Introduction

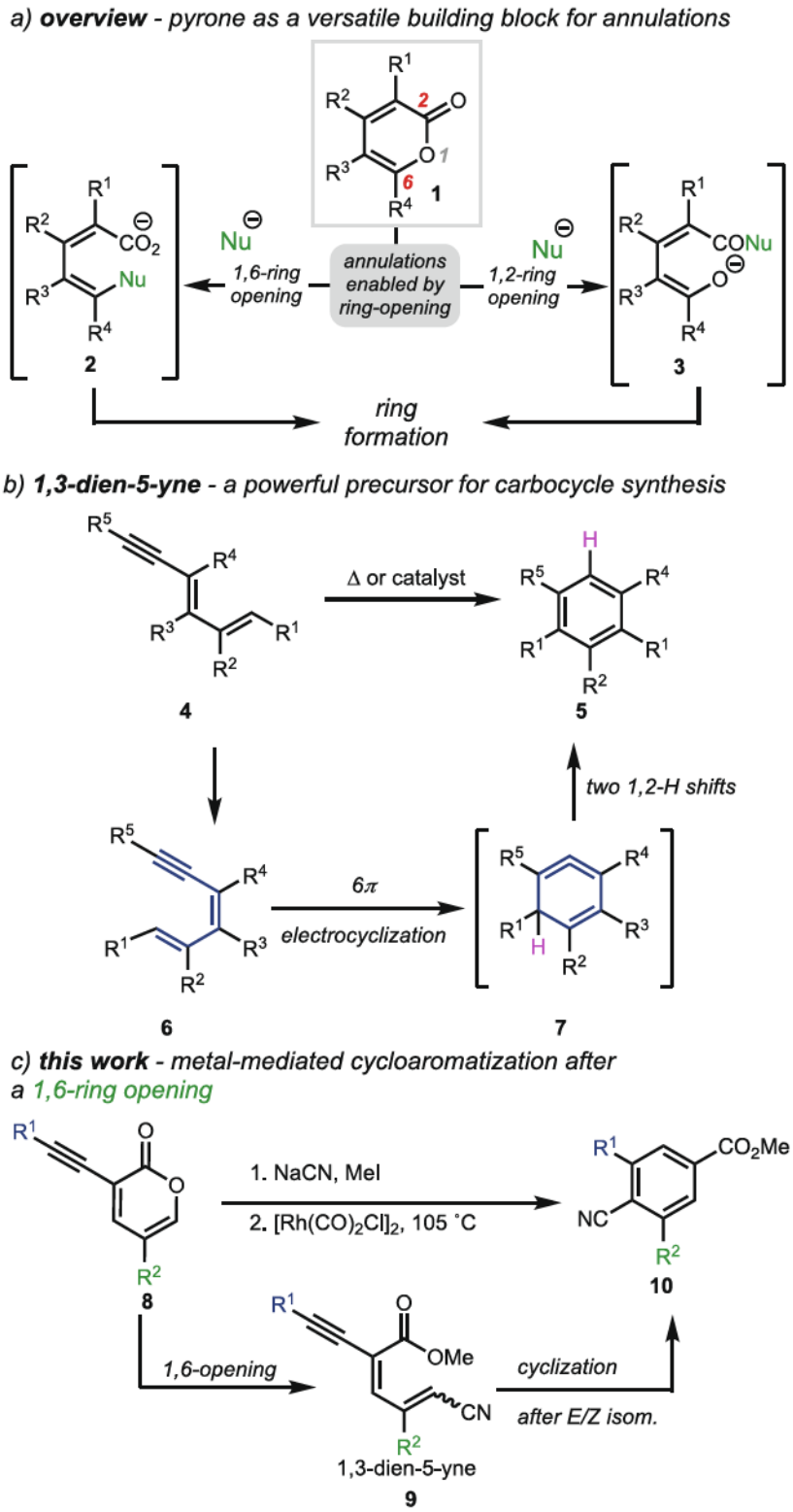
2-Pyrones (**1**, Scheme 1a) have been exploited as substrates in myriad annulative processes for almost a century. [1] Direct pericyclic annulations of 2-pyrones, such as [4 + 2]-cycloadditions [2] and 4π electrocyclizations, [3] have proven to be effective tactics for accessing synthetically versatile bicycles. Previously, we have developed novel annulation reactions enabled by the nucleophilic 1,6- [4,5] or 1,2- [6] openings of 2-pyrones to access diverse ring systems via intermediates **2** or **3**, for example. Our continuing efforts in this area have focused on expanding the scope of this versatile pyrone remodeling strategy to build other scaffolds. Here, we describe the synthesis of substituted benzoates from 2-pyrones by taking advantage of a Hopf cyclization.

The Hopf cyclization was first reported in 1969, when the pyrolysis of 1,3-hexadien-5-yne (**4**, $R_{1\text{-}5}$ = H, Scheme 1b) was found to give benzene (**5**, $R_{1\text{-}5}$ = H). [7] Under thermal conditions, 1,3-dien-5-ynes are known to undergo *E*/*Z*-isomerization to the optimal geometry for cyclization. The mechanistic studies with 1,3-hexadien-5-yne that followed Hopf's initial report revealed that at relatively low temperatures for these types of processes (using flash vacuum pyrolysis; 200–400 ℃), the aromatization proceeded through an electrocyclization and two sequential 1,2 H-shifts to furnish the aromatized product (**5**). [8–10] The thermal cycloaromatization of 1,3-dien-5-ynes has mostly found application in the synthesis of polycyclic aromatic hydrocarbons. [11,12] Likely, it has not been more broadly applied because of the harsh conditions that are required as well as the attendant limitations in scope since many secondary products are formed. [13] Over the last 25 years, several transition metal-catalyzed methods have emerged for effecting the Hopf cyclization at much lower temperatures, often producing excellent yields of the desired cycloaromatization products. [13,14].

We sought to combine 2-pyrone remodeling tactics developed in our laboratory with the Hopf cyclization as a way to access substituted benzoates from alkynyl 2-pyrones. We envisioned that site-selective cross-coupling of alkynes at the C3 position of 2-pyrones [15] would provide access to compounds such as **8** (Scheme 1c). A selective 1,6-ring opening of **8** with NaCN would then unveil a 1,3-dien-5-yne (**9**). Intermediates of this type could then be further elaborated to substituted benzoates (**10**) under transition metal-mediated Hopf cyclization conditions. However, we anticipated several potential challenges with this transformation. First, all known Hopf cyclizations occur with substrates where the dienyne is aligned for the cyclization step (i.e., no need for *E*/*Z* isomerization). [14] Second, there are few practical examples of Hopf cyclizations using a 1,3-dien-5-yne where neither of the alkene groups is a part of an aromatic ring. [14] Finally, there are few examples of 1,3-dien-5-yne annulation reactions that occur with electron-withdrawing groups on the terminal alkene group [16–18]. Merlic demonstrated that with an electron-rich terminal alkene and an electron-poor ruthenium catalyst (RuCl(*p*-cymene) PPh_3) the desired cyclization product could be obtained via a

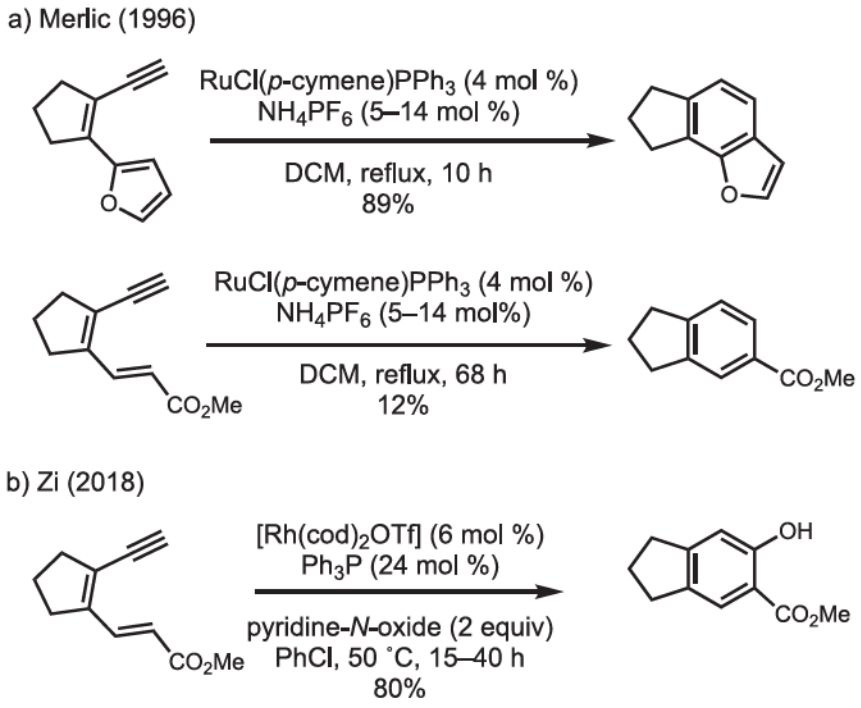
* Corresponding author.
E-mail address: rsarpong@berkeley.edu (R. Sarpong).

https://doi.org/10.1016/j.tetlet.2022.154272
0040-4039/



Scheme 1. Combining the versatility of 2-pyrones with the Hopf cyclization to access substituted benzoates.

vinylidene intermediate in high yield (89%, Scheme 2a). [17] However, for substrates bearing an electron-deficient alkene group, the yield decreased to 12% even after extended reaction times. In 2018, Zi reported a rhodium-catalyzed oxidative cycloaromatization of dienynes with electron-deficient terminal alkenes to form phenols and naphthols in 56–89% isolated yields (Scheme 2b). [18] Presumably, after forming a vinylidene intermediate from the terminal alkyne and $Rh(cod)_2OTf$, pyridine-*N*-oxide oxidizes the vinylidene to a Rh-bound ketene, which undergoes the desired 6π electrocyclization to afford the cycloaromatized product. Notably, both the Merlic and Zi examples occur with substrates bearing terminal alkyne groups whereas we sought to employ substrates that pos-

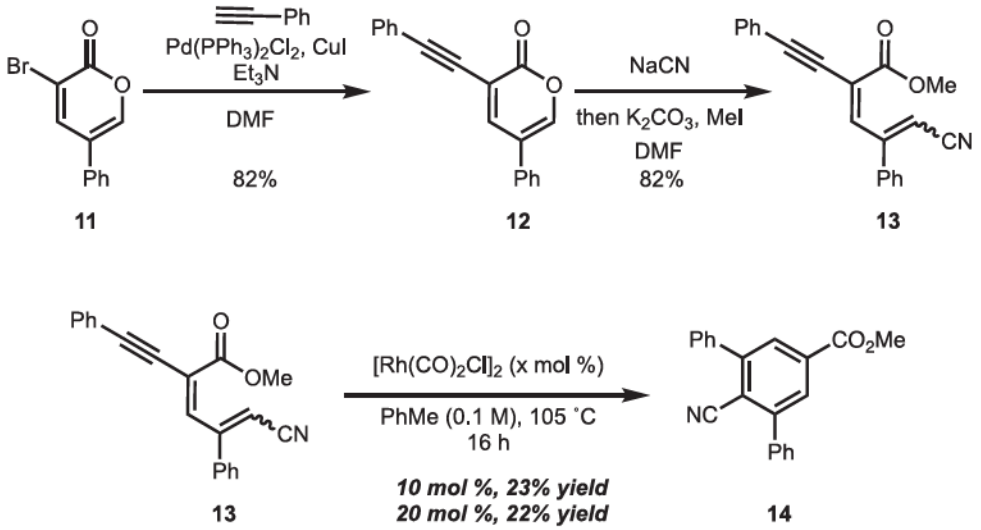


Scheme 2. Existing 1,3-dien-5-yne cycloaromatizations with an electron-withdrawing group on terminal alkene.

sess internal alkyne groups. With these challenges in mind, we set out to achieve the desired carbocyclization of 1,3-dien-5-ynes (i.e., **9**) which could be readily accessed from 2-pyrones.

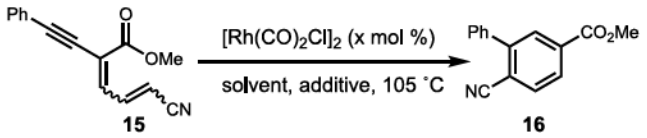
Results and discussion

We commenced our investigations with the synthesis of diphenyl dienyne **13** to explore the desired Hopf cyclization step. On the basis of precedent from Cho and coworkers, [15] a Sonogashira coupling between 3-Br-5-phenyl-2-pyrone (**11**) and phenylacetylene proceeded smoothly to afford alkynyl pyrone **12** in 82% yield (Scheme 3). Next, **12** was subjected to cyanide ion-mediated ring-opening [4,5] to furnish **13**, setting the stage to explore the key metal-mediated Hopf cyclization. Our initial investigations focused on identifying metal complexes that efficiently effected cyclization of dienyne **13**. Several transition metal complexes were surveyed (see the Supporting Information for more information) on the basis of precedent for these transformations. [13,19–21,22] However, most conditions led to non-specific decomposition and/or partial recovery of starting material with some *E*/*Z* isomerization occurring. We observed the desired benzoate (**14**) in 23% yield using 10 mol % of $[Rh(CO)_2Cl]_2$, building on the precedent of Dankwardt, [22] who demonstrated in 2001 that this Rh(I) complex effects a 6-*endo*-dig cyclization of a silyl enol ether aryl alkyne precursor to form a silyl-protected naphthol at elevated temperatures. Interestingly, when phenyl dienyne **15**, which lacks a phenyl group at C5 of the pyrone precursor was subjected to the same conditions, we isolated the desired product (**16**) in 33% yield. Due to the ease of accessing the phenyl dienyne intermediate (i.e., **15**) and the higher observed yield with this substrate, we decided to



Scheme 3. Synthesis of diphenyl dienyne **13** and initial exploration of the key cyclization step.

Table 1
Optimization of the annulation reaction with **15** and $[Rh(CO)_2Cl]_2$ to desired substituted benzoate **16**. [a] Isolated yields. [b] TFP = tri(2-furyl)phosphine. [c] Reaction was conducted at 80 °C.

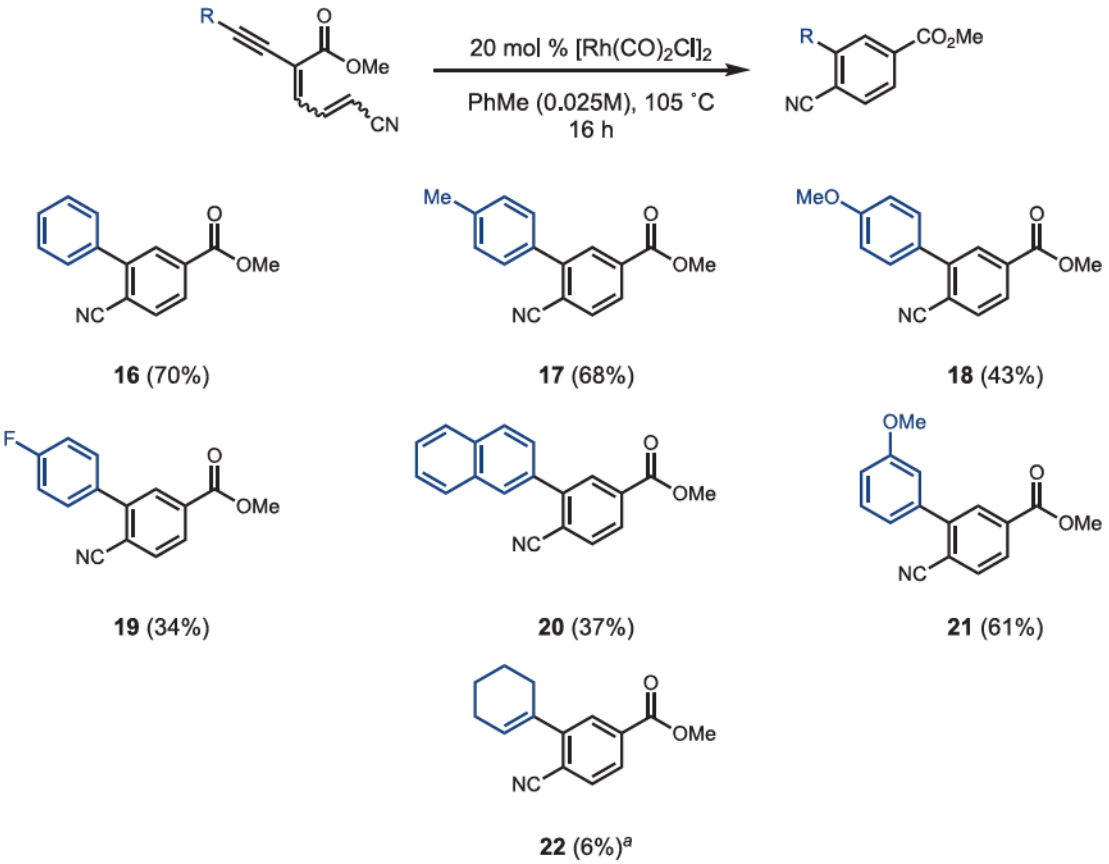


entry	mol % [Rh]	solvent	additive	yield[a]
1	10 mol %	PhMe (0.05 M)	-	33%
2	10 mol %	PhMe (0.05 M)	CO atm.	23%, 49% RSM
3	10 mol %	PhMe (0.05 M)	10 mol % TFP[b]	6%, 30% RSM
4	10 mol %	PhMe (0.025 M)	-	62%
5	**20 mol %**	**PhMe (0.025 M)**	-	**70%**
6	5 mol %	PhMe (0.025 M)	-	SM
7	20 mol %	PhCl (0.025 M)	-	42%
8	20 mol %	*p*-xylene (0.025 M)	-	49%
9	20 mol %	PhH (0.025 M)[c]	-	30%

continue optimizing the reaction conditions with **15** as our substrate.

Optimization of the key annulation reaction with **15** and $[Rh(CO)_2Cl]_2$, as shown in Table 1 below, commenced with an additive screen. We wondered if the low yield and efficiency could be attributed to the instability of the Rh(I) complex under these conditions. Therefore, we conducted the reaction under an atmosphere of carbon monoxide (CO) using a balloon, or with the addition of 10 mol % of tri(2-furyl)phosphine (TFP) (entries 2 and 3), a ligand known to bind to metal complexes similarly to CO, albeit with a weaker π-acceptor ability than CO. [23–25] Our goal with these reactions was to determine whether these ligand additives would stabilize the Rh(I) complex. Conducting the reaction under these conditions led to diminished yields. However, an increase in the recovered starting material was observed, which we presume indicates that the Rh(I) complex was stabilized by the additional equivalents of ligand—at the expense of freeing a coordination site that would be necessary for catalysis. We also hypothesized that partly, the low efficiency and yield must arise from dimerization or polymerization of the dienynes. In an attempt to inhibit undesired intermolecular reactions and favor the desired intramolecular cyclization, the reaction mixture was diluted to 0.025 M (entry 4). Gratifyingly, an increased yield (from 33% to 62%) was observed upon dilution. Diluting the reaction mixture may suppress undesired intermolecular reactivity, which would otherwise lead to non-specific decomposition products and decreased yield. Finally, we found that increasing the Rh complex loading to 20 mol % led to a slight increase in yield to 70% (entry 5). Although we chose to continue our studies at this high loading of the Rh complex, this reaction still proceeds at lower catalyst loadings. However, at 5 mol % loading no discernable conversion was observed (entry 6). An abbreviated solvent screen (entries 7–9) identified toluene to be the optimal solvent for this transformation. A more detailed optimization table is provided in the Supporting Information.

With optimized conditions in hand, we investigated the scope of this operationally simple benzoate synthesis (Scheme 4). Alky-



Scheme 4. Scope of the substituted benzoate synthesis. [a] Reaction conducted at 120 °C.

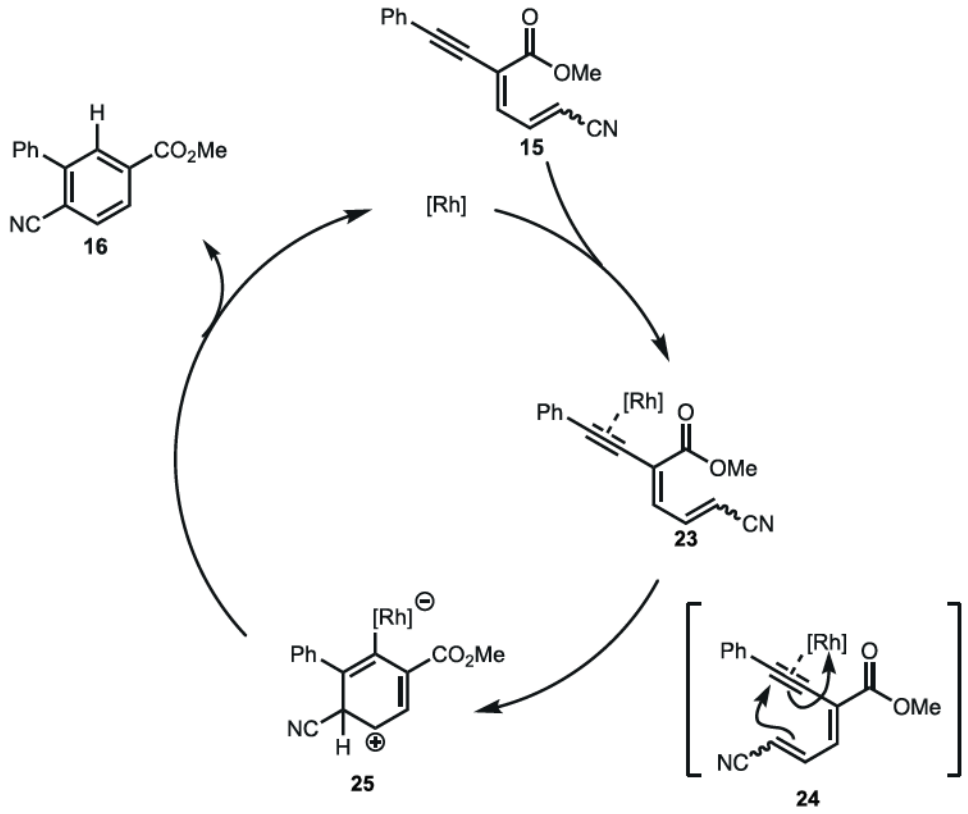


Fig. 1. Proposed Lewis acid mechanism.

nyl-pyrone substrates with varied substitution patterns were readily synthesized using Sonogashira couplings of various acetylenes with 3-trifloxy-2-pyrone. Although 4 tolyl (**17**) and 3 methoxyphenyl (**21**) bearing dienynes were tolerated well in this reaction, substrates bearing an electron-donating (**18**) or electron-withdrawing (**19**) group on the alkyne led to diminished yields. Additionally, for non-aromatic alkynyl substituents, such as in a substrate bearing a cyclohexenyl alkyne substituent, very little reactivity was observed (6% of desired benzoate **22** was obtained at 120 ℃). In addition, when we subjected diphenyl dienyne **13** to the optimized conditions, we observed no reactivity under those conditions. The scope of this methodology is limited to substrates where C5 of the alkynyl 2-pyrone precursor bears a H and the alkyne bears an aryl group.

A proposed mechanism for the Rh(I)-mediated cycloaromatization where the Rh(I) serves as a Lewis acid is shown in Fig. 1. The Lewis acidic Rh(I) complex is hypothesized to bind to the alkyne and enhance its electrophilicity. This coordination facilitates a 6-*endo*-dig cyclization to generate intermediate **19**; analogous to the proposal by Dankwardt. [22] Notably, we were able to identify conditions for this transformation with substrates bearing an electron-withdrawing cyano group at the terminus of the alkene group. At this stage, it is unclear when *E/Z* isomerization occurs to afford the desired alkene geometry for cyclization. Zwitterionic intermediate **25** could then undergo proton transfer to provide the benzoate product (**16**) and regenerate the active Rh(I) complex, which will re-enter the catalytic cycle. [26] We have not conducted extensive studies to support this proposed mechanism.

Conclusion

In summary, we have developed a novel pyrone remodeling strategy, which capitalizes on the 1,6-ring opening of 2-pyrones followed by a Rh-mediated cyclization to construct diverse benzoates. This key step was optimized for substrates bearing an electron-withdrawing group on the terminal alkene group. Notably, neither alkene group of the Hopf cyclization substrate is embedded in an aromatic ring system (unlike in previously reported systems), and the 1,3-dien-5-yne substrates studied here presumably undergo *E/Z* isomerization prior to the key cycloaromatization step, heightening the challenge in realizing the transformation reported here. Future studies will seek to apply this transformation in the total synthesis of natural products.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

R. S. thanks the National Science Foundation (CHE-1700982) for funding. K.E.G. thanks the NSF for a graduate research fellowship (DGE 1752814). We thank Dr. Hasan Celik and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in the CoC-NMR are supported in part by NIH S10OD024998.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.154272.

References

[1] D. Dobler, M. Leitner, N. Moor, O. Reiser, Eur. J. Org. Chem. 2021 (2021) 6180–6205.
[2] Q. Cai, Chin. J. Chem. 37 (2019) 946–949.
[3] S.C. Coote, Eur. J. Org. Chem. 2020 (2020) 1405–1423.
[4] V. Palani, C.L. Hugelshofer, I. Kevlishvili, P. Liu, R. Sarpong, J. Am. Chem. Soc. 141 (2019) 2652–2660.
[5] V. Palani, C.L. Hugelshofer, R. Sarpong, J. Am. Chem. Soc. 141 (2019) 14421–14432.
[6] V. Palani, M.A. Perea, K.E. Gardner, R. Sarpong, Chem. Sci. 12 (2021) 1528–1534.
[7] H. Hopf, H. Musso, Angew. Chem. Int. Ed. Engl. 8 (1969) 680.
[8] H. Hopf, H. Berger, G. Zimmermann, U. Nüchter, P.G. Jones, I. Dix, Angew. Chem. Int. Ed. Engl. 36 (1997) 1187–1190.
[9] G. Zimmermann, Eur. J. Org. Chem. 2001 (2001) 457–471.
[10] I. Fernández, F.M. Bickelhaupt, F.P. Cossío, Chem. – Eur. J. 20 (2014) 10791–10801.
[11] L.T. Scott, M.M. Hashemi, D.T. Meyer, H.B. Warren, J. Am. Chem. Soc. 113 (1991) 7082–7084.
[12] P.W. Rabideau, A.H. Abdourazak, H.E. Folsom, Z. Marcinow, A. Sygula, R. Sygula, J. Am. Chem. Soc. 116 (1994) 7891–7892.
[13] E. Aguilar, R. Sanz, M.A. Fernández-Rodríguez, P. García-García, Chem. Rev. 116 (2016) 8256–8311.
[14] D.M. Hitt, J.M. O'Connor, Chem. Rev. 111 (2011) 7904–7922.
[15] J.-H. Lee, J.-S. Park, C.-G. Cho, Org. Lett. 4 (2002) 1171–1173.
[16] K. Maeyama, N. Iwasawa, J. Org. Chem. 64 (1999) 1344–1346.
[17] C.A. Merlic, M.E. Pauly, J. Am. Chem. Soc. 118 (1996) 11319–11320.
[18] M.-G. Rong, T.-Z. Qin, X.-R. Liu, H.-F. Wang, W. Zi, Org. Lett. 20 (2018) 6289–6293.
[19] P. García-García, A. Martínez, A.M. Sanjuán, M.A. Fernández-Rodríguez, R. Sanz, Org. Lett. 13 (2011) 4970–4973.
[20] P. García-García, M.A. Fernández-Rodríguez, E. Aguilar, Angew. Chem. Int. Ed. 48 (2009) 5534–5537.
[21] T. Shibata, Y. Ueno, K. Kanda, Synlett 2006 (2006) 411–414.
[22] J.W. Dankwardt, TetrahedronLett. 42 (2001) 5809–5812.
[23] M. Ackermann, A. Pascariu, T. Höcher, H.-U. Siehl, S. Berger, J. Am. Chem. Soc. 128 (2006) 8434–8440.
[24] W.-Y. Wong, F.-L. Ting, W.-L. Lam, J. Inorg. Chem. 2 (2008) 50–55.
[25] N.G. Andersen, B.A. Keay, Chem. Rev. 101 (2001) 997–1030.
[26] K. Komeyama, R. Igawa, K. Takaki, ChemCommun. 46 (2010) 1748.