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Rhodium-catalyzed hydroformylation of alkynes employing a self-assembling ligand system†

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Hydroformylation of alkynes is an underdeveloped atom-economic and redox-neutral method to prepare enals. Applying a new electron poor self-assembling ligand system provides the first general rhodium-catalyst for the chemo- and stereoselective hydroformylation of dialkyl- as well as diaryl-substituted alkynes to furnish enals in excellent chemo- and stereoselectivity.

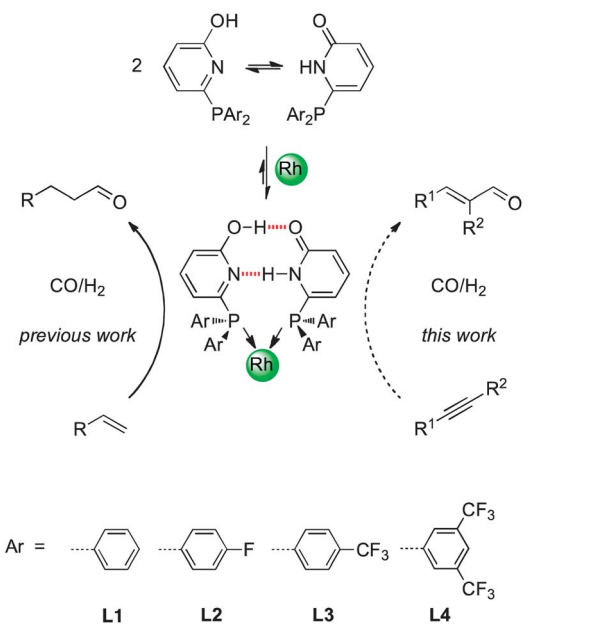
The hydroformylation of olefins is one of the most important industrial applications of homogeneous catalysis with about 9 million tons of oxo products produced annually. From a synthetic point of view, this reaction is highly attractive due to its intrinsic atom economy, enabling the functionalization of an alkene through carbon–carbon bond formation employing synthesis gas as an inexpensive carbon source.[1] The aldehydes generated are valuable intermediates that enable synthetic transformations, and can even be used in tandem reactions.[2] Even though the hydroformylation reaction celebrates its 75th anniversary this year, being discovered in 1938 by Otto Roelen,[3] many selectivity issues remain to be solved to unravel its full synthetic potential.

Inspired by DNA-base pairing, we have developed self-assembling bidentate ligand systems relying on complementary hydrogen bonding. In particular, ligands based on the pyridone/hydroxypyridine tautomer system form highly active and regioselective rhodium catalysts for linear regioselective alkene hydroformylation (Scheme 1).[4] These catalysts enable extraordinarily mild reaction conditions (ambient pressure and room temperature) to be used,[5] which has led to their application in natural product synthesis.[6]

While hydroformylation of alkenes has been widely studied, the corresponding hydroformylation of alkynes is less developed.[7] Despite this, direct alkyne hydroformylation offers an atom and redox economic approach for the production of synthetically versatile enals.[8] Most known synthetic approaches employ either reduction and/or oxidation steps which are not redox efficient.[9,10] An exception is the elegant ruthenium-catalyzed redox neutral isomerization of propargylic alcohols to enals developed by Trost and Livingston (Scheme 2).[11]

Early studies on the hydroformylation of alkynes found that the reaction occurred with poor chemoselectivity and low yields because the formation of hydrogenated products could not be suppressed.[12] During the past two decades, more efficient catalysts have been reported such as the rhodium/Biphephos system introduced by Buchwald *et al.*[13] This catalyst allows chemoselective hydroformylation of symmetrical dialkyl-substituted alkynes. However, with diaryl-substituted alkynes poor chemoselectivity is observed due to alkyne hydrogenation.

A heterobimetallic catalyst $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$ developed by Hidai *et al.*[14] required harsh reaction conditions and suffered from chemoselectivity problems (hydrogenation) as well as problems with *E*/*Z*-selectivity. Alper and Van den



Scheme 1 Self-assembling catalyst systems for the hydroformylation of alkenes and alkynes.

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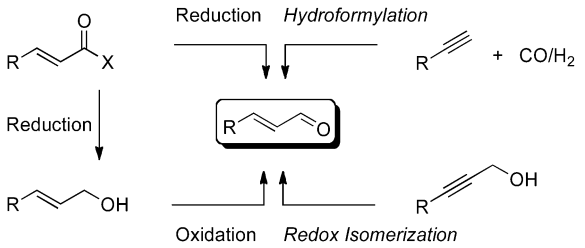
† Electronic supplementary information (ESI) available: Experimental procedures and detailed characterization data for all new compounds. CCDC 923423 and 923424. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc50725d



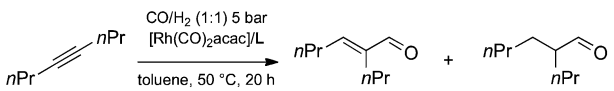
Scheme 2 Synthetic pathways to enals.

Hoven[15] used a zwitterionic rhodium/triphenylphosphite complex to allow the selective hydroformylation of thiophenyl substituted alkynes. However, a catalyst that enables chemo- and stereoselective hydroformylation of diarylalkynes and terminal arylalkynes is unknown.

We herein report that new electron-poor self-assembling ligands (**L2–L4**, Scheme 1) based on the pyridone/hydroxypyridine platform furnish a highly active rhodium catalyst that enables the chemo- and stereoselective hydroformylation of dialkyl-, diarylalkynes to produce *E*-enals in good to excellent yields.

We commenced our investigation by studying the hydroformylation of 4-octyne. While rhodium catalysts derived from triphenylphosphine did not show any reactivity under the reaction conditions chosen, the 6-DPPon (**L1**) derived catalyst furnished the desired enal with low conversion but high chemo- and stereoselectivity (Table 1, entries 1 and 2). In order to increase the catalyst activity, we speculated, whether analogous to alkene hydroformylation, increasing the ligand's π-acceptor ability may increase the catalyst activity.[1] We therefore prepared and tested the acceptor substituted 6-DPPon ligands **L2–L4** (Scheme 1).†

Table 1 Hydroformylation of 4-octyne (**1a**)[a]



1a **2a** **3a**

Entry	L	Conv. (%)[c]	**2a** : **3a**[c]
1	PPh_3	0	— : —
2	6-DPPon (**L1**)	2	100 : 0
3	**L2**	20	100 : 0
4	**L3**	54	98 : 2
5	**L4**	95	97 : 3
6[b]	Biphephos	51	95 : 5

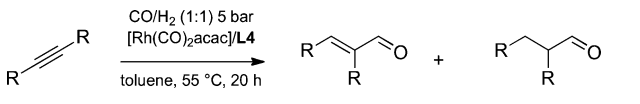
[a] Reaction conditions: CO/H_2 (1 : 1) 5 bar, $[Rh(CO)_2acac]$/**L**/4-octyne (**1a**) = 1 : 3 : 100 in 2 ml toluene, c_0(**1a**) = 0.6 M, 20 h at 50 °C. [b] Reaction conditions: CO/H_2 (1 : 1) 5 bar, $[Rh(CO)_2acac]$/**L**/4-octyne (**1a**) = 1 : 1.5 : 100 in 2 ml toluene, c_0(**1a**) = 0.6 M, 20 h at 55 °C. [c] The conversion and **2a** : **3a** product ratio were determined by GC and/or ^{1}H-NMR spectroscopy. 6-DPPon = 6-diphenylphosphinopyridin-2(1*H*)-one.

Pleasingly, applying the *para*-fluoro-substituted ligand **L2**, a tenfold increase in catalyst activity compared to the 6-DPPon ligand **L1** was noted (Table 1, entry 3). Increasing the electron withdrawing strength further (**L3**, **L4**) led to a further increase in catalyst activity (entries 4 and 5), with ligand **L4** providing the most active catalyst. This new catalyst system is twice as active as the best described previously (rhodium/Biphephos, entry 6).[13]

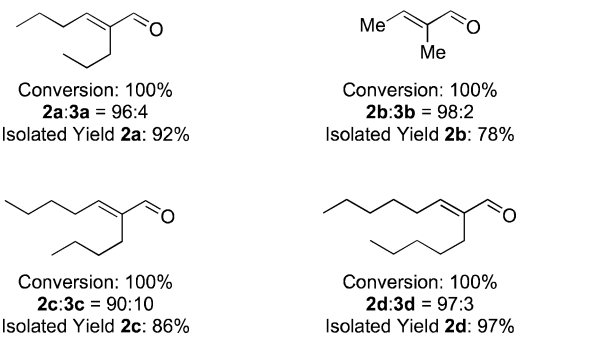
Increasing the temperature to 55 °C allowed the chemo- and stereoselective hydroformylation of different dialkyl substituted alkynes, including 2-butyne, to give the corresponding *E*-enals **2a–d** in good to excellent yields (Table 2).

We next turned our attention to the challenging diarylalkynes. The hydroformylation of tolane (**4a**) was studied first. The rhodium/Biphephos system gave complete conversion, however, a mixture of products was obtained (Scheme 3). In addition to the desired enal **5a** (58%), the corresponding saturated aldehyde (14%) and *cis*-stilbene **6a** (28%) were formed. Conversely, employing our self-assembly ligand **L4** under otherwise identical conditions, the desired enal **5a** was obtained in 93% yield, while enal and alkyne hydrogenation were largely suppressed (Scheme 3).

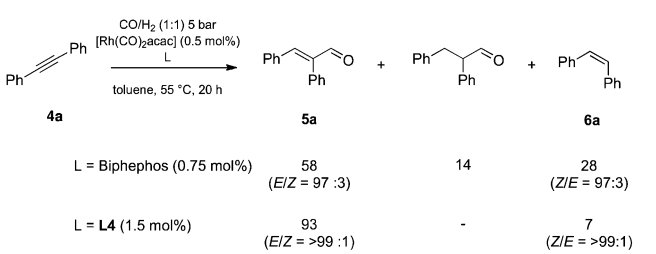
Table 2 Hydroformylation of symmetrical aliphatic substituted internal alkynes[a]



1a-d **2a-d** **3a-d**

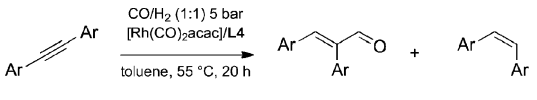


[a] Reaction conditions: CO/H_2 (1 : 1) 5 bar, $[Rh(CO)_2acac]$/**L4**/**1a–d** = 1 : 3 : 100 in 2 ml toluene, c_0(**1a–d**) = 0.6 M, 20 h at 55 °C. The conversion and product ratio were determined by GC and/or ^{1}H-NMR spectroscopy.

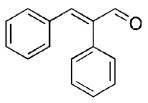


Scheme 3 Hydroformylation of tolane with rhodium/Biphephos and rhodium/**L4** catalysts.

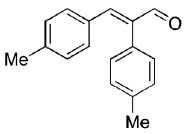
Table 3 Hydroformylation of symmetrical aryl substituted internal alkynes[a]



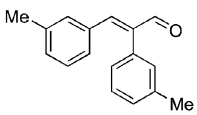
4a-n **5a-n** **6a-n**



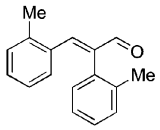
Conversion: 100%
5a:**6a** = 93:7
Isolated Yield **5a**: 92%



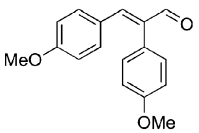
Conversion: 100%
5b:**6b** = 97:3
Isolated Yield **5b**: 93%



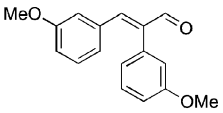
Conversion: 100%
5c:**6c** = 94:6
Isolated Yield **5c**: 86%



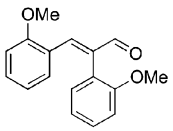
Conversion: 100%
5d:**6d** = 96:4
Isolated Yield **5d**: 93%



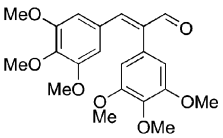
Conversion: 100%
5e:**6e** = 98:2
Isolated Yield **5e**: 92%



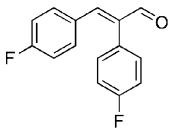
Conversion: 100%
5f:**6f** = 91:9
Isolated Yield **5f**: 90%



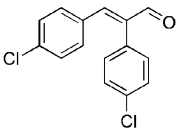
Conversion: 100%
5g:**6g** = 95:5
Isolated Yield **5g**: 78%



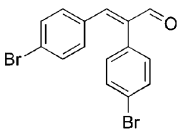
Conversion: 69%
5h:**6h** = 100:0
Isolated Yield **5h**: 61%



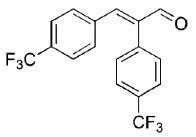
Conversion: 100%
5i:**6i** = 92:8
Isolated Yield **5i**: 90%



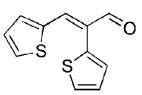
Conversion: 100%
5j:**6j** = 83:17
Isolated Yield **5j**: 78%



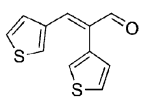
Conversion: 100%
5k:**6k** = 84:16
Isolated Yield **5k**: 78%



Conversion: 83%
5l:**6l** = 58:42
Isolated Yield **5l**: 33%



Conversion: 100%
5m:**6m** = 88:12
Isolated Yield **5m**: 82%



Conversion: 100%
5n:**6n** = 96:4
Isolated Yield **5n**: 91%

[a] Reaction conditions: CO/H_2 (1 : 1) 5 bar, $[Rh(CO)_2acac]$/**L4**/**4a–n** = 1 : 3 : 200 in 2 ml toluene, c_0(**4a–n**) = 0.6 M, 20 h at 55 °C. The conversion and product ratio were determined by GC and/or ^{1}H-NMR spectroscopy.

To explore the generality of our catalyst for diarylalkyne hydroformylation, a series of diarylalkynes obtained *via* Sonogashira coupling,[16] was subjected to hydroformylation. We were pleased to find that on applying our rhodium/**L4** catalyst all alkynes underwent efficient hydroformylation to furnish the corresponding diaryl-substituted *E*-enals in generally excellent yields (Table 3). Alkyne hydrogenation was mostly suppressed.

Only with electron poor aryl substituents was the amount of hydrogenation product significant (**4l**). Pleasingly, aryl bromides are tolerated, allowing for subsequent derivatization. The constitution and configuration of the enals were determined by NMR spectroscopy, and unambiguously confirmed in two cases (**5a** and **5i**) by X-ray crystallography.†

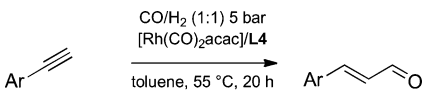
We also investigated the hydroformylation of terminal arylacetylenes, which have never been successfully hydroformylated before. Subjection of terminal alkynes **7a–c** to our hydroformylation conditions provided for the first time the corresponding *E*-enals **8a–c** in fair to good yields (Table 4). The enals could be separated *via* chromatography from other side products (saturated aldehydes, for details see the ESI†). In particular enal **8c** is of interest since it can be used for the synthesis of the natural product boropinol B (Scheme 4).[17]

Boropinol B has been isolated from the dried roots of the plant *Boronia pinnata*. Extracts from this plant, along with boropinol B, contained a number of other phenylpropanoide compounds displaying an inhibitory effect on tumor-promotion as well as significant inhibitory effects on Eppstein–Barr virus early antigen (EBV-EA) activation.[17]

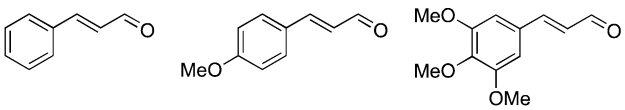
Our synthesis commenced from the commercially available aryl iodide **9**. Sonogashira cross coupling with TMS-acetylene furnished alkyne **10**. TMS-deprotection and hydroformylation gave enal **8c** in 62% isolated yield. Luche reduction of the aldehyde and etherification yielded boropinol B, which represents its first total synthesis.

In conclusion, we have reported the first general catalyst for the chemo- and stereoselective hydroformylation of dialkyl- as well as diaryl-substituted alkynes. Furthermore, for the first time terminal alkynes could be reacted to furnish *E*-enals in

Table 4 Hydroformylation of terminal aryl substituted alkynes[a]



7a-c **8a-c**

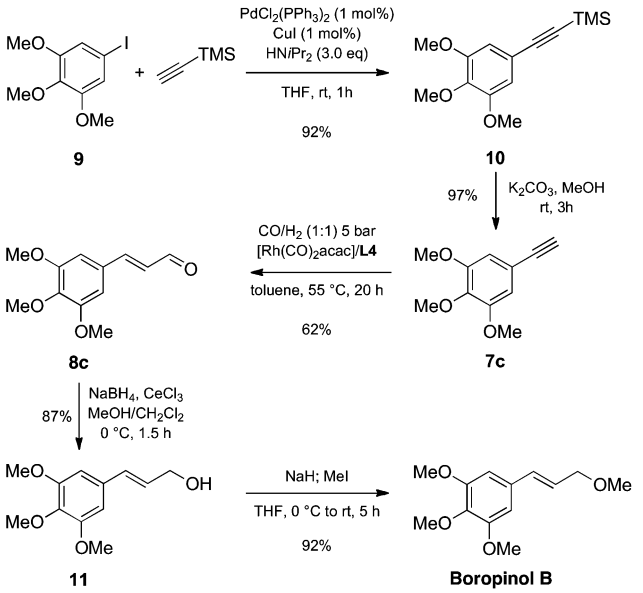


Conversion: 85%
Isolated Yield **8a**: 39%

Conversion: 92%
Isolated Yield **8b**: 45%

Conversion: 100%
Isolated Yield **8c**: 62%

[a] Reaction conditions: CO/H_2 (1 : 1) 5 bar, $[Rh(CO)_2acac]$/**L4**/**7a–c** = 1 : 3 : 100 in 2 ml toluene, c_0(**7a–c**) = 0.6 M, 20 h at 55 °C. The conversion was determined by GC and/or ^{1}H-NMR spectroscopy.



Scheme 4 Synthesis of boropinol B.

preparatively useful amounts. This has enabled a short and efficient first total synthesis of boropinol B.

Acknowledgements

This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038) and the Krupp Foundation. We thank Umicore, BASF and Wacker for generous gifts of chemicals. We also thank Andreas Filippi for technical support, Dr Manfred Keller for solution of the X-ray crystal structure and Dr Jörg Wieland for preliminary experiments.

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