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Authors: Yu-Feng Liang, Ralf Steinbock, Annika Münch, Dietmar Stalke, and Lutz Ackermann

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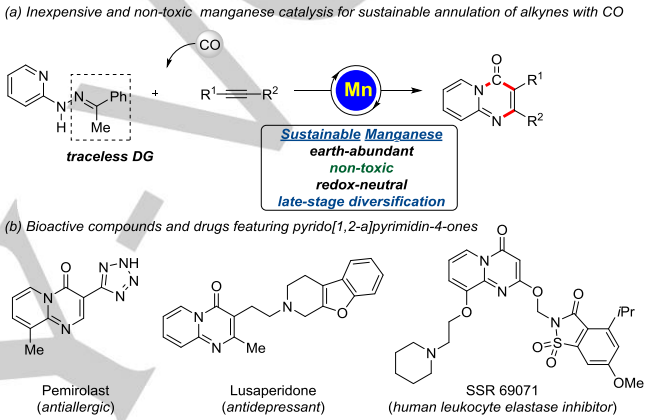
Manganese-Catalyzed Carbonylative Annulations for Redox-Neutral Late-Stage Diversification

Yu-Feng Liang, Ralf Steinbock, Annika Münch, Dietmar Stalke, and Lutz Ackermann*[a]

Abstract: *An inexpensive, non-toxic manganese catalyst enabled unprecedented redox-neutral carbonylative annulations under ambient pressure. The manganese catalyst outperformed all other typically used base and precious metal catalysts. The outstanding versatility of the manganese catalysis manifold was reflected by ample substrate scope, setting the stage for effective late-stage manipulations under racemization-free conditions on a wealth of marketed drugs and natural products, including alkaloids, amino acids, steroids and carbohydrates.*

Transition metal-catalyzed carbonylations of organic compounds with cost-effective carbon monoxide have emerged as a step-economical strategy to access carbonyl-containing molecules.[1] Among a variety of carbonylative transformations, chelation-assisted dehydrogenative annulations have been identified as an atom-economical approach for the synthesis of bioactive heterocycles.[2] To this end, oxidative carbonylative annulations have been accomplished with various heteroatom-containing groups, including imines,[3] amines,[4] anilines,[5] amides,[6] phenols,[7] or pyridines.[8] Despite these undisputable advances, major challenges remain to be addressed in order to unleash the full potential of this strategy. First, carbonylative alkyne annulations were thus far predominantly accomplished with the aid of precious transition metals, such as rhodium, palladium, iridium, and ruthenium, while the use of more sustainable earth-abundant 3d metal catalysts continues to be scarce.[9] Second, the oxidative nature of the dehydrogenative annulations calls for sacrificial oxidants, largely requiring (super)stoichiometric amounts of toxic metal oxidants. Third, the prerequisite directing groups are normally not integral part of the target molecules, translating into multi-step protocols for the directing group installation, manipulation and removal.[10] In sharp contrast, we have now uncovered a chelation-enabled[11] traceless carbonylative annulation by inexpensive manganese[12] catalysts,[13] setting the stage for a redox-neutral strategy towards pyrido[1,2-*a*]pyrimidin-4-ones (Scheme 1a) - ubiquitous structural motifs of medicinally-relevant compounds (Scheme 1b).[14] Notable features of our findings include (i) first manganese-catalyzed carbonylative alkyne annulations, (ii) a traceless directing group approach for external oxidant-free cyclizations, (iii) user-friendly syntheses of bioactive pyrido[1,2-*a*]pyrimidin-4-ones under ambient pressure and (iv) powerful late-stage diversifications of structurally complex natural products and drugs. It is furthermore noteworthy that the unique performance of the manganese[15] catalysis manifold was reflected by outperforming typically used noble rhodium, ruthenium, palladium, and iridium catalysts – a strong testament to the outstanding power of sustainable manganese catalysis with the third most earth abundant transition metal.



Scheme 1. Manganese-catalyzed carbonylative annulations.

We initiated our studies by probing various reaction conditions for the envisioned carbonylative annulation of 2-pyridyl hydrazone **1a** and alkyne **2a** (Table 1, and Table S1 in the Supporting Information). Thus, among a variety of transition metal compounds, $Mn_2(CO)_{10}$ emerged as the only catalytically competent complex. In sharp contrast, commonly used catalysts based on cobalt, ruthenium, rhenium, iron, molybdenum, rhodium, nickel, palladium or iridium fell short in providing the desired product **3aa**, illustrating the unique performance of the manganese catalysis regime. Toluene proved to be the solvent of choice for the thermal[16] annulation, and the connectivity of the product **3aa** was unambiguously established by single-crystal X-ray diffraction. A set of control experiments confirmed the essential nature of the manganese catalyst.

[*] Dr. Y.-F. Liang, R. Steinbock, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstraße 2, 37077 Gottingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de/

A. Münch, Prof. Dr. D. Stalke,
Institut für Anorganische Chemie
Georg-August-Universität Göttingen
Tammannstraße 4, 37077 Göttingen (Germany)
E-mail: dstalke@chemie.uni-goettingen

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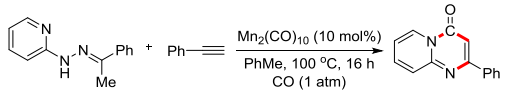
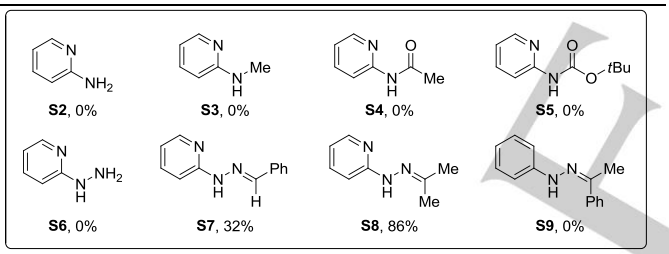
Table 1. Establishing carbonylative alkyne annulation.[a]



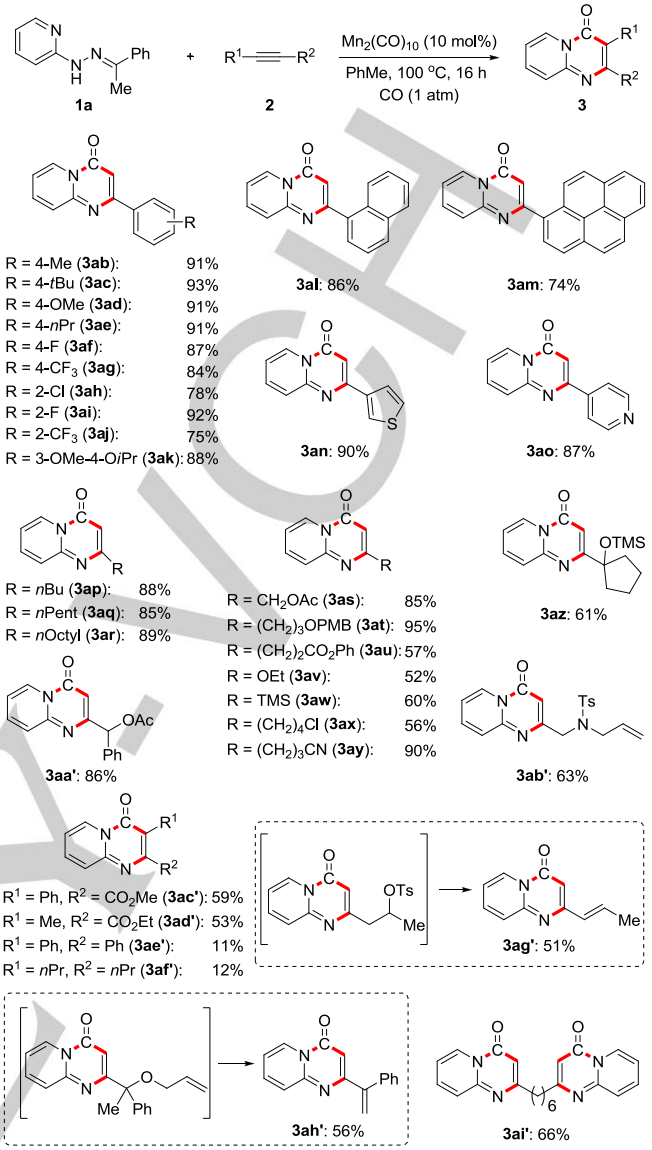
1a **2a** **3aa**: 91%

Entry	Deviation from standard conditions	Yield of **3aa** [%][b]
1	**S2**–**S9** instead of **1a**	Listed below
2	Without $Mn_2(CO)_{10}$	0
3	$MnCl_2$ instead of $Mn_2(CO)_{10}$	0
4	$Mn(OAc)_2$ instead of $Mn_2(CO)_{10}$	0
5	$Co_2(CO)_8$ instead of $Mn_2(CO)_{10}$	0
6	$Ru_3(CO)_{12}$ instead of $Mn_2(CO)_{10}$	0
7	$Re_2(CO)_{10}$ instead of $Mn_2(CO)_{10}$	0
8	$Cp_2Fe_2(CO)_4$ instead of $Mn_2(CO)_{10}$	0
9	$Mo(CO)_6$ instead of $Mn_2(CO)_{10}$	0
10	$Rh_2Cl_2(CO)_4$ instead of $Mn_2(CO)_{10}$	0
11	$Pd(OAc)_2$ instead of $Mn_2(CO)_{10}$	0
12	$Ni(COD)_2$ instead of $Mn_2(CO)_{10}$	0
13	$[Cp^*IrCl_2]_2$ instead of $Mn_2(CO)_{10}$	0
14	1,4-Dioxane instead of PhMe	86
15	DMF instead of PhMe	0
16	$PhCF_3$ instead of PhMe	54
17	80 °C instead of 100 °C	75
18	Reaction carried out in dark	91



[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $Mn_2(CO)_{10}$ (10 mol%), PhMe (1.0 mL), CO (1 atm), 100 °C, 16 h. [b] Yield of isolated products.[20]

With the optimized manganese catalyst in hand, we next tested its versatility with diversely decorated alkynes **2** (Scheme 2). The outstanding robustness of our carbonylative alkyne annulation was thus mirrored by fully tolerating a wealth of sensitive functional groups, including ester, chloro, thiophene, pyridino or cyano substituents. The widely applicable manganese catalyst was further amenable to both terminal and internal alkynes with excellent levels of chemo-, positional- and regio-selectivity control. In addition to aryl and alkyl alkynes, diynes were identified as viable substrates, thereby delivering the bispyrido[1,2-*a*]pyrimidin-4-one **3ai'** in a single step.



Scheme 2. Redox-neutral carbonylative annulation of alkynes **2.**

We were pleased to find that a variety of hydrazones **1** could be efficiently employed in the redox-neutral alkyne annulation, again featuring high functional group tolerance (Scheme 3). It is particularly noteworthy that medicinally relevant purines[17] could be functionalized to form the annulated product **3pa**, the molecular structure of which was unambiguously confirmed by X-ray diffraction analysis.

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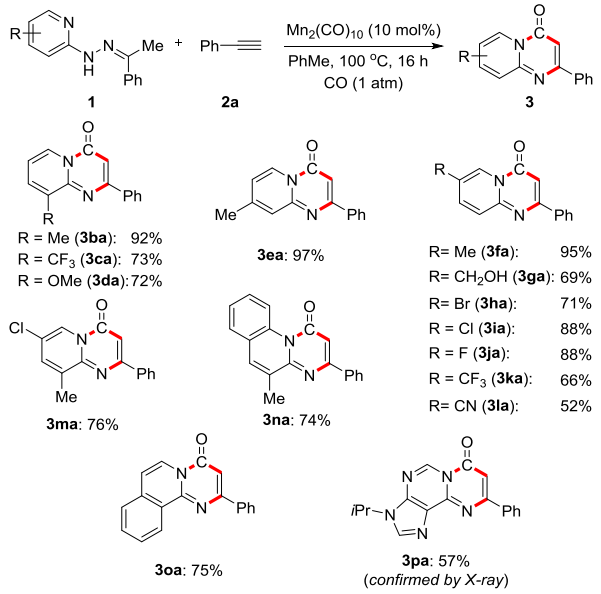
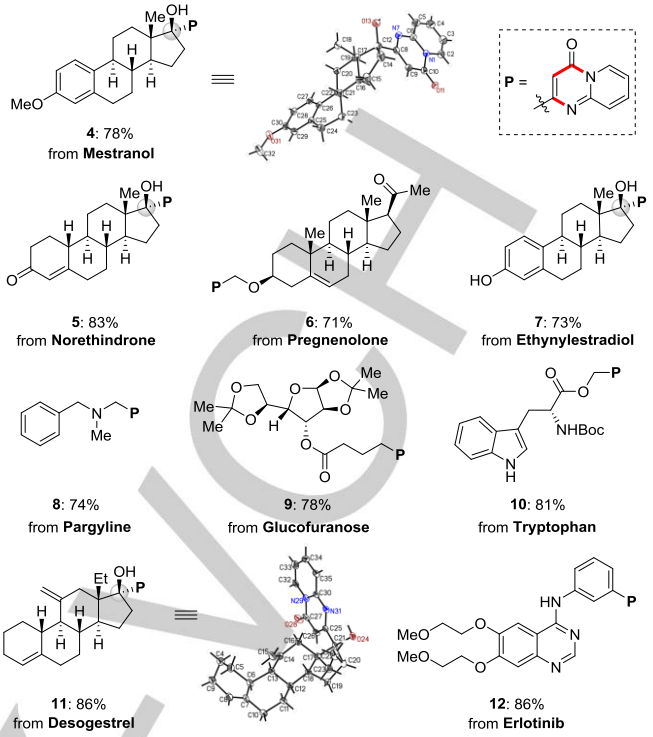


Scheme 3. Hydrazones **1** for traceless alkyne annulation.[20]

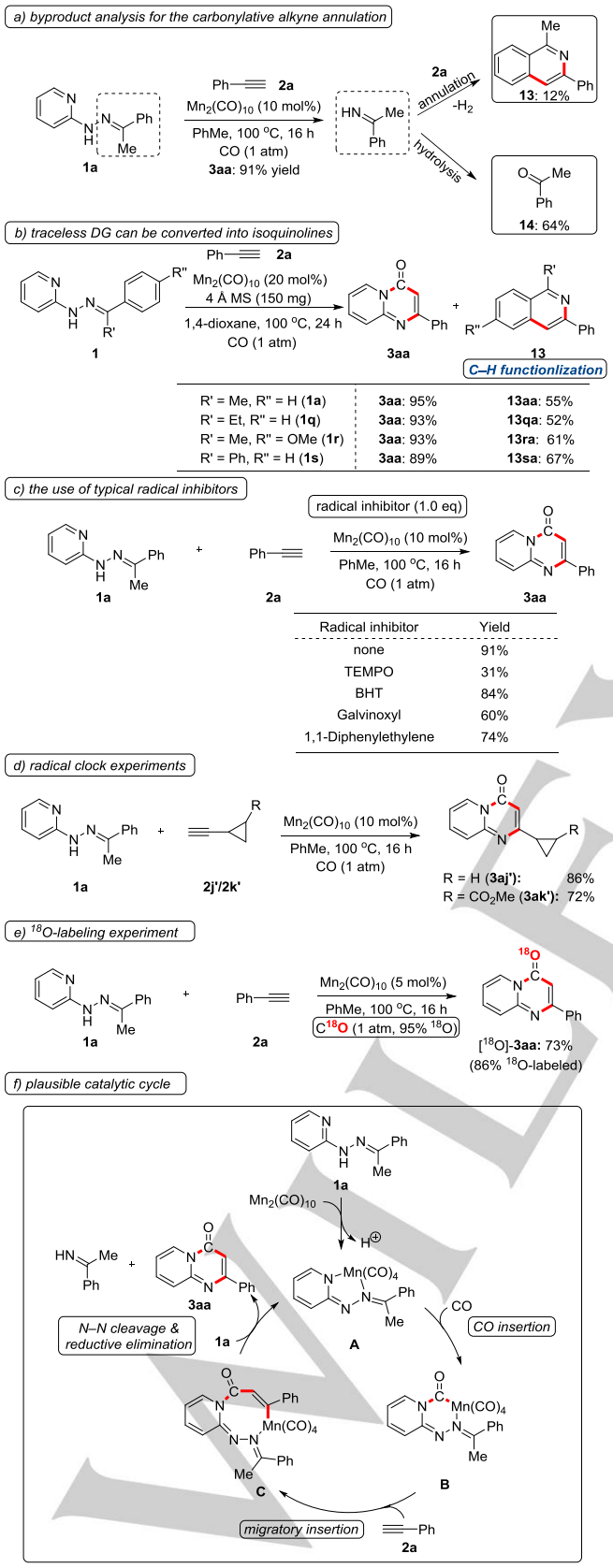
The late-stage manipulation of natural products and synthetic drugs is of key importance for the identification of bioactive compounds with improved properties.[18] Hence, we were particularly delighted to find that the outstanding versatility of our manganese-catalyzed carbonylative annulation set the stage for the late-stage diversification of structurally complex drug molecules of prominence in pharmaceutical industries and medicinal chemistry (Scheme 4). Specifically, the estrogen prodrug Mestranol chemo-selectively underwent the redox-neutral alkyne annulation without racemization of the stereogenic centers, as confirmed by single-crystal X-ray diffraction analysis. Yet, the manganese catalysis regime was not restricted to Mestranol modifications. Indeed, a wealth of structurally complex drugs and natural products could be smoothly converted to the desired products **4**–**12** in a traceless fashion. To this end, progesterone drug Norethindrone, endogenous steroid Pregnenolone, orally-active estrogen Ethynylestradiol, monoamine oxidase inhibitor Pargyline, carbohydrate glucofuranose, α-amino acid tryptophan, oral contraceptive Desogestrel, and tyrosine kinase inhibitor Erlotinib were identified as viable substrates. The structural diversity of the thus obtained products within a variety of natural product classes is a strong testament to the robustness of the manganese-catalyzed alkyne annulation, with major potential for applications to medicinal chemistry and biomolecular sciences as well as pharmaceutical and agrochemical industries.



Scheme 4. Late-stage diversification of structurally complex natural products and drugs.[20]

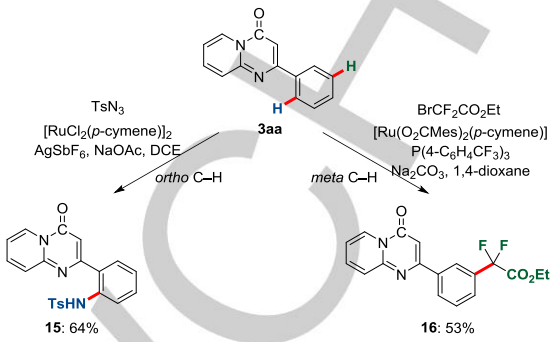
Given the unique versatility of the manganese-catalyzed carbonylative alkyne annulation, we became intrigued by delineating its mode of action. To this end, mass spectrometric analysis provided support for a bidentate coordination of the hydrazones **1** (Figure S-1 in the Supporting Information). The traceless nature of our chelation assisted manifold was confirmed by careful analysis of the crude reaction mixture, revealing the formation of by-products **13** and **14** (Scheme 5a), the latter of which being formed by C–H/N–H functionalization.[12l] These observations were then exploited for the development of an unprecedented complexity-increasing double alkyne annulation, which provided atom-economical access to isoquinolines and pyridopyrimidinones in a single reaction (Scheme 5b). The use of typical radical scavengers indicated homolytic bond cleavages not to be operative (Scheme 5c), which was further supported by the complete conservation of the cyclopropyl motif in the radical clock-type substrates **2j'** and **2k'** (Scheme 5d). Detailed kinetic analysis by *in-operando* infrared-spectroscopy did not reveal a significant induction period, but rather a sigmoidal curve (Figure S-2 in the Supporting Information). In addition, the kinetic profile of the carbonylative alkyne annulation was not affected by the CO pressure (Figure S-3 in the Supporting Information), being indicative of the CO insertion not to be rate-determining. Experiments with isotopically ^{18}O-labeled CO clearly showed that the carbonyl moiety in the products largely originated from gaseous CO (Scheme 5e). Based on our mechanistic studies, we propose a plausible catalytic cycle to commence by an initial coordination of the manganese catalyst by the hydrazone **1** to afford the complex **A** (Scheme 5f), as was supported by high resolution mass spectrometry. Subsequently, facile insertion of CO generates key intermediate **B**, while migratory insertion of alkyne **2** delivers the eight-membered metalacycle **C**. Then, the key C–N formation is enabled by imine extrusion, with proto-

demetalation regenerating the catalytically active manganese complex **A**.



Scheme 5. Key mechanistic findings and proposed reaction mechanism.

Finally, the synthetic utility of our manganese-catalyzed carbonylative annulation was highlighted by ruthenium(II)-catalyzed C–H activation of the thus obtained products **3** in a bifurcating *ortho*- or remote *meta*-fashion[19] (Scheme 6).



Scheme 6. Post modification by *ortho*- and *meta*-C–H functionalizations.

In summary, we have devised the unprecedented manganese-catalyzed carbonylative alkyne annulation in a redox-neutral fashion. The traceless approach avoids the use of stoichiometric toxic metal oxidants and enables the assembly of bioactive pyridopyrimidinones in a modular fashion. Detailed mechanistic studies have provided support for a facile CO insertion. The manganese catalyst outperformed all other typically used catalysts based on base and precious transition metals. The outstanding synthetic utility of our manganese catalysis was reflected by the versatile late-stage diversification of numerous marketed drugs and natural products, including steroids, alkaloids, amino acids and carbohydrates.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation • traceless • annulation • manganese • late-stage

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[20] CCDC 1586715 (**3aa**), 1586714 (**3pa**), 1586951 (**4**), and 1587175 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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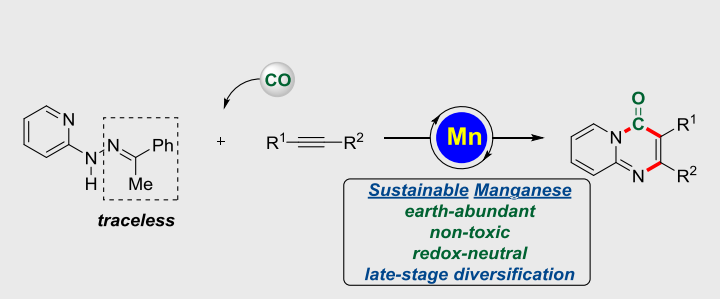

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Smart Man: Traceless carbonylative annulations by sustainable manganese catalysis set the stage for enabling late-stage diversification in a redox-neutral fashion.