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Synthesis of unprotected glyco-alkynones *via* molybdenum-catalyzed carbonylative Sonogashira cross-coupling reaction†

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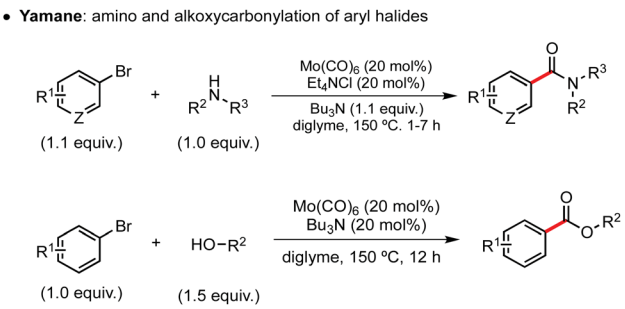
Herein we report a novel Mo-catalyzed carbonylative Sonogashira cross-coupling between 2-iodoglycals and terminal alkynes. The reaction displays major improvements compared to a related Pd-catalyzed procedure previously published by our group, such as utilizing unprotected sugar derivatives as starting materials and tolerance to substrates bearing chelating groups. In this work we also demonstrate the utility of the glyco-alkynone products as platform for further functionalization by synthesizing glyco-flavones *via* Au-catalyzed 6-*endo*-dig cyclization.

Metal-catalyzed carbonylative reactions have a history of many decades of development that began in the second half of the last century[1] The ubiquity of carbonyl-containing compounds and the efficiency of these reactions turned it into a popular transformation in many fields of chemistry, from natural products synthesis and drug development to industrial multi-ton production of commodity chemicals.[2] This three-component reaction delivers carbonyl-containing compounds by connecting carbon electrophiles to carbon and heteroatom nucleophiles through a CO bridge in an atom-economical fashion. Some commonly employed nucleophiles are amines,[3] alcohols,[4] boronic acids,[5] terminal alkynes[6] and alkyl halides.[7]

While noble metals have been in the forefront of the development of carbonylative coupling reactions, significant advancements have been achieved more recently in the use of some Earth-abundant metals (Mn, Fe, Co, Ni and Cu).[2h] The reports in the field are much more scarce, however, when it comes to group VI metals, with transformations being restricted to amine and alcohol nucleophiles, described in reports first published by Yamane and Roberts (Scheme 1).[8] These reactions take place at high temperatures and are believed to follow a classic carbonylation mechanism: oxidative addition, CO insertion with the formation of acyl-metal intermediates, nucleophile coordination and reductive elimination. Since then, carbonylative reactions mediated by group VI metals have only been applied to the synthesis of heterocyclic compounds in a handful of publications.[9]

Inspired by this chemistry and continuing a research program in our laboratory devoted to the synthesis of biologically relevant C2-substituted glycals,[10] we questioned whether Mo-catalyzed carbonylative coupling reactions could deliver carbonyl-containing glycals under Pd-free conditions from 2-iodoglycal electrophiles. Moreover, by eliminating palladium from the reaction medium, we wondered if unprotected 2-iodoglycals could be used as electrophiles,[11] which would represent a major improvement from previous reports (Scheme 2A).[10,12]

To test this idea, we chose the carbonylative Sonogashira coupling as our target reaction, as this is an unprecedented transformation under molybdenum catalysis, therefore synthetically relevant in its own right. Furthermore, the glyco-alkynone products are attractive molecules that can operate as platform for further functionalization in synthetic programs aiming complex sugar-containing targets.



Scheme 1 Mo-mediated amino- and alkoxycabonylation of aryl halides.

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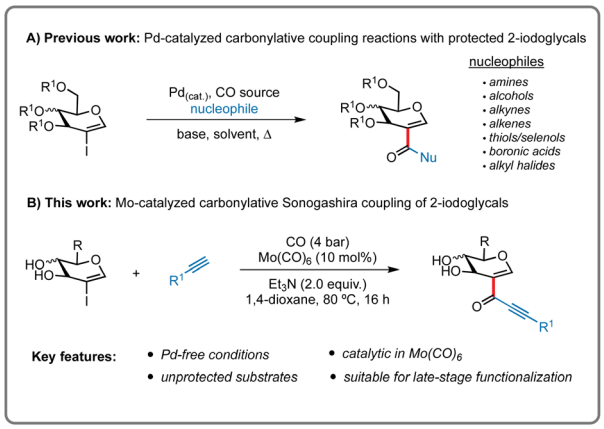
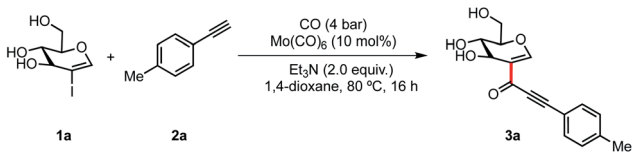


Scheme 2 Metal-catalyzed carbonylative coupling reactions of 2-iodoglycals.

We initiated our studies by carrying out an optimization campaign based on the reaction of 2-iodo-D-glucal (**1a**) and 4-ethynyltoluene (**2a**) (Table 1). We identified $Mo(CO)_6$ as the best choice of catalyst, even though the reaction still takes place with other sources of molybdenum, such as Na_2MoO_4 (entry 2), presumably by the *in situ* formation of the metal carbonyl complex. As expected, the reaction still proceeds in reasonable yield with $PdCl_2$ (entry 3), but not with other metals such as $NiCl_2$ or $FeCl_2$. The use of DIPEA as base resulted in diminished yield, while inorganic bases completely shut down the reaction (entries 5 and 6). A solvent screening showed that **3a** can be obtained in a series of solvents, albeit in lower yields (26% with MeCN, 40% with THF and 32% with DMF) (entry 7). Finally, a control experiment demonstrated that $CO_{(g)}$ is needed in this reaction, presumably to regenerate the catalytic species $Mo(CO)_6$ (entry 8).

Having established good reaction conditions, we next explored the generality of this method (Table 2).

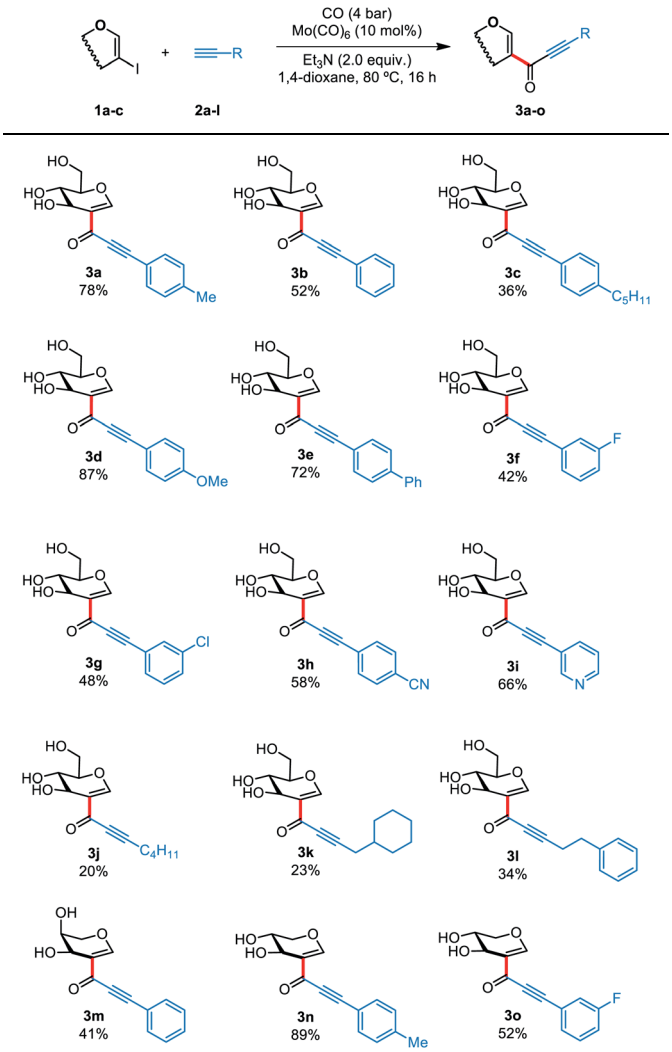
Table 1 Optimization of reaction conditions[a]



	Variation from standard conditions	Yield[b]
1	None	78%
2	Na_2MoO_4 instead of $Mo(CO)_6$	58%
3	$PdCl_2$ instead of $Mo(CO)_6$	64%
4	$NiCl_2$ or $FeCl_2$ instead of $Mo(CO)_6$	0%
5	DIPEA instead of Et_3N	27%
6	Cs_2CO_3, K_2CO_3 instead of Et_3N	0%
7	MeCN, THF of DMF instead of 1,4-dioxane	26–40%
8	Co $CO_{(g)}$	0%

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (10 mol%), base (2.0 equiv.), CO (4 bar), solvent (5 mL), 80 °C, 16 h. [b] Isolated yield.

Table 2 Mo-catalyzed carbonylative Sonogashira cross-coupling of 2-iodoglycals with terminal alkynes[a]



[a] Reaction conditions: 2-iodoglycal (0.5 mmol), terminal alkyne (1.5 mmol), $Mo(CO)_6$ (10 mol%), Et_3N (2.0 equiv.), CO (4 bar), 1,4-dioxane (5 mL), 80 °C, 16 h.

Using 2-iodo-D-glucal as electrophile, terminal alkynes bearing electron-rich aromatic rings delivered the desired products in moderate to good yields (**3a–3e**), while electron-poor groups gave alkynones **3f–i** in slightly diminished yields. It is noteworthy that coordinating groups such as those present in **2h** and **2i** were tolerated by our methodology. This result combined with the fact that this reaction proceeds well with unprotected glycals indicates that the catalyst is less prone to be deactivated by coordination, a major improvement from the Pd-catalyzed coupling previously reported by our group.[10a] Terminal alkynes bearing alkyl groups were also amenable to this transformation, however, products **3j–3l** were obtained only in low yields. Finally, we wished to test how different sugar derivatives perform under the standard reaction conditions, thus 2-iodo-L-arabinal and 2-iodo-D-xylal were reacted with

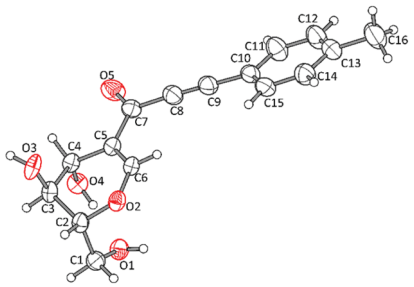


Fig. 1 Thermal ellipsoid representation of compound **3a**.

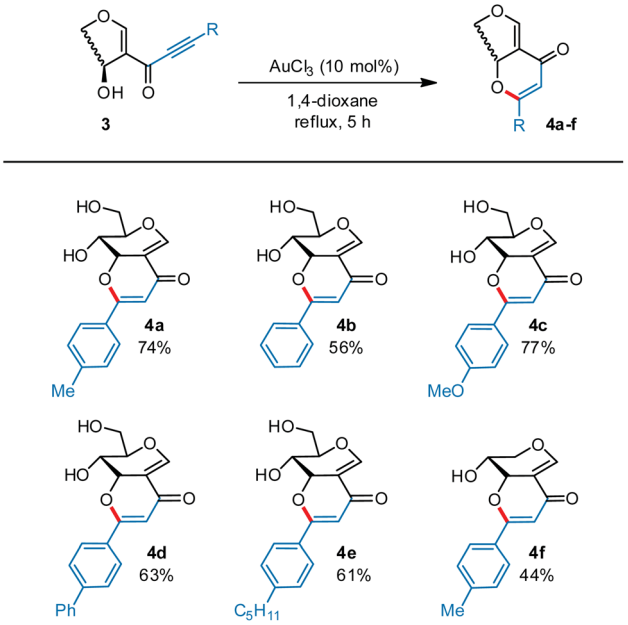
terminal alkynes **2m** and **2n**, delivering **3m–o** in yields comparable to those obtained with 2-iodo-D-glucal.

The structure of compound **3a** was unambiguously confirmed by single-crystal X-ray analysis. The ORTEP view is shown in Fig. 1 (details in the ESI†).

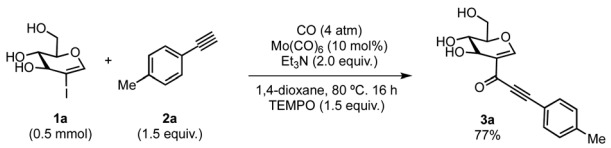
In order to demonstrate the synthetic utility of the glyco-alkynone products, we next tested their reactivity toward Au-catalyzed 6-*endo*-dig cyclization.[13] Our goal was to display the internal alkyne as a valuable platform for further modification and, at the same time, obtain biologically relevant flavones.[14]

Overall, this Au-catalyzed cyclization occurred smoothly with a range aromatic glyco-alkynones, which gave glyco-flavones **4a–f** in moderate to good yields. Electron-deficient and aliphatic alkynones (**3h**, **3i** and **3k**), on the other hand, failed to deliver the expected product, possibly due to a lower affinity towards gold coordination (Scheme 3).

To shed light on the reaction mechanism of this transformation, a control experiment with the addition of the radical-trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was carried out. The reaction proceeded in



Scheme 3 Au-catalyzed 6-*endo*-dig cyclization of glyco-alkynones. Reaction conditions: glyco-alkynone 3 (0.2 mmol), $AuCl_3$ (10 mol%), 1,4-dioxane (2 mL), 80 °C, 3 h.



Scheme 4 Radical-trapping experiment with TEMPO.

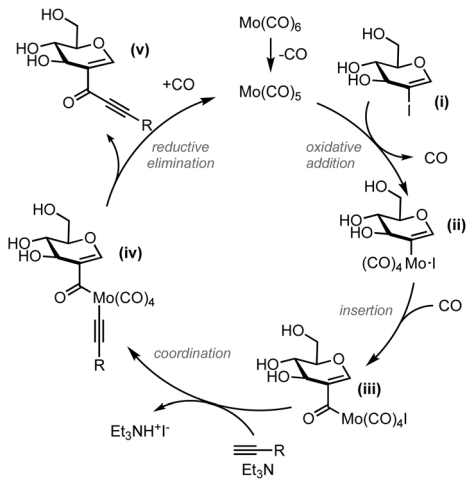


Fig. 2 Proposed catalytic cycle for the Mo-catalyzed carbonylative Sonogashira reaction.

good yield with no suppression being observed, which rules out the intermediacy of radical species (Scheme 4).[15]

Based on this result and on literature precedents, we propose the reaction mechanism depicted in Fig. 2. Oxidative addition of the 2-iodoglycal to molybdenum generates complex **(ii)**. Insertion of carbon monoxide leads to acylmolybdenum **(iii)**, as previously proposed by Yamane and others.[8,16] Coordination of a terminal alkyne to this complex gives **(iv)** which, after reductive elimination, delivers the alkynone product **(v)** and regenerates the active Mo(0) species.

Conclusions

In summary, we developed a Pd-free carbonylative coupling reaction between 2-iodoglycals and terminal alkynes that rely on inexpensive $Mo(CO)_6$ as catalyst and tolerates unprotected sugar derivatives as substrate. The products obtained are also prone to further functionalization as was demonstrated by the synthesis of six glyco-flavones *via* gold catalysis. An in-depth investigation of the reaction mechanism and new applications of this newly developed method are currently in progress in our laboratory.

Author contributions

MPD and AASP carried out the synthetic work. RAB collected X-ray crystallography data. MPD, HAE, HAS designed and wrote the manuscript. All authors approved the final version of the manuscript before submission.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 (*a*) V. W. Reppe, *Justus Liebigs Ann. Chem.*, 1953, **582**, 1; (*b*) A. Schoenberg, I. Bartoletti and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318; (*c*) A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327; (*d*) A. Schoenberg and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 7761; (*e*) N. Miyaura and A. Suzuki, *Chem. Lett.*, 1981, 879; (*f*) S. Cacchi, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1985, **26**, 1109; (*g*) S. Cacchi, P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1986, **33**, 3931.

2 (*a*) A. Brennführer, H. Neumann and M. Beller, *ChemCatChem*, 2009, **1**, 28; (*b*) X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1; (*c*) P. Guatam and B. C. Bhanage, *Catal. Sci. Technol.*, 2015, **5**, 4663; (*d*) P. H. Gehrtz, V. Hirschbeck, B. Ciszek and I. Fleischer, *Synthesis*, 2016, **48**, 1573; (*e*) Y. Bai, D. C. Davis and M. Dai, *J. Org. Chem.*, 2017, **82**, 2319; (*f*) Y. Li, Y. Hu and X.-F. Wu, *Chem. Soc. Rev.*, 2018, **47**, 172; (*g*) K. Ma, B. S. Martin, X. Yin and M. Dai, *Nat. Prod. Rep.*, 2019, **36**, 174; (*h*) J.-B. Peng, F.-P. Wu and X.-F. Wu, *Chem. Soc. Rev.*, 2019, **119**, 2090; (*i*) Z. Chen, L.-C. Wang and X.-F. Wu, *Chem. Commun.*, 2020, **56**, 6016; (*j*) Z. Yin, J.-X. Xu and X.-F. Wu, *ACS Catal.*, 2020, **10**, 6510; (*k*) S. Zhang, H. Neumann and M. Beller, *Chem. Soc. Rev.*, 2020, **49**, 3187; (*l*) D. Das and B. M. Bhanage, *Adv. Synth. Catal.*, 2020, **362**, 3022.

3 (*a*) S. Fuse, R. Takahashi and T. Takahashi, *Eur. J. Org. Chem.*, 2015, 3430; (*b*) R. Shi, H. Zhang, L. Lu, P. Gan, Y. Sha, H. Zhang, Q. Liu, M. Beller and A. Lei, *Chem. Commun.*, 2015, **51**, 3247; (*c*) Y. Li, F. Zhu, Z. Wang and X.-F. Wu, *ACS Catal.*, 2016, **6**, 5561; (*d*) R. S. Mane and B. M. Bhanage, *Adv. Synth. Catal.*, 2017, **359**, 2621; (*e*) Q. Xing, H. Lv, C. Xia and F. Li, *Chem. Commun.*, 2017, **53**, 6914.

4 (*a*) M. Beller, W. Mägerlein, A. F. Indolese and C. Fischer, *Synthesis*, 2001, 1098; (*b*) R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754; (*c*) B. T. Sargent and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 7520; (*d*) Y. Wang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2017, **56**, 3191; (*e*) H. Minami, K. Nogi and H. Yorimitsu, *Org. Lett.*, 2019, **21**, 2518.

5 (*a*) P. Gautam and B. M. Bhanage, *J. Org. Chem.*, 2015, **80**, 7810–7815; (*b*) X. Qi, L.-B. Jiang, H.-P. Li and X.-F. Wu, *Chem.–Eur. J.*, 2015, **21**, 17650; (*c*) P. Gautam, M. Dhiman, V. Polshettiwar and B. M. Bhanage, *Green Chem.*, 2016, **18**, 5890; (*d*) Y. Wang, Y. Wu, Y. Li and Y. Tang, *Chem. Sci.*, 2017, **8**, 3852; (*e*) P. Gautam, R. Gupta and B. M. Bhanage, *Eur. J. Org. Chem.*, 2017, 3431; (*f*) D. Bhattacherjee, M. Rahman, S. Ghosh, A. Kumar, A. K. Bagdi, G. V. Zyryanov, O. N. Chupakhin, P. Das and A. Hajra, *Adv. Synth. Catal.*, 2021, **363**, 1597.

6 (*a*) W. Li and X.-F. Wu, *Org. Biomol. Chem.*, 2015, **13**, 509; (*b*) L. Akerbladh, P. Nordeman, M. Wejdemar, L. R. Odell and M. Larhed, *J. Org. Chem.*, 2015, **80**, 1464; (*c*) C. Tan, P. Wang, H. Liu, X.-L. Zhao and Y. Liu, *Chem. Commun.*, 2015, **51**, 10871; (*d*) G. Sun, M. Lei and L. Hu, *RSC Adv.*, 2016, **6**, 28442; (*e*) K. Xiang, P. Tong, B. Yan, L. Long, C. Zhao, Y. Zhang and Y. Li, *Org. Lett.*, 2019, **21**, 412; (*f*) W. Mansour, R. Suleiman, M. Fettouhi and B. El Ali, *ACS Omega*, 2020, **5**, 23687.

7 (*a*) D. R. Pye, L.-J. Cheng and N. P. Mankad, *Chem. Sci.*, 2017, **8**, 4750; (*b*) S. Sumino, T. Ui and I. Ryu, *Org. Lett.*, 2013, **15**, 3142; (*c*) J.-B. Peng, B. Chen, X. Qi, J. Ying and X.-F. Wu, *Adv. Synth. Catal.*, 2018, **360**, 4153; (*d*) Y. Weng, C. Zhang, Z. Tang, M. Shrestha, W. Huang, J. Qu and Y. Chen, *Nat. Commun.*, 2020, **11**, 392; (*e*) L.-J. Cheng and N. P. Mankand, *Acc. Chem. Res.*, 2021, **54**, 2261.

8 (*a*) W. Ren and M. Yamane, *J. Org. Chem.*, 2010, **75**, 3017; (*b*) W. Ren and M. Yamane, *J. Org. Chem.*, 2010, **75**, 8410; (*c*) B. Roberts, D. Liptrot, L. Alcaraz, T. Luker and M. J. Stocks, *Org. Lett.*, 2010, **12**, 4280; (*d*) W. Ren, A. Emi and M. Yamane, *Synthesis*, 2011, **14**, 2303.

9 (*a*) B. Roberts, D. Liptrot, T. Luker, M. J. Stocks, C. Barber, N. Webb, R. Dods and B. Martin, *Tetrahedron Lett.*, 2011, **52**, 3793; (*b*) M. Nakka, R. Tadikonda, S. Nakka and S. Vidavalur, *Adv. Synth. Catal.*, 2016, **358**, 520; (*c*) J. S. Rao, A. V. Rao, T. Krishna, V. N. Murthy, J. Rajesh and A. Raghunadh, *RSC Adv.*, 2016, **6**, 67534.

10 (*a*) M. P. Darbem, C. H. A. Esteves, I. M. Oliveira, J. S. Reis, D. C. Pimenta and H. A. Stefani, *RSC Adv.*, 2019, **9**, 9468; (*b*) H. A. Esteves, M. P. Darbem, D. C. Pimenta and H. A. Stefani, *Eur. J. Org. Chem.*, 2019, 7384; (*c*) M. P. Darbem, K. S. Kanno, I. M. Oliveira, C. H. A. Esteves, D. C. Pimenta and H. A. Stefani, *New J. Chem.*, 2019, **43**, 696; (*d*) M. P. Darbem, H. A. Esteves, I. M. Oliveira, D. C. Pimenta and H. A. Stefani, *ChemCatChem*, 2020, **12**, 576; (*e*) A. A. Soares-Paulino and H. A. Stefani, *Eur. J. Org. Chem.*, 2020, 3847; (*f*) M. P. Darbem, H. A. Esteves, I. M. Oliveira and H. A. Stefani, *Eur. J. Org. Chem.*, 2020, 5220.

11 M. Malinowski, T. V. Tran, M. de Robichon, N. Lubin-Germain and A. Ferry, *Adv. Synth. Catal.*, 2020, **362**, 1184.

12 (*a*) A. Bordessa, A. Ferry and N. Lubin-Germain, *J. Org. Chem.*, 2016, **81**, 12459; (*b*) M. Robichon, A. Bordessa, N. Lubin-Germain and A. Ferry, *J. Org. Chem.*, 2019, **84**, 3328; (*c*) N. Hussain, M. Bhardwaj, A. Ahmed and D. Mukherjee, *Org. Lett.*, 2019, **21**, 3034–3037; (*d*) A. Ahmed, N. Hussain, M. Bhardwaj, A. K. Chhalodia, A. Kumar and D. Mukherjee, *RSC Adv.*, 2019, **9**, 22227.

13 B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937.

14 (*a*) P. C. Ferriola, V. Cody and E. Middleton, *Biochem. Pharmacol.*, 1989, **38**, 1617; (*b*) A. K. Verma and R. Pratap, *Tetrahedron*, 2012, **68**, 8523; (*c*) A. G. Golub, V. G. Bdzhola, O. V. Ostrynska, I. V. Kyshenia, V. M. Sapelkin, A. O. Prykhod'ko, O. P. Kukharenko and S. M. Yarmoluk, *Med. Chem.*, 2013, **21**, 6681; (*d*) T. Yatabe, X. Jin, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2015, **54**, 13302; (*e*) C. Jiang, Z. Xiong, S. Jin, P. Gao, Y. Tang, Y. Wang, C. Du, X. Wang, Y. Liu, B. Lin, Y. Liu and M. A. Cheng, *Chem. Commun.*, 2016, **52**, 11516; (*f*) X. Zhu, I. L. K. Wong, K.-F. Chan, J. Cui, M. C. Law, T. C. Chong,

X. Hu, L. M. C. Chow and T. H. Chan, *J. Med. Chem.*, 2019, **62**, 8578; (*g*) A. M. de Matos, A. Martins, T. Man, D. Evans, M. Walter, M. C. Oliveira, O. López, J. G. F. Bolaños, P. Dätwyler, B. Ernst, M. P. Macedo, M. A. Contino, N. A. Colabufo and A. P. Raute, *Pharmaceuticals*, 2019, **12**, 98; (*h*) N. Zhang, J. Yang, K. Li, J. Luo, S. Yang, J.-R. Song, C. Chen and W.-D. Pan, *Molecules*, 2019, **24**, 2723; (*i*) A. H. E. Hassan, K.-T. Lee and Y. S. Lee, *Eur. J. Med. Chem.*, 2020, **187**, 111965; (*j*) S. Tian, T. Luo, Y. Zhu and J.-P. Wan, *Chin. Chem. Lett.*, 2020, **31**, 3073.

15 (*a*) M. M. Caitlin, S. R. Matthew and E. Alexanian, *Org. Lett.*, 2016, **18**, 4148; (*b*) R. P. Dominic, C. Li-Jie and N. P. Mankad, *Chem. Sci.*, 2017, **8**, 4750; (*c*) K. L. Parvathi, V. M. Sarma, C. Sridhar and B. K. Raghu, *ChemistrySelect*, 2019, **4**, 11553.

16 (*a*) K. Sangu, T. Watanabe, J. Takaya and N. Iwasawa, *Synlet*, 2007, **6**, 929; (*b*) J. Takaya, K. Sangu and N. Iwasawa, *Angew. Chem., Int. Ed.*, 2009, **48**, 7090; (*c*) N. Iranpoor, H. Firouzabadi, S. Motevalli and M. Talebi, *Tetrahedron*, 2013, **69**, 418.