

pubs.acs.org/OPRD

The Design of an In-Ex Tube for Gas Related Organic Reactions

Zhiping Yin and Xiao-Feng Wu*®

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany

S Supporting Information

ABSTRACT: Here, an interesting in-ex tube was designed for gas-related organic reactions. By using this specially designed reaction tube, several gas-reliant organic reactions are applicable, including CO, SO₂, and H₂. Moderate to good yields of the desired products were produced easily.

n modern organic synthesis, a large percentage of the synthetic methodologies are gas reliant. For the nontoxic or nonflammable gas related reactions, such as CO₂, their manipulation is still relatively easy and security demand is low.¹ However, for gases such as CO, SO₂, and H₂, special attention is required for their manipulation in synthetic applications. For example, in the case of carbon monoxide, due to its high toxicity, synthetic chemists are reluctant to apply CO gas related procedures in the laboratory.² Hence, many CO surrogates and reaction systems have been developed for the in situ or ex situ generation of CO gas for usage.³ For the in situ systems, drawbacks exist from the aspect of cost and waste generation; for the ex situ systems, problems such as gas leaking and difficulties in flask cleaning and maintenance become new problems.

Our research group has been interested in CO chemistry during the past few years. A part of our work has been focused on developing CO surrogates based carbonylation procedures. Recently, we explored the applications of formic acid and derivatives as CO sources in carbonylative cross-coupling transformations. With acid anhydride or DCC as activating reagents, formic acid can be activated and release one molecule of CO.⁴ In the case of using acid anhydride as the activator, 2 equiv of acid will be produced as the byproduct and need to be neutralized by a base in the reaction system. In the case of using DCC as the activating reagent, 1,3-dicyclohexylurea will be formed as the byproduct and increase the difficulty in obtaining the desired product purity (Scheme 1). These problems become new challenges requiring resolution!

With this background, the design of a new reactor is considered. We intend to continue using formic acid as the CO source, due to its advantages including being nontoxic, easy to

Scheme 1. In Situ Activation of Formic Acid



store, and inexpensive, and keep the byproducts out of the reaction system (Scheme 2). Hence, we need a separate tube to

Scheme 2. Idea for New Reactor Design



produce CO from formic acid for another tube where the reaction takes place. But the two tubes are in the same environment. With these parameters to consider, a picture of the new reactor, so-called '*in–ex* tube', becomes clear: a smaller tube (with holes in the middle) in the reaction tube for ex situ CO production. With this *in*-*ex* tube, the byproducts can be



ACS Publications © XXXX American Chemical Society

Received: October 16, 2017

kept out of the reaction tube, successfully avoiding problems in product purification and additional waste generation.

Then experiments were performed to proven the concept. First, we chose iodobenzene and aniline as the substrates under the conditions we developed for aminocarbonylation of aryl iodides; 55% of the desired amide can be produced with 2 equiv of NEt₃ as the base (Scheme 3, eq 1). A carbonylative Suzuki

Scheme 3. Palladium-Catalyzed Carbonylations of Iodobenzene



reaction between iodobenzene and phenyl boronic acid can be realized as well (Scheme 3, eq 2). Then a carbonylative Sonogashira reaction was tested in this *in*-*ex* tube and a 78% yield of the corresponding alkynone can be produced without any optimization (Scheme 3, eq 3). In these experiments, in order to further prove the value of this new reactor, the combination of formic acid and sulfuric acid (Morgan reaction) was used for carbon monoxide generation.⁵

Additionally, reactions with SO_2 and hydrogen were carried out as well (Scheme 4).⁶ Because of the high toxicity of SO_2

Scheme 4. Reactions with SO₂ and H₂



and the high flammability of H_2 , their manipulation and storage require special attention. In our testings, SO_2 and H_2 were produced from Na_2SO_3 and Zn, respectively, in the presence of H_2SO_4 . Delightfully, 58% and 82% of the corresponding products can be formed, respectively.

In summary, in this short communication, an in-ex tube has been designed and applied in gas related organic reactions. In our testings, CO, SO₂, and H₂ are all applicable and gave the corresponding products in moderate to good yields without any optimization. We believe this tube will allow gas-reliant reactions to be performed in an "efficient and easy" manner.

General Procedure. To the reaction tube were added iodobenzene (0.5 mmol, 102 mg), aniline (1 mmol, 93 mg), $Pd(OAc)_2$ (5.6 mg, 25 μ mol), PPh_3 (13.1 mg, 50 μ mol), Et_3N

(101 mg, 1 mmol), and DMF (2 mL). Next, formic acid (230 mg, 5 mmol) was added to the in-tube. Then the two tubes were combined and sealed with a plastic septum. The whole system was vacuumed through a Schlenk line and maintained under an argon atmosphere. Concentrated sulfuric acid (0.28 mL, 5 mmol) was injected into the in-tube in three portions via syringe. Finally, the reaction was immersed in an oil bath and stirred at 100 $^{\circ}$ C for 24 h. Part of the sulfuric acid can be injected during the reaction as well.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.7b00332.

General comments, analytic data, and NMR spectra of products (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: Xiao-Feng.Wu@catalysis.de.

ORCID [©]

Xiao-Feng Wu: 0000-0001-6622-3328

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Analytic support from Dr. W. Baumann, Dr. C. Fisher, S. Buchholz, S. Schareina, and Matthias Auer is gratefully acknowledged. We also appreciate general support from Professors Matthias Beller and Armin Börner in LIKAT.

REFERENCES

 (1) (a) Aresta, M.; Dibenedetto, A.; Angelini, A. Chem. Rev. 2014, 114, 1709–1742.
 (b) Aresta, M. Coord. Chem. Rev. 2017, 334, 150– 183.
 (c) Wang, W.-H.; Himeda, Y.; Muckerman, J. T.; Manbeck, G. F.; Fujita, E. Chem. Rev. 2015, 115, 12936–12973.

(2) For selected reviews on carbonylation, see: (a) Kollär, L. Modern Carbonylation Methods; Wiley-VCH: Weinheim, 2008. (b) Barnard, C. F. J. Organometallics 2008, 27, 5402-5422. (c) Brennfuhrer, A.; Neumann, H.; Beller, M. Angew. Chem., Int. Ed. 2009, 48, 4114-4133. (d) Wu, X. F.; Neumann, H.; Beller, M. Chem. Soc. Rev. 2011, 40, 4986-5009. (e) Wu, X.-F.; Neumann, H. ChemCatChem 2012, 4, 447-458. (f) Gabriele, B.; Mancuso, R.; Salerno, G. Eur. J. Org. Chem. 2012, 2012, 6825-6839. (g) Wu, X. F.; Neumann, H.; Beller, M. Chem. Rev. 2013, 113, 1-35. (h) Peng, J.-B.; Qi, X.; Wu, X.-F. ChemSusChem 2016, 9, 2279-2283.

(3) For selected reviews on carbonylation using CO surrogates, see: (a) Morimoto, T.; Kakiuchi, K. Angew. Chem., Int. Ed. 2004, 43, 5580-5588. (b) Odell, L. R.; Russo, F.; Larhed, M. Synlett 2012, 23, 685-698. (c) Konishi, H.; Manabe, K. Synlett 2014, 25, 1971-1986. (d) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. Angew. Chem., Int. Ed. 2014, 53, 6310-6320. (e) Gautam, P.; Bhanage, B. M. Catal. Sci. Technol. 2015, 5, 4663-4702. (f) Sam, B.; Breit, B.; Krische, M. J. Angew. Chem., Int. Ed. 2015, 54, 3267-3274. (g) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. Acc. Chem. Res. 2016, 49, 594-605. (h) Peng, J.-B.; Qi, X.; Wu, X.-F. Synlett 2017, 28, 175-194. (i) Cao, J.; Zheng, Z.-J.; Xu, Z.; Xu, L.-W. Coord. Chem. Rev. 2017, 336, 43-53. (4) (a) Peng, J.-B.; Qi, X.; Wu, X.-F. Synlett 2017, 28, 175-194. (b) Seo, Y.-S.; Kim, D.-S.; Jun, C.-H. Chem. - Asian J. 2016, 11, 3508-3512. (c) Ren, W.; Chang, W.; Dai, J.; Shi, Y.; Li, J.; Shi, Y. J. Am. Chem. Soc. 2016, 138, 14864-14867. (d) Hou, J.; Xie, J.-H.; Zhou, Q.-L. Angew. Chem., Int. Ed. 2015, 54, 6302-6305. (e) Qi, X.; Li, C.-L.; Jiang, L.-B.; Zhang, W.-Q.; Wu, X.-F. Catal. Sci. Technol. 2016, 6, 3099-3107. (f) Qi, X.; Li, C.-L.; Wu, X.-F. Chem. - Eur. J. 2016, 22, 5835–5838. (g) Jiang, L.-B.; Li, R.; Li, H.-P.; Qi, X.; Wu, X.-F. ChemCatChem 2016, 8, 1788–1791. (h) Qi, X.; Jiang, L.-B.; Li, C.-L.; Li, R.; Wu, X.-F. Chem. - Asian J. 2015, 10, 1870–1873. (i) Qi, X.; Jiang, L.-B.; Li, H.-P.; Wu, X.-F. Chem. - Eur. J. 2015, 21, 17650–17656. (j) Qi, X.; Li, H.-P.; Wu, X.-F. Chem. - Asian J. 2016, 11, 2453–2457. (k) Qi, X.; Li, R.; Wu, X.-F. RSC Adv. 2016, 6, 62810–62813. (l) Jiang, L.-B.; Qi, X.; Wu, X.-F. Tetrahedron Lett. 2016, 57, 3368–3370.

(5) (a) Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu,
I. Org. Lett. 2013, 15, 2794–2797. (b) Morgan, J. S. J. Chem. Soc.,
Trans. 1916, 109, 274–283. (c) Kaushik, S. M.; Rich, R. L.; Noyes, R.
M. J. Phys. Chem. 1985, 89, 5722–5825. (d) Bowers, P. G.; Hodes, K.
J. Phys. Chem. 1988, 92, 2489–2492.

(6) (a) Ye, S.; Wu, J. Chem. Commun. 2012, 48, 7753–7755. (b) Ye, S.; Wu, J. Chem. Commun. 2012, 48, 10037–10039. (c) Li, W.; Li, H.; Langer, P.; Beller, M.; Wu, X.-F. Eur. J. Org. Chem. 2014, 2014, 3101–3103. (d) Zheng, D.; Li, Y.; An, Y.; Wu, J. Chem. Commun. 2014, 50, 8886–8888. (e) Ye, S.; Wang, H.; Xiao, Q.; Ding, Q.; Wu, J. Adv. Synth. Catal. 2014, 356, 3225–3230. (f) An, Y.; Zheng, D.; Wu, J. Chem. Commun. 2014, 50, 11746–11748. (g) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Angew. Chem., Int. Ed. 2014, 53, 10204–10208. (h) Li, W.; Beller, M.; Wu, X.-F. Chem. Commun. 2014, 50, 9513–9516.