


 Cite this: *RSC Adv.*, 2022, 12, 2145

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

 Mariana P. Darbem,^a Henrique A. Esteves,^b Robert A. Burrow,^c Antônio A. Soares-Paulino,^a Daniel C. Pimenta^d and Hélio A. Stefani^d*^a

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.

 Received 15th November 2021
 Accepted 10th December 2021

DOI: 10.1039/d1ra08388k

rsc.li/rsc-advances

Metal-catalyzed carbonylative reactions have a history of many decades of development that began in the second half of the last century¹ 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 alkynes⁶ and alkyl halides.⁷

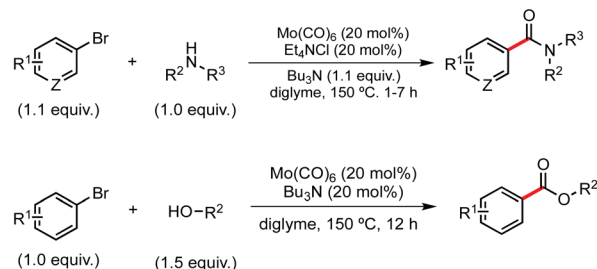
While noble metals have been in the forefront of the development of carbonylative coupling reactions, significant advancements have been achieved more recently in the use of some Earth-abundant metals (Mn, Fe, Co, Ni and Cu).^{2h} The reports in the field are much more scarce, however, when it comes 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-iodoglycyl 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.

• **Yamane:** amino and alkoxy carbonylation of aryl halides



Scheme 1 Mo-mediated amino- and alkoxy carbonylation of aryl halides.

^aDepartamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, Avenida Prof. Lineu Prestes, 580 – Bl. 13, São Paulo, 05508-000, Brazil. E-mail: hstefani@usp.br

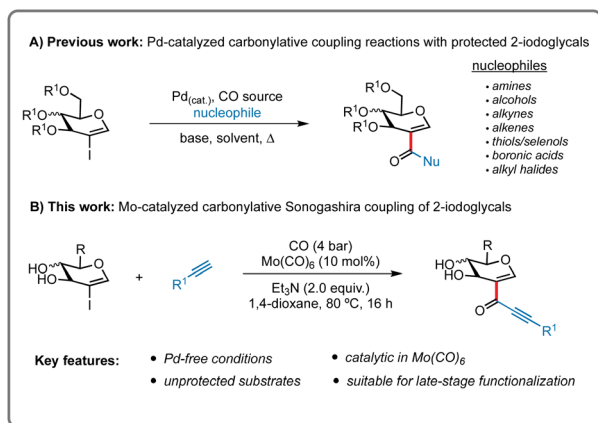
^bYusuf Hamied Department of Chemistry, University of Cambridge, Cambridge, CB2 1EW, UK

^cDepartamento de Química, Universidade Federal de Santa Maria, Santa Maria, 97105-340, Brazil

^dInstituto Butantan, São Paulo, 05503-900, Brazil

† Electronic supplementary information (ESI) available. CCDC 2085190. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra08388k





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 Na₂MoO₄ (entry 2), presumably by the *in situ* formation of the metal carbonyl complex. As expected, the reaction still proceeds in reasonable yield with PdCl₂ (entry 3), but not with other metals such as NiCl₂ or FeCl₂. 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).

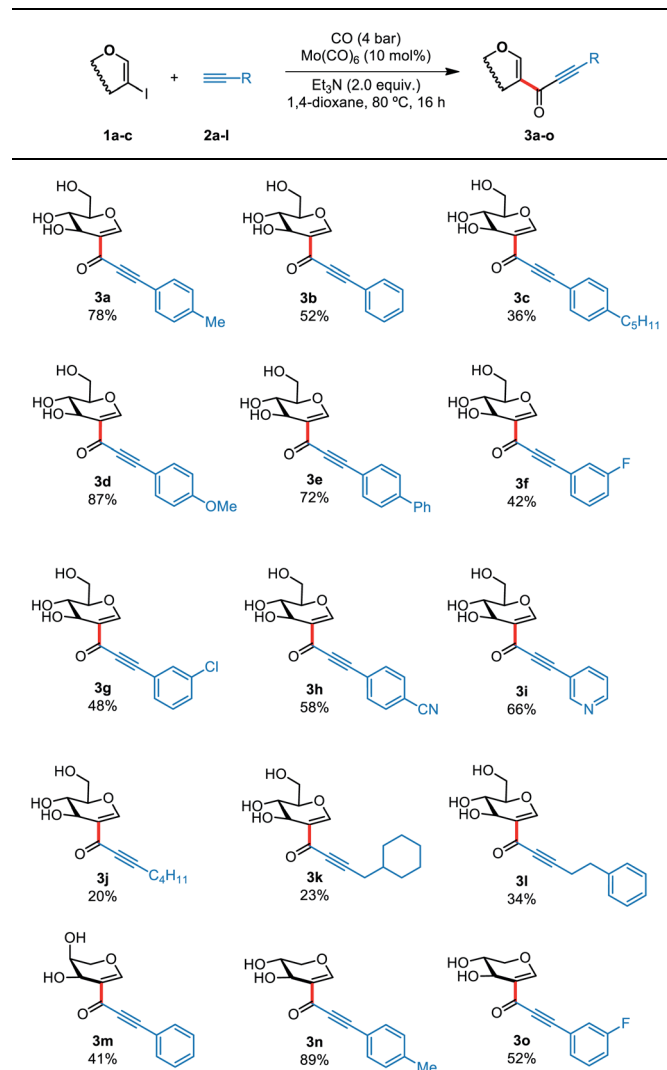
Having established good reaction conditions, we next explored the generality of this method (Table 2).

Table 1 Optimization of reaction conditions^a

Variation from standard conditions	Yield ^b
1 None	78%
2 Na ₂ MoO 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 ₃ N	27%
6 Cs ₂ CO ₃ , K ₂ CO ₃ instead of Et ₃ N	0%
7 MeCN, THF or 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-iodoglycyl (0.5 mmol), terminal alkyne (1.5 mmol), Mo(CO)₆ (10 mol%), Et₃N (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



Conflicts of interest

The authors declare no competing financial interest.

Notes and references

- (a) V. W. Reppe, *Justus Liebig's 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.
- (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.
- (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.
- (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.
- (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. Bhattacharjee, 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.
- (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.
- (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.
- (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.
- (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.
- (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.
- M. Malinowski, T. V. Tran, M. de Robichon, N. Lubin-Germain and A. Ferry, *Adv. Synth. Catal.*, 2020, **362**, 1184.
- (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.
- B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937.
- (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. Kyszenia, 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, *Synlett*, 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.

