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Tandem Regioselective Hydroformylation-Hydrogenation of Internal Alkynes employing a Supramolecular Catalyst

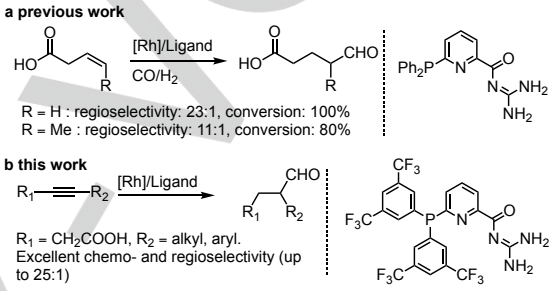
Weiwei Fang,[a] and Bernhard Breit*[a]

Abstract: New supramolecular ligands containing an acyl guanidine function were designed based on the strategy of increasing the π-acceptor ability of phosphine ligands by introducing electron-withdrawing groups. By applying this novel catalytic system, a general protocol for the Rh-catalyzed hydroformylation-hydrogenation of unsymmetrical internal alkynes functionalized with a carboxylic acid was expounded furnishing aliphatic aldehydes in high regio- and chemoselectivities. Control experiments are provided that prove the enzyme-like supramolecular catalyst mode of action.

*N*atural enzymes efficiently combine molecular recognition and catalysis in one functional assembly, which offers significantly higher rate constants and selectivities than corresponding bimolecular reactions due to the formation of enzyme-substrate complexes resulting in a transition state stabilization.[1] Inspired by this, supramolecular catalysis has been a long-term objective for chemists, with the ultimate goal to construct catalytic systems capable of mimicking natural enzymes.[2,3] Simple hydrogen bonding interactions between the substrate and functional groups of catalyst have shown to greatly improve the selectivity of transition metal catalysis.[4-9] In this context we recently reported on acyl guanidinium-functionalized phosphines[5,6], exhibiting excellent activities and regioselectivities in the Rh-catalyzed hydroformylation (HF) of vinylacetic acid[5a] and its analogues[5b], which furnished aliphatic aldehydes in good regioselectivities (Scheme 1a). However, limitations of this catalyst system became apparent when we attempted to use internal alkenes. Hence, only a methyl-substituted *Z*-configured substrate could be utilized which sets narrow synthetic limitations. Since a *Z*-configured alkene is generally obtained from an internal alkyne through *cis*-hydrogenation employing a Lindlar-type catalyst, we envisioned whether we could employ internal alkynes directly. With an appropriate supramolecular catalyst, a corresponding tandem regioselective HF-hydrogenation might furnish the same type of products with a largely extended substrate scope.

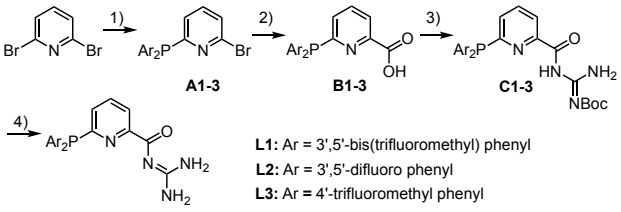
In the past decades, the HF of unsymmetrical internal alkynes has been widely neglected to date and only very few examples were reported with rather low regioselectivity.[10] In 2013, we introduced a Rh/self-assembling ligand system for chemoselective HF of symmetrical and terminal alkynes with excellent stereoselectivity.[11g] Therefore, the design of new types of phosphine ligands for highly regioselective HF of unsymmetrical internal alkynes is a great challenge in this area at current stage.

In continuation of our long-standing research interests in developing supramolecular concepts for homogeneous catalysis [5,6,11], we herein report on new appropriately designed electron-poor phosphine ligands equipped with an acyl guanidine functionality. Using this new supramolecular catalyst system, tandem Rh-catalyzed HF-hydrogenation of unsymmetrical internal alkynes functionalized with carboxylic acid was realized in high regio- and chemoselectivity providing facile access to aliphatic aldehydes (Scheme 1b).



Scheme 1. Rh-catalyzed HF-hydrogenation of unsymmetrical internal alkynes using a supramolecular ligand

We commenced our investigation by designing new phosphine ligands with enhanced π-acceptor ability.[11g] We reckoned that the introduction of additional electron-withdrawing groups such as CF_3 and F to the aryl substituents at the phosphine scaffold could enhance the coordination ability of the catalyst to alkynes while simultaneously facilitating CO dissociation, resulting in higher catalytic activity (Scheme 2a). Moreover, the installation of the acyl guanidinium group (as a recognition unit for carboxylic acid) in the *meta* position with respect to the phosphine unit would allow for two-point binding and thus conformational orientation of the substrate via hydrogen bonding interactions.[5a]



Scheme 2. Ligand synthesis: 1) *n*BuLi, -78 °C, DCM; Ar_2PCl. 2) *n*BuLi, -78 °C, DCM; CO_2. 3) Boc-guanidine, N-methyl morphine, BOP, DMF and 4) TFA, 1,3-dimethoxybenzene; Na_2CO_3.

The general synthetic protocol for accessing the respective ligands **L1-3** is depicted in Scheme 2. Compounds **A1-3** were easily formed by coupling of the corresponding chloro diarylphosphines with mono-lithiated 2,6-dibromopyridine. Bromine lithium exchange of **A1-3** followed by quenching with CO_2 furnished the carboxylic acids **B1-3**. The coupling reaction between **B1-3** and mono-Boc-protected guanidine led to **C1-3**.

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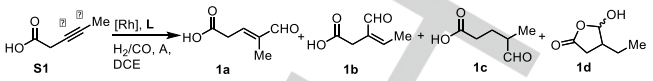
Subsequent deprotection and neutralization furnished pure ligands **L1-3** as colorless solids.

To evaluate catalytic performances of the new ligands in regioselective HF-hydrogenation of unsymmetrical internal alkynes, 3-pentynoic acid **S1** was selected as a model substrate (Table 1). When the reaction was performed in toluene at 55 °C with 1 mol% of [$Rh(CO)_2acac$] and 5 mol% of **L1** under 6 bar of CO/H_2 (1:1), low conversion (11%) was obtained and an α,β-unsaturated aldehyde **1a** was obtained as the main product in excellent regioselectivity (γ/β >25) (Entry 1). In consideration of complete protonation of the acyl guanidinium function to incease the hydrogen bonding interaction between the ligand and substrate[6a], 5 mol% TsOH was added. Gladly, the conversion of **S1** increased to 79% and the main product was changed to the aliphatic aldehyde **1c**, however the ratio of γ/β decreased (Table S1). Other solvents such as DCE, CH_2Cl_2 and THF were examined with DCE providing the most promising result (Entry 2). Furthermore, the addition of acid co-catalysts showed a significant effect on the reaction results: stronger acids such as TFA and CSA led to **1c** in a higher yield with excellent regioselectivity (Entries 4 and 5), and similar results to that of TsOH were obtained when TfOH, MsOH and $PhSO_3H$ were used. Conversely, using much weaker acids such as AcOH and H_3PO_4 only resulted in very poor results (Table S3). For operational simplicity, crystalline CSA was chosen for further optimization of reaction conditions. Decreasing the amount of CSA from 5 to 2.5 mol% resulted in a lower conversion and chemoselectivity of **1c** (96% vs. 26%), but the regioselectivity remained unaffected (γ/β >25, Table S4, for reaction temperature effect see Table S5). The reaction time could be shortened to 12 h with similar results (Entries 5 and 7). As expected, the electron withdrawing groups of ligands showed a significant effect on the activity and selectivity of the supramolecular catalyst systems. **L1** with the strongest electron withdrawing ability proved to be the best ligand, which clearly confirmed our initial strategy used in the ligand design (Entries 7-13). The parent diphenylphosphine-substituted ligand **L5** did not show any catalytic activity at all (Entry 11).

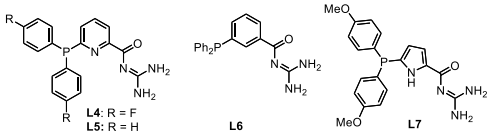
With the optimized conditions in hand, we sought to examine the general scope of the supramolecular catalytic protocol. As shown in Table 2, a variety of unsymmetrical internal alkynes underwent efficient HF-hydrogenation processes, affording corresponding aliphatic aldehydes in good to excellent yields with outstanding chemo- and regioselectivity. The chain length of the R group (**1c**-**6c**) hardly affected the efficiency and selectivity, and the desired aldehydes were obtained in 90-94% yields with regioselectivity up to 25:1. However, a bulkier secondary alkyl substituent decreased chemo- and regioselectivity (**2c** vs. **7c**) but still favored the formation of the γ-product with a quite remarkable selectivity of 7:1. Substrates with functional groups such as PMB ethers and even unprotected hydroxyl groups were well tolerated and products with good regioselectivity were observed, but in slightly lower yield (**8c** and **9**). Unexpectedly, when 6-hydroxy-3-hexynoic acid **S9** was used, the butenolide **9a'** was formed, which has shown to have interesting hepatoprotective properties.[12] Its formation might involve attack of the free hydroxyl group at the rhodium-acyl intermediate

Table 1. Reaction optimization[a]



Entry	L	A	Yields/% (**1a**/**1b**/**1c**/**1d**)	Select. **1c**/%	Ratio (γ/β)	Conv. /%
1[b]	**L1**	\	10/<1/0/0	0	>25	11
2	**L1**	TsOH	1/<1/87/11	85	7	99
3	**L1**	TfOH	36/<1/46/1	53	>25	94
4	**L1**	TFA	0/0/96/3	96	28	100
5	**L1**	CSA	0/0/96(**90**)/4	96	25	100
6	**L1**	MsOH	1/2/72/22	68	3	96
7[c]	**L1**	CSA	0/<1/95(**92**)/4	95	22	100
8[c]	**L2**	CSA	3/1/5/2	20	3	35
9[c]	**L3**	CSA	1/1/1/1	8	2	11
10[c]	**L4**	CSA	0/0/0/0	0	\	84
11[c]	**L5**	CSA	0/0/0/0	0	\	12
12[c]	**L6**	CSA	0/0/0/0	0	\	44
13[c]	**L7**	CSA	0/0/0/0	0	\	34

[a] [$Rh(CO)_2acac$]/**L**/additive/**S1** = 1:5:5:100, c(**S1**) = 0.5 M, DCE (2 mL), CO/H_2 (1:1, 6 bar), 55 °C, 20 h. Yield was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene (TMB) as the internal standard and isolated yield was shown in parentheses. Selectivity (Select.), ratio of γ/β [n(**a**+**c**)/n(**b**+**d**)] and conversion (conv.) were determined by analysis of the reaction mixture by NMR spectroscopy. [b] Toluene was used. [c] 12 h. DCE = 1,2-dichloroethane, TsOH = *p*-toluenesulfonic acid, TfOH = trifluoromethanesulfonic acid, CSA = camphorsulfonic acid, MsOH = methanesulfonic acid. $PhSO_3H$ = benzenesulfonic acid. AcOH = acetic acid



followed by a double bond isomerization forming the butenolide, which is a structural key element of a multitude of pharmaceuticals.[13]

Next, we turned our attention to the HF-hydrogenation of unsymmetrical internal aryl alkynes. For these substrates a higher pressure of syngas (10 bar) was necessary to achieve high yields and chemoselectivity. 4-Phenyl-3-butynoic acid **S10** furnished the desired aldehyde **10c** in 79% yield with good chemo- and regioselectivity (95%, γ/β up to 25:1). For substituted aryls, the relative position of the substituent on the phenyl ring affected the chemoselectivity (**11c** vs. **12c** and **13c**), but excellent regioselectivity was maintained throughout all substitution patterns (γ/β up to 25:1). Substrates with electron withdrawing groups (such F and CF_3) revealed higher chemoselectivity rather than those having an electron donating group (OMe) (96% and 95% vs. 90%, **15c** and **16c** vs. **14c**) and

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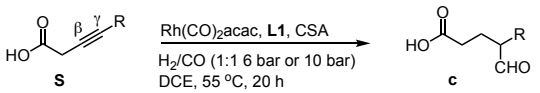
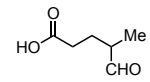
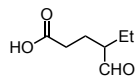
all displayed high γ-regioselectivity. Polyaromatic- and heterocyclic substituents were also well tolerated (**17c** and **18c**).

Table 2. Substrate scope.[a]

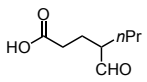




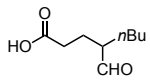
1c
Conv. >99%
Yield: 90%
Select.: 96%
γ/β: >25:1



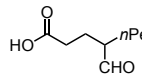
2c
Conv. >99%
Yield: 94%
Select.: 99%
γ/β: >25:1



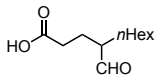
3c
Conv. >99%
Yield: 90%
Select.: 95%
γ/β: 19:1



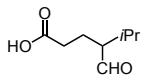
4c
Conv. >99%
Yield: 92%
Select.: 94%
γ/β: 22:1



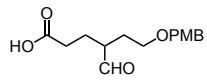
5c
Conv. >99%
Yield: 90%
Select.: 97%
γ/β: >25:1



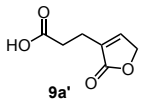
6c
Conv. >99%
Yield: 90%
Select.: 94%
γ/β: >25:1



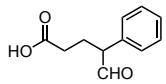
7c
Conv. >99%
Yield: 65%
Select.: 85%
γ/β: 7:1



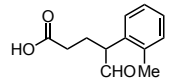
8c
Conv. >99%
Yield: 77%
Select.: 93%
γ/β: 15:1



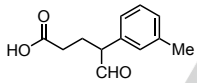
9a'
Conv. 100%
Yield: 65%
9a'/9c': 3:1
γ/β: >25:1



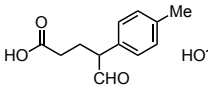
10c
Conv. >99%
Yield: 79%
Select.: 95%
γ/β: >25:1



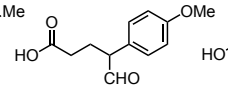
11c
Conv. >99%
Yield: 63%
11a/**11c**: 1:2
γ/β: >25:1



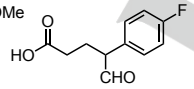
12c
Conv. >99%
Yield: 75%
Select.: 98%
γ/β: >25:1



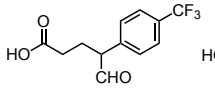
13c
Conv. >99%
Yield: 73%
Select.: 94%
γ/β: >25:1



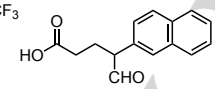
14c
Conv. >99%
Yield: 68%
Select.: 90%
γ/β: 21:1



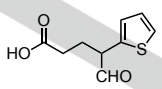
15c
Conv. >99%
Yield: 75%
Select.: 96%
γ/β: >25:1



16c
Conv. >99%
Yield: 68%
Select.: 95%
γ/β:>25:1



17c
Conv. >99%
Yield: 77%
Select.: 96%
γ/β: >25:1

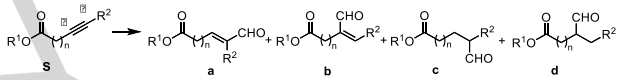


18c[b]
Conv. >99%
Yield: 51%
Select.: 91%
γ/β: >25:1

[a] [Rh(CO)$_2$acac]/**L1**/CSA/**S** = 1:5:5:100, c(**S**) = 0.5 M. Isolated yield. Selectivity (Select.), ratio of γ/β [n(**a**+**c**)/n(**b**+**d**)] and conversion (conv.) were determined by analysis of the reaction mixture by NMR spectroscopy. [b] CO/H$_2$ (1:1, 16 bar) and the yield was determined by NMR spectroscopy using TMB as the internal standard. PMB = 4-methoxybenzyl.

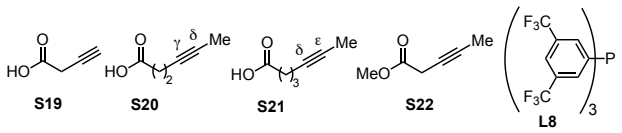
To clarify the role of ligand **L1** in the course of this HF-hydrogenation reaction, control experiments were undertaken as depicted in Table 3. Using a rhodium catalyst derived from a monodentate ligand, **L8**, gave no product **1c** and only a mixture of unsaturated aldehydes **1a** and **1b** was observed in very low yields with rather poor regioselectivity, and the presence of CSA hardly affected the outcome of the reactions using ligand **L8**, further indicating that CSA serves to protonate the guanidine function.[6a] Similar to the result of **L5**, no formation of any aldehydes was observed when using triphenylphosphine (Table S12). As expected, very inferior results were obtained when MeOH was used as the solvent, because its presence would disturb hydrogen bonding interaction of the ligand and substrate. Under the same reaction condition, the **L1**-derived catalyst showed no activity towards a terminal alkyne, 3-butynoic acid **S19** and similar results were also obtained using **L8** (Table S12). Lower activity and worse selectivity were found when 4-hexynoic acid **S20** and 5-heptynoic acid **S21** were involved, which indicated that the distance between the carboxylic acid functionality and the reactive alkyne group has a dramatic impact. Further evidence came from the fact that methyl ester **S22**, lacking the complementary functionality, reacted slowly and with low selectivity. Similar results were observed for the internal aryl substrate **S10** and its methyl ester **S23** (Table S12), and it provided a solid support that the substrate preorientation via the hydrogen bonding interactions elegantly controlled the selectivity and enhanced the activity of catalysts.

Table 3. Control experiments[a]



Entry	L	S	Yields/% (**a**/**b**/**c**/**d**)	Select. **c**/%	Ratio (γ/β)	Conv. /%
1	**L8**	**S1**	4/11/0/0	0	<1	23
2[b]	**L8**	**S1**	10/10/1/1	4	1	28
3[c]	**L1**	**S1**	3/2/0/0	0	1	16
4[d]	**L1**	**S19**	0/0/0/0	0	\	27
5[e]	**L1**	**S20**	21/5/15/0	34	4	40
6[f]	**L1**	**S21**	3/3/2/0	20	1	10
7	**L1**	**S22**	<1/1/<1/0	32	2	43

[a] [Rh(CO)$_2$acac]/**L**/CSA/**S** = 1:5:5:100, c(**S**) = 0.5 M, DCE (2 mL), CO/H$_2$ (1:1, 6 bar), 55 °C, 12 h. Yield was determined by NMR spectroscopy using TMB as the internal standard. Selectivity (Select.), ratio of γ/β [n(**a**+**c**)/n(**b**+**d**)] and conversion (conv.) were determined by analysis of the reaction mixture by NMR spectroscopy. [b] Without of CSA. [c] MeOH was used. [d] TsOH was used. [e] ratio (δ/γ). [f] ratio (ε/δ).



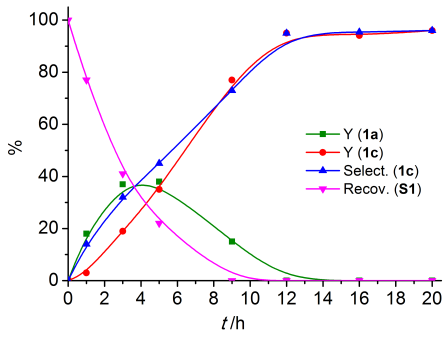
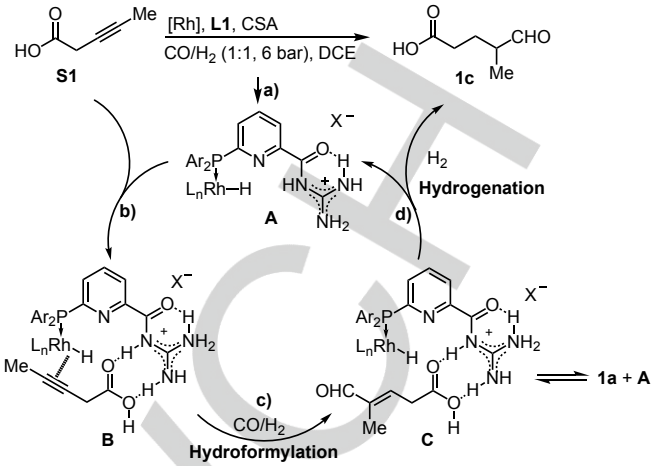


Figure 1. Rh-catalyzed HF-hydrogenation of **S1** as a function of reaction time.

This new method involves two catalytic reactions: HF and hydrogenation. The formation of the main product of **9a'**, containing the α,β-unsaturated γ-lactone moiety, indicated that the HF could be the first step, then followed by hydrogenation. So control experiments for detecting the possible intermediate in the reaction of **S1** at different reaction times were carried out. The α,β-unsaturated aldehyde **1a** was produced in 18% yield after 1 h, and in line with the increasing reaction time, its amount initially increased, reaching its maximum percentage at 40% before levelling off to zero (Figure 1). At the same time, the amount of **1c** as well as its chemoselectivity were always increasing during the process, and a yield of 95% was achieved after 12 h. Notably, the regioselectivity was well maintained at a high level (γ/β up to 22:1, Table S9). Based on these studies, it can be reasoned that the HF of alkynes occurs first, forming the enal **1a**, which was further subsequently hydrogenated under the reaction conditions, releasing the final saturated aldehyde **1c**. Based on our previous report[5a], (Z)-pent-3-enoic acid (Z-**S24**) which would be the product in case an alkyne hydrogenation occurs first and which could also possibly be transferred into **1c** using the catalyst derived from ligand **L5**. However, no traces of Z-**S24** could be detected during the course of this new tandem reaction. Furthermore, reaction results with low activity and selectivity were obtained when Z- and E-**S24** were studied in this new catalytic system (Table S12).

On the basis of the above results and the generally accepted mechanism of HF catalyzed by Rh-triarylphosphine complexes, we propose a mechanism consisting of four consecutive steps, which is reminiscent of the working mode of enzymes.[14] a) The presence of CSA would protonate the functional guanidine group of ligand **L1**, forming an intermediate **A** with a guanidinium salt. b) **A** could efficiently bind the substrate via hydrogen bonding interaction in a way that the substrate is well preoriented closely to the Rh center and activated by forming an intermediate **B**. c) γ-Selective HF within the supramolecular substrate-catalyst **B** occurred resulting in a complex **C**, consisted of α,β-unsaturated aldehyde **1a** and catalyst. d) Further hydrogenation within complex **C** would furnish the desired product **1c**, and regenerates the catalyst **A**. However, at this stage we cannot exclude a mechanism by which two guanidinium ligands interact with the carboxylic acid function, as has been found previously for a related HF of β,γ-unsaturated alkenes.[5c]



Scheme 3. Proposed reaction mechanism.

To conclude, we have designed and synthesized a series of new supramolecular ligands, containing a functional guanidine group with increasing π-acceptor ability of the phosphine donor ligands. A protocol for a tandem Rh-catalyzed HF-hydrogenation of unsymmetrical internal alkynes functionalized with carboxylic acid in highly regio- and chemoselectivity was successfully established, which yielded aliphatic aldehydes as desired products. This study further highlighted the unique advantages of supramolecular catalysis mimicking natural enzymes and an investigation of corresponding rationally designed chiral ligands are being undertaken in our lab.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes • enzyme mimics • ligand design • regioselective hydroformylation • supramolecular catalysis

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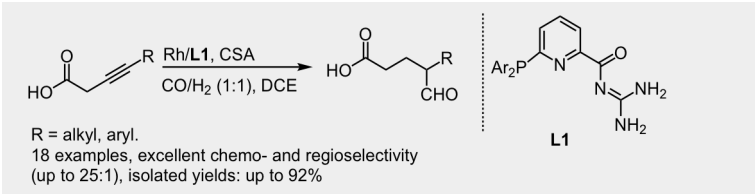

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Tandem Regioselective Hydroformylation-Hydrogenation of Internal Alkynes employing a Supramolecular Catalyst

A new supramolecular catalyst enables a tandem Rh-catalyzed hydroformylation-hydrogenation of unsymmetrical internal alkynes functionalized with carboxylic acids in β-position gave access to aliphatic aldehydes in high regio- and chemoselectivity. Control experiments prove enzyme-like catalyst behavior.