CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Ruthenium(II)-Catalyzed Double Annulation of Quinones: Step-Economical Access to Valuable Bioactive Compounds

Authors: Eufrânio N. da Silva Júnior, Renato L. de Carvalho, Renata G. Almeida, Luisa G. Rosa, Felipe Fantuzzi, Torben Rogge, Pedro M. S. Costa, Claudia Pessoa, Claus Jacob, and Lutz Ackermann

To be cited as: *Chem. Eur. J.* 10.1002/chem.202001434

Link to VoR: http://dx.doi.org/10.1002/chem.202001434

Supported by
ACES

WILEY-VCH

10.1002/chem.202001434

WILEY-VCH

COMMUNICATION

Ruthenium(II)-Catalyzed Double Annulation of Quinones: Step-Economical Access to Valuable Bioactive Compounds

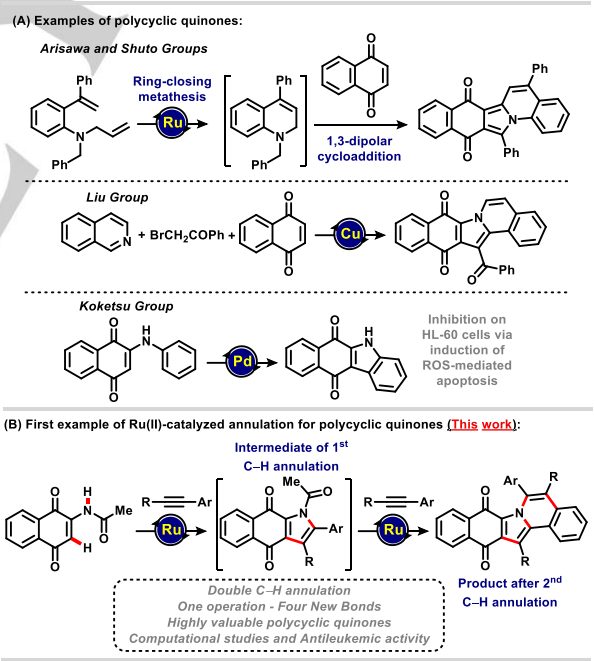
Eufrânio N. da Silva Júnior,*[a,b] Renato L. de Carvalho,[a,b] Renata G. Almeida,[b] Luisa G. Rosa,[b] Felipe Fantuzzi,[c] Torben Rogge,[a] Pedro M. S. Costa,[d] Claudia Pessoa,[d] Claus Jacob,[e] and Lutz Ackermann*[a,f]

Abstract: Double ruthenium(II)-catalyzed alkyne annulations of quinones were accomplished. Thus, we report a strategy that provides step-economical access to valuable quinones with a wide range of applications. C–H/N–H activations for alkyne annulations of naphthoquinones provided challenging polycyclic quinoidal compounds by forming four new bonds in one step. The singular power of the thus-obtained compounds was reflected by their antileukemic activity.

Polycyclic quinones represent an important class of substances with outstanding biological activities[1] and diverse applications for example as dyes.[2] Consequently, there is a continued strong demand for effective methods to access this class of compounds in a direct and efficient fashion.[3] Metal-catalyzed reactions are an effective and reliable approach for the construction of such compounds (Scheme 1A).[4] Ruthenium-alkylidene Grubbs catalysts have been used to perform ring-closing metathesis to afford polycyclic compounds.[5] Nitrogenated quinones were also prepared by three-component reactions via C–H[6] difunctionalization of naphthoquinones.[7] The antitumor potential of polycyclic quinonoid compounds prepared via palladium catalysis was described by the Koketsu group.[8] The compounds exhibited important antileukemic activity and a mechanism of action associated with the generation of reactive oxygen species (ROS).

As part of a broad program focused on the development of transition metal-catalyzed reactions involving quinones, we and others have developed synthetic methods for preparing functionalized quinones based on C–H iodination,[9] oxygenation,[10] alkenylation,[11] sequential C–H iodination/thiolation[12] and selenation.[13] Most of these methods are limited to functionalizations at the position C-5, while the construction polycyclic quinoidal motifs remains a challenge. Thus, on the basis of our experience in developing annulative reactions[14] for the construction of heterocyclic rings, we have identified C–H activation/annulation as a complementary method for the construction of the desired cyclic systems.

In this work, we report on the development and scope of a new protocol for preparing polycyclic quinones, which provides for the first time a versatile and efficient alternative for the synthesis of molecules that represent a great synthetic challenge via ruthenium(II)-catalyzed double annulation reaction (Scheme 1B).



Scheme 1. C–H activation/annulation for polycyclic quinone assembly.

Our initial attempts to achieve the double annulation process focused on the reaction between naphthoquinone **1a** and diphenylacetylene (**2a**) (Table 1). $[RuCl_2(p\text{-cymene})]_2$ in combination with $Cu(OAc)_2$ as the catalyst known for its efficiency to perform annulation reactions,[15] provided the desired product **3a** in only 44% yield with DCE as the solvent (entry 1). This initial result was highly encouraging when considering the challenging formation of four new bonds in only a single step. Despite the successful preparation of product **3a**, subsequent efforts have

[a] R. L. de Carvalho, Prof. Dr. E. N. da Silva Júnior, Dr. T. Rogge, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen (Germany). E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
[b] R. L. de Carvalho, R. G. Almeida, L. G. Rosa, Prof. Dr. E. N. da Silva Júnior
Institute of Exact Sciences, Department of Chemistry, Federal University of Minas Gerais, UFMG, 31270-901, Belo Horizonte, MG (Brazil). E-mail: eufranio@ufmg.br
[c] Dr. F. Fantuzzi
Institute for Inorganic Chemistry, Julius-Maximilians-Universität Würzburg, Am Hubland, 97074, Würzburg (Germany).
[d] P. M. S. Costa, Prof. Dr. C. Pessoa
Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, CE, 60430-270 (Brazil).
[e] Prof. Dr. C. Jacob
Division of Bioorganic Chemistry, School of Pharmacy, University of Saarland, 66123 Saarbrücken (Germany).
[f] Prof. Dr. L. Ackermann
German Center for Cardiovascular Research (DZHK), Potsdamer Strasse 58,10785 Berlin (Germany)

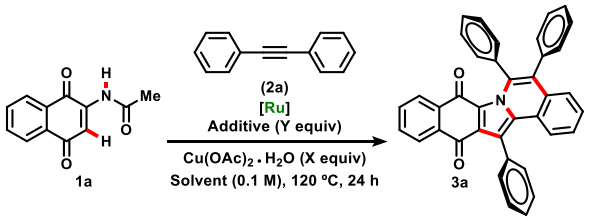
Supporting information for this article is given via a link at the end of the document.

10.1002/chem.202001434

COMMUNICATION

been undertaken aiming at alternative ruthenium-based catalysts, in order to improve the efficiency of the reaction. Accordingly, $Ru(O_2CMes)_2$(*p*-cymene), $Ru(OPiv)_2(PPh_3)_2$, $RuCl_3$ and $RuBr_3$ were also probed as the ruthenium source, but the efficacy was not improved (entries 2-5). Increasing the catalyst loading of $[RuCl_2$(*p*-cymene)$]_2$ did not lead to an improvement (entry 6). Next, we evaluates the effectiveness of different solvents for the assembly of product **3a** , albeit with limited success (entries 7-10). However, further experimentation revealed DCE as the optimal solvent for this transformation, and, consequently, we decided to probe the presence of additives to generate a cationic ruthenium(II) catalyst. Here, KPF_6, KOAc, NaOAc, and NaOPiv were evaluated as additives (entries 11-14). Further refinement led to the reaction conditions outlined in entries 15 and 18, delivering product **3a** 80% yield (See SI for experimental details).

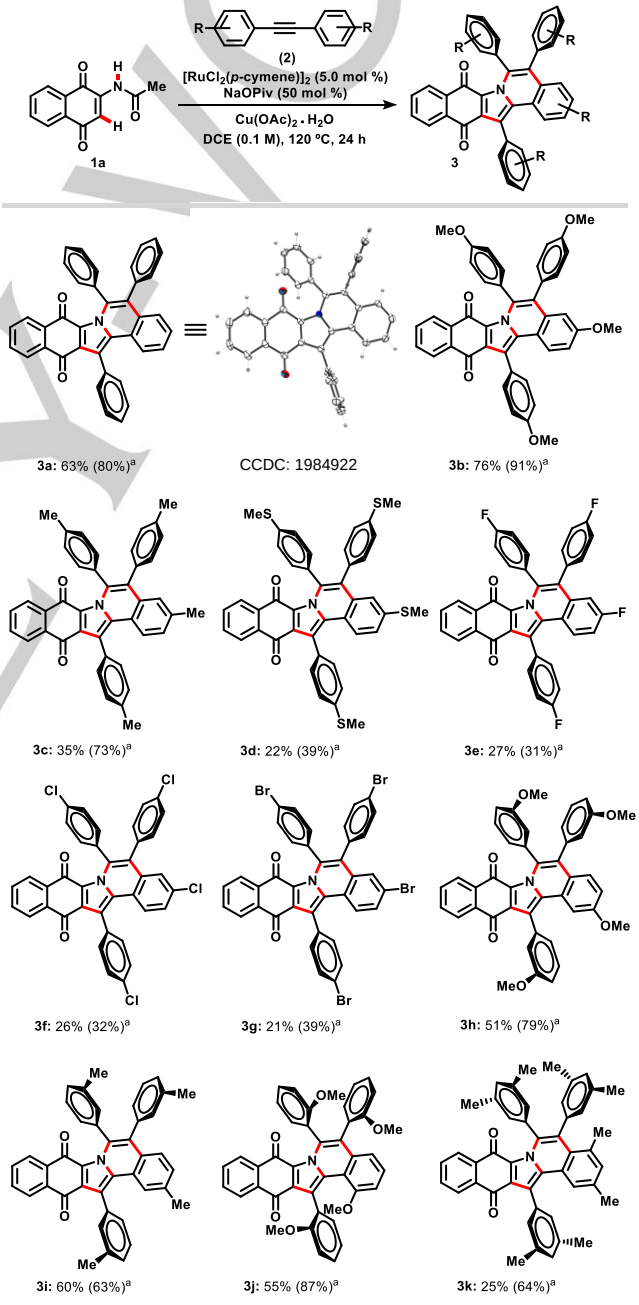
Table 1. Optimization studies for ruthenium(II)-catalyzed C–H activation/annulation.[a]



Entry	[Ru] (mol %)	Solvent	Additive (Y equiv)	$Cu(OAc)_2$ (X equiv)	Yield 3a (%)
1	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	-	2.0	44
2	$Ru(O_2CMes)_2$(*p*-cymene) (5)	DCE	-	2.0	16
3	$Ru(OPiv)_2(PPh_3)_2$ (5)	DCE	-	2.0	NR
4	$RuCl_3$ (10)	DCE	-	2.0	NR
5	$RuBr_3$ (10)	DCE	-	2.0	NR
6	$[RuCl_2$(*p*-cymene)$]_2$ (10)	DCE	-	2.0	11
7	$[RuCl_2$(*p*-cymene)$]_2$ (5)	*t*-AmOH	-	2.0	16
8	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DMF	-	2.0	16
9	$[RuCl_2$(*p*-cymene)$]_2$ (5)	$CHCl_3$	-	2.0	12
10	$[RuCl_2$(*p*-cymene)$]_2$ (5)	*o*-xylene	-	2.0	16
11	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	KPF_6 (0.2)	2.0	27
12	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	KOAc (0.2)	2.0	50
13	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	NaOAc (0.2)	2.0	48
14	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	NaOPiv (0.2)	2.0	55
15	**$[RuCl_2$(*p*-cymene)$]_2$ (5)**	**DCE**	**NaOPiv (0.5)**	**2.0**	**63**
16	$[RuCl_2$(*p*-cymene)$]_2$ (5)	DCE	NaOPiv (1.0)	2.0	47
17	$[RuCl_2$(*p*-cymene)$]_2$ (2 × 2.5)[a]	DCE	NaOPiv (0.5)	2.0	21
18	**$[RuCl_2$(*p*-cymene)$]_2$ (2 × 5)[a]**	**DCE**	**NaOPiv (0.5)**	**2.0**	**80**
19	$[RuCl_2$(*p*-cymene)$]_2$ (2 × 5)[a]	DCE	NaOPiv (0.5)	4.0	29
20	-	DCE	-	2.0	NR

Reaction conditions: **1a** (0.20 mmol), **2a** (4.0 equiv), catalyst (5.0-10.0 mol %), additive (0.20-1.00 equiv), $Cu(OAc)_2{\cdot}H_2O$ (2.0-4.0 equiv), solvent (2.0 mL), 120 °C, 24 h. NR = no reaction. In all cases, the starting material was recovered. Yields refer to the isolated product. [a]An additional amount of 2.5 or 5.0 mol % of catalyst was added after 12 h.

To investigate the viable scope of the ruthenium-catalyzed double annulation process, our method was employed for the synthesis of various naphthoquinoidal compounds. Initially, we explored the influence of the alkyne substitution pattern (Scheme 2). Thus, 2-acetylamino-1,4-naphthoquinone (**1a**) was used as quinone component and both electron-donating (EDG) as well as electron-withdrawing (EWG) substituents were probed in the C–H annulation reaction. The reaction with diphenylacetylenes containing EDGs proceeded smoothly, affording the targets **3b**, **3h** and **3j** in moderate yields. The exception here was product **3c**, which was obtained in somewhat lower yield. A decreased yield of annulated quinolone **3k** was observed with two methyl groups being present in the respective alkyne **2k**, probably due to the steric effect caused by the substituent groups. Then, we evaluated the presence of EWGs and, as expected, the efficiency of the process decreased as the alkyne becomes more electron-deficient. The yields of all the compounds described here could be increased when an additional 5 mol % of the catalyst was added after 12h.



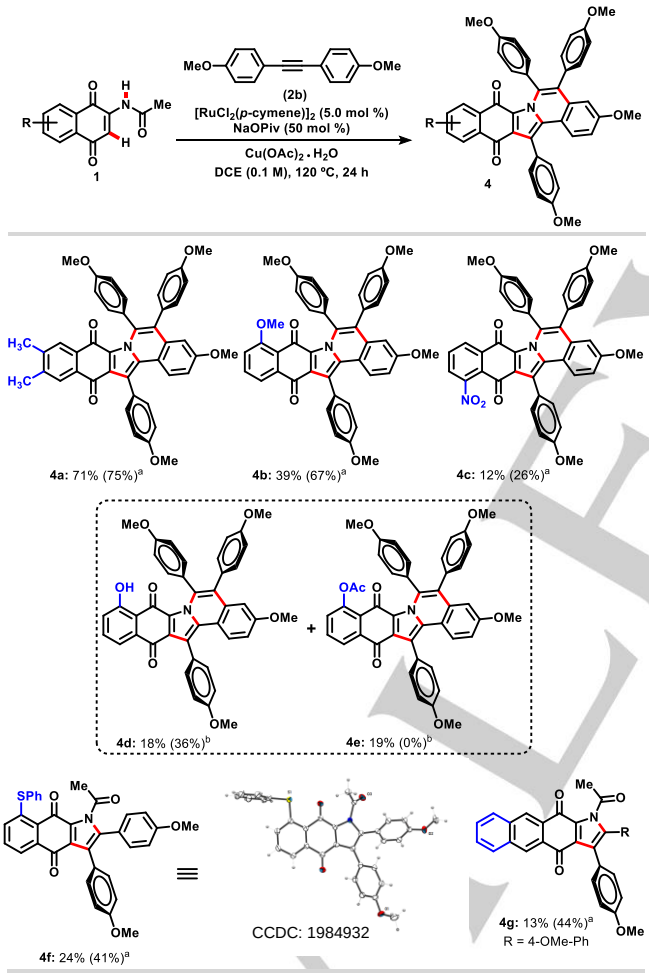
[a]An additional 5.0 mol % of catalyst was added after 12 h.

Scheme 2. Double annulation reaction between quinone **1a** and alkynes **2**.

10.1002/chem.202001434

COMMUNICATION

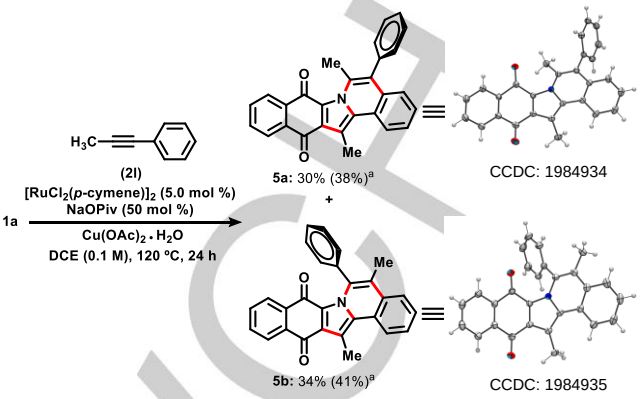
The effectiveness of the annulation process herein developed was also proven with the use of A-ring substituted quinones **1b**-**g** (Scheme 3). Naphthoquinone **1b** possessing C-7 and C-8 substitution underwent an efficient annulation reaction with 71% yield. Quinone **1c** with a methoxy group at C-5 delivered the product in 39% yield. As expected, a more electron-deficient benzenoid ring decreased the reactivity of the quinoidal system and, consequently, nitro-substituted quinone **4c** was produced in only 12% yield. When the corresponding quinone **1e** bearing a hydroxyl group was used, the expected products **4d** and **4e** were obtained in 18% and 19% yield, respectively. The reaction in the absence NaOPiv allowed the preparation of product **4d** as a single product. Surprisingly, when sulphur-containing quinone **1f** and 2-acetamide-1,4-antraquinone (**1g**) were used, only the products **4f** and **4g** via the first C–H/N–H annulation process were isolated. The products were unambiguously characterized by X-ray crystallographic analysis.



[a]An additional 5.0 mol % of catalyst was added after 12 h. [b]Without NaOPiv.

Scheme 3. Double annulation reaction between quinones **1** and alkyne **2b**.

Finally, the use of unsymmetrically-substituted alkynes was also explored. Compound **1a** was reacted with 1-phenyl-1-propyne (**2l**) affording compounds **5a** and **5b** in a 1:1 ratio. The product structures were also unambiguously confirmed by X-ray analysis and ORTEP-3 projections for both compounds are presented in the Scheme 4.



Scheme 4. Double annulation reaction between quinone **1a** and asymmetric alkyne **2l**. [a]An additional 5.0 mol % of catalyst was added after 12 h.

Based on previous mechanistic studies,[14,16] we propose a plausible catalytic cycle to commence with sequential C–H/N–H activation steps to form key intermediate **6** (Scheme 5). Coordination of **2a** followed by migratory insertion leads to the first C–C coupling and the formation of **B**. The next step is the reductive elimination of the intermediate **3a'** after ruthenium-mediated C–N coupling and regeneration of the active catalytic ruthenium(II) species by reoxidation. Intermediate **3a'**, which bears a terminal pyrrole ring, undergoes a subsequent transformation, where a new sequence of C–H/N–H activation steps leads to intermediate **7**. After coordination of **2a** and migratory insertion, a seven-membered metallacycle is formed (intermediate **E**). Product **3a** is then generated after ruthenium-mediated C–N coupling followed by reductive elimination.

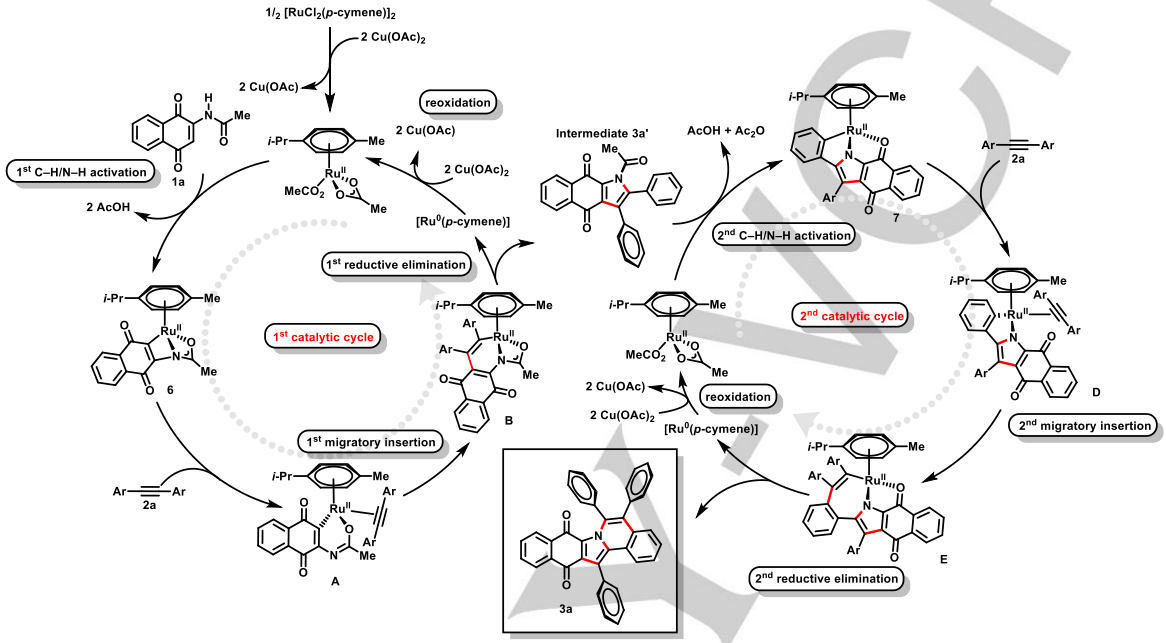
Given the remarkable formation of four new bonds by our strategy, we became attracted to better understand the C–C and C–N coupling steps through density functional theory (DFT) calculations (Figure 1). Geometry optimizations and frequency calculations were performed at the ωB97XD/def2-DZVPP[17] level of theory and single point energies at the SMD-ωB97XD/def2-TZVPP[17,18] level of theory. The energy barrier for the first migratory insertion starting from the alkyl-coordinated intermediate **A** is merely 10.7 kcal mol^{-1}, while intermediate **B** is stabilized by 31.6 kcal mol^{-1} in comparison to **A**. However, the initial C–N coupling is achieved through an energy barrier of 25.9 kcal mol^{-1}. In the second catalytic cycle, the energy barrier of the migratory insertion step is 14.5 kcal mol^{-1} and the following intermediate **E** is favorable by 12.6 kcal mol^{-1} in comparison to **D**. However, the second C–N coupling has an energy barrier of 43.3 kcal mol^{-1}, with **E** and **F** being nearly equiergic. This value indicates the reductive elimination to be rate-determining, and is in line with the reaction proceeding at 120 °C, while in select cases only the first annulation was thus observed (*vide supra*). Comparable results were obtained using Truhlar's M06 functional[19] with D3 correction.[20]

In order to investigate the electronic structure of the polycyclic quinones synthesized, we furthermore performed additional computational studies for the species **1a**, **3a'** and **3a** at the B3LYP[21]-D3(BJ)[22]/def2-TZVPP+SMD(DCE)[17] level of theory

10.1002/chem.202001434
WILEY-VCH

COMMUNICATION

(Figure 2). Our calculations show that, while the HOMO of naphthoquinone **1a** is mainly localized on the C=C bonds of the quinoidal ring, for product **3a'** it is delocalized through the π-space of the pyrrole ring and its aryl substituents. After the second annulation and formation of the final product **3a**, the HOMO delocalizes only through the pyrrole ring and the newly formed π-extended system. In contrast, the LUMO is localized on the quinoidal ring for all compounds irrespective of the level of π-extension. The HOMO-LUMO gap decreases systematically as the π-system is extended in a similar fashion as in *n*-acenes.[23] Thus, we expect that adapting our synthetic strategy for preparing high-order polycyclic quinones could eventually lead to the development of novel organic semiconducting materials.



Scheme 5. Proposed catalytic cycle.

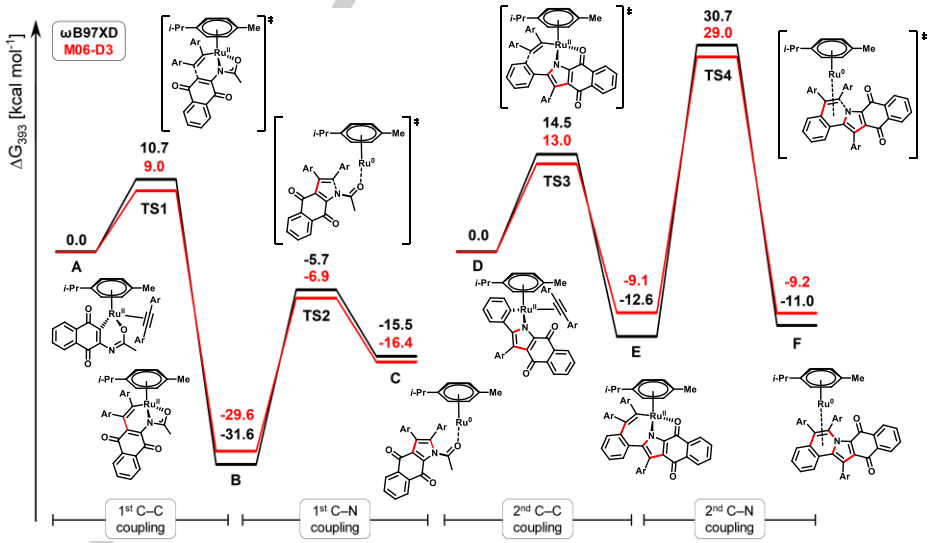


Figure 1. Relative Gibbs free energy profile for the C–C and C–N coupling steps of the reaction of **1a** with **2a** at the ωB97XD/def2-TZVPP+SMD(DCE) (—) and M06-D3/def2-TZVPP+SMD(DCE) (—) levels of theory.

Finally, we evaluated the novel quinoidal compounds against cancer cell lines (Table S20 in the SI). Compounds **3d** and **4g** exhibited antitumor activity against leukaemia cancer cells (HL-60) with IC_{50} values of 2.92 and 3.17 μM, respectively. We evaluated the compounds against five other tumour cell lines (NCI-H460, HCT-116, SNB-19, MCF-7 and PC3) and against one normal cell line (L-929) and the compounds were not active in these cell lines. These results are indicative of the substances featuring considerable potential selectivity for leukaemia cells. More detailed studies are in progress in our laboratories to understand the aspects related to the cytotoxicity presented by these compounds against leukaemia cancer cells.

10.1002/chem.202001434

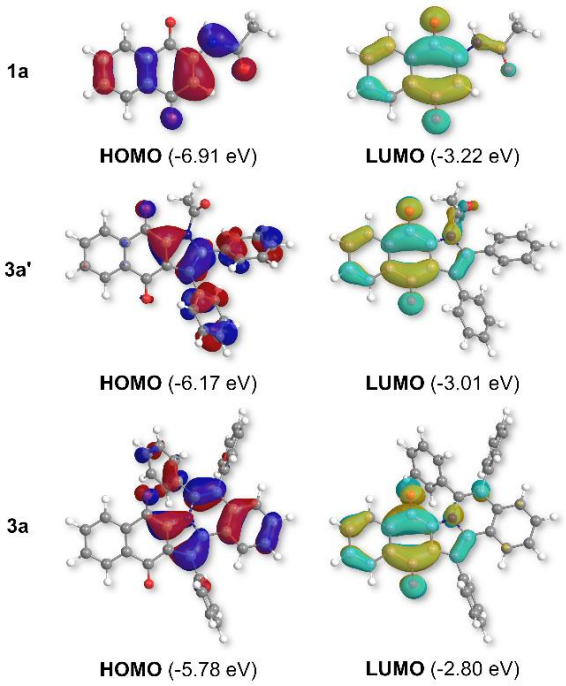


Figure 2. Energies and shapes of frontier orbitals (HOMO and LUMO) of **1a**, **3a'** and **3a** calculated at the B3LYP-D3(BJ)/def2-TZVPP+SMD(DCE) level of theory.

In summary, we have reported on the first ruthenium(II)-catalyzed C–H/N–H double annulation of quinones with various alkynes. We have described an effective and robust method for the formation of four bonds in an expedient and versatile fashion, affording quinoidal compounds with value in medicinal chemistry, with potential application in the treatment of cancer. Thus, the annulation reaction is viable with ample scope and formation of challenging compounds in just one step. Additionally, we performed computational studies in order to provide more information about the catalytic cycle of this reaction and the electronic structure of the intermediates and products. Finally, we also conducted antitumor studies against cancer cells, highlighting the biological activity of the compounds obtained herein.

Acknowledgements

This research was funded by grants from CNPq (404466/2016-8 and PQ 305741/2017-9), FAPEMIG (PPM-00638-16 and PPM-00635-18), CAPES and INCT-Catálise. ENSJ thanks Capes-Humboldt research fellowship for experienced researchers (Proc. No. 88881.145517/2017-01) and Return Fellowship of the Alexander-von-Humboldt foundation. LA acknowledges funding from the DFG (Gottfried-Wilhelm-Leibniz prize). ENSJ and CJ thank CAPES and DAAD for research cooperation project under the PROBRAL programme (Proc. No. 99999.008126/2015-01). FF acknowledges Capes-Humboldt research fellowship for postdoctoral researchers and JMU Würzburg for HPC resources.

We thank Dr. Christopher Golz (Göttingen University) for assistance with the Xray diffraction analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes • annulation • C–H activation • quinones • ruthenium • cancer

[1] (a) T. Rodrigues, M. Werner, J. Roth, E. H. G. da Cruz, M. C. Marques, P. Akkapeddi, S. A. Lobo, A. Koeberle, F. Corzana, E. N. da Silva Júnior, O. Werz, G. J. L. Bernardes, *Chem. Sci.* **2018**, *9*, 6899-6903; (b) S. L. de Castro, F. S. Emery, E. N. da Silva Júnior, *Eur. J. Med. Chem.* **2013**, *69*, 678-700; (c) D. Kallifidas, H.-S. Kang, S. F. Brady, *J. Am. Chem. Soc.* **2012**, *134*, 19552-19555; (d) R. H. Thomson, Naturally Occurring Quinones, Academic Press, London, **1971**, 2nd edn.; (e) R. H. Thomson, Naturally Occurring Quinones III Recent Advances, Chapman and Hall, London, **1987**, 3rd edn; (f) G. Powis, *Pharmacol. Ther.* **1987**, *35*, 57; (c) P. J. O'Brien, *Chem. Biol. Interact.* **1991**, *80*, 1; (g) E. A. Hillard, F. C. Abreu, D. C. Ferreira, G. Jaouen, M. O. F. Goulart, C. Amatore, *Chem. Commun.* **2008**, *23*, 2612.

[2] Z. Chen, T. M. Swager, *Org. Lett.* **2007**, *9*, 997-1000.

[3] J. M. Wood, E. N. da Silva Júnior, J. F. Bower, *Org. Lett.* **2020**, *22*, 265-269.

[4] (a) B. R. Ambler, B. W. H. Turnbull, S. R. Suravarapu, M. M. Uteuliyev, N. O. Huynh, M. J. Krische, *J. Am. Chem. Soc.* **2018**, *140*, 9091-9094; (b) M. Bender, B. W. H. Turnbull, B. R. Ambler, M. J. Krische, *Science* **2017**, *357*, 779-781.

[5] (a) M. Arisawa, Y. Fujii, H. Kato, H. Fukuda, T. Matsumoto, M. Ito, H. Abe, Y. Ito, S. Shuto, *Angew. Chem. Int. Ed.* **2013**, *52*, 1003-1007; (b) Y. Fujii, T. Takehara, T. Suzuki, H. Fujioka, S. Shuto, M. Arisawa, *Adv. Synth. Catal.* **2015**, *357*, 4055-4062.

[6] For selected reviews, see: (a) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.9b00495; (b) S. M. Khake, N. Chatani, *Trends Chem.* **2019**, *1*, 524–539; (c) A. Dey, S. K. Sinha, T. K. Achar, D. Maiti, *Angew. Chem. Int. Ed.* **2019**, *58*, 10820-10843; (d) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452; (e) C. S. Wang, P. H. Dixneuf, J. F. Soule, *Chem. Rev.* **2018**, *118*, 7532–7585; (f) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222; (g) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101; (h) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332; (i) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; (j) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754-8786; (k) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281–292; (l) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918.

[7] Y. Liu, J.-W. Sun, *J. Org. Chem.* **2012**, *77*, 1191-1197.

[8] N. Suematsu, M. Ninomiya, H. Sugiyama, T. Udagawa, K. Tanaka, M. Koketsu, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2243-2247.

[9] G. A. M. Jardim, E. N. da Silva Júnior, J. F. Bower, *Chem. Sci.* **2016**, *7*, 3780-3784.

[10] G. G. Dias, T. Rogge, R. Kuniyil, C. Jacob, R. F. S. Menna-Barreto, E. N. da Silva Júnior, L. Ackermann, *Chem. Commun.* **2018**, *54*, 12840-12843.

[11] G. G. Dias, T. A. do Nascimento, A. K. A. de Almeida, A. C. S. Bombaça, R. F. S. Menna-Barreto, C. Jacob, S. Warratz, E. N. da Silva Júnior, L. Ackermann, *Eur. J. Org. Chem.* **2019**, 2344-2353.

[12] G. A. M. Jardim, W. X. C. Oliveira, R. P. de Freitas, R. F. S. Menna-Barreto, T. L. Silva, M. O. F. Goulart, E. N. da Silva Júnior, *Org. Biomol. Chem.* **2018**, *16*, 1686-1691.

[13] G. A. M. Jardim, I. A. O. Bozzi, W. X. C. Oliveira, C. Mesquita-Rodrigues, R. F. S. Menna-Barreto, R. A. Kumar, E. Gravel, E. Doris, A. L. Braga, E. N. da Silva Júnior, *New J. Chem.* **2019**, *43*, 13751-13763.

[14] For selected references, see: (a) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281-295; (b) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; (c) S. Peng, S. Liu, S. Zhang, S. Cao, J. Sun, *Org. Lett.* **2015**, *17*, 5032-5035; (d) J. Jayakumar, K. Parthasarathy, Y.-H. Chen, T.-H. Lee, S.-C. Chuang, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2014**, *53*, 9889-9892; (e) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585-9587; (f) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487-7490; (g) M. Satoshi, U. Nobuyoshi, H. Koji, S. Tetsuya, M. Masahiro, *Chem. Lett.* **2010**, *39*, 744-746. For representative examples from our laboratories, see: (h) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2019**, *141*, 17198-17206; (i) C. Zhu, R. Kuniyil, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 5338-5342; (j) E. Gońka, L. Yang, R. Steinbock, F. Pesciaioli, R. Kuniyil, L. Ackermann, *Chem. Eur. J.* **2019**, *25*, 16246-16250; (k) C. Tian, U. Dhawa, A. Scheremetjew, L. Ackermann, *ACS Catal.* **2019**, *9*, 7690-7696; (l) R. Mei, J. Koeller, L. Ackermann, *Chem. Commun.* **2018**, *54*, 12879-12882; (m) R. Mei, H. Wang, S. Warratz, S. A. Macgregor, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 6759-6763; (n) W. Ma, L. Ackermann, *Synthesis* **2014**, 2297-2304; (o) J. Li, L. Ackermann, *Tetrahedron* **2014**, *70*, 3342-3348; (p) W. Song, L. Ackermann, *Chem. Commun.* **2013**, *49*, 6638-6640; (q) C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190-9198, and references cited therein.

[15] W. Ma, K. Graczyk, L. Ackermann, *Org. Lett.* **2012**, *14*, 6318-6321.

[16] (a) J. Mo, T. Müller, J. C. A. Oliveira, S. Demeshko, F. Meyer, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12874-12878; (b) W.-J. Kong, L. H. Finger, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 6342-6346; (c) I. Funes-Ardoiz, F. Maseras, *Chem. Eur. J.* **2018**, *24*, 12383-12388; (d) R. Mei, N. Sauermann, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2018**, *140*, 7913-7921; (e) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201-2208; (f) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2012**, *18*, 12873-12879; (g) B. Li, T. Roisnel, C. Darcel, P. H. Dixneuf, *Dalton Trans.* **2012**, *41*, 10934-10937; (h) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379-6382.

[17] (a) J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615-6620. (b) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.

[18] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[19] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[20] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[21] (a) S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200–1211. (b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789. (c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652. (d) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

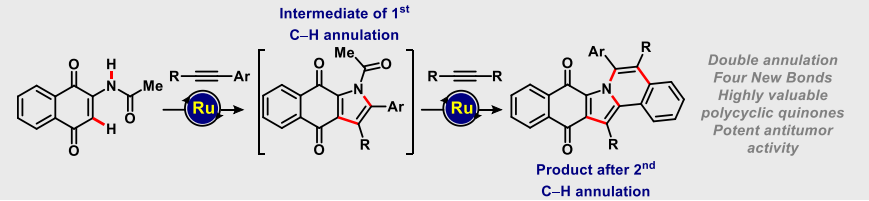
[22] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456–1465.

[23] (a) J. E. Anthony, *Angew. Chemie Int. Ed.* **2008**, *47*, 452–483. (b) M. Kitamura, Y. Arakawa, *J. Phys. Condens. Matter* **2008**, *20*, 184011. (c) M. Watanabe, Y. J. Chang, S.-W. Liu, T.-H. Chao, K. Goto, M. M. Islam, C.-H. Yuan, Y.-T. Tao, T. Shinmyozu, T. J. Chow, *Nat. Chem.* **2012**, *4*, 574–578. (d) M. Pinheiro, L. F. A. Ferrão, F. Bettanin, A. J. A. Aquino, F. B. C. Machado, H. Lischka, *Phys. Chem. Chem. Phys.* **2017**, *19*, 19225–19233.

10.1002/chem.202001434

WILEY-VCH

COMMUNICATION



Ruthenium(II)-catalyzed C–H/N–H double annulation were realized for the formation of polycyclic quinones enabling the assembly of antitumor compounds.

Eufrânio N. da Silva Júnior, Renato L. de Carvalho, Renata G. Almeida, Luisa G. Rosa, Felipe Fantuzzi, Torben Rogge, Pedro M. S. Costa, Claudia Pessoa, Claus Jacob, and Lutz Ackermann**

Page No. – Page No.

Ruthenium(II)-Catalyzed Double Annulation of Quinones: Step-Economical Access to Valuable Antitumor Compounds