Synthetic Methods

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Rhodium-Catalyzed Hydroformylation of 1,1-Disubstituted Allenes Employing the Self-Assembling 6-DPPon System**

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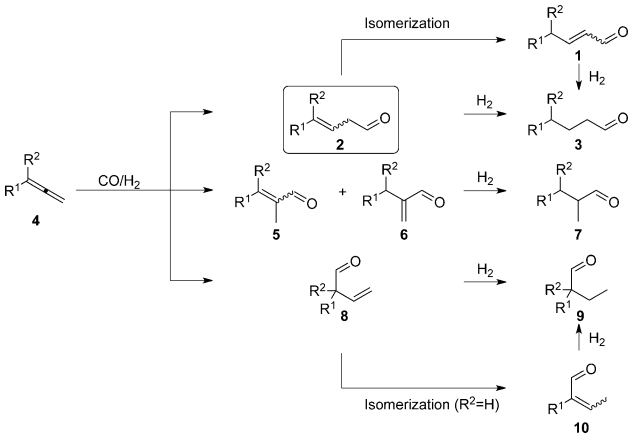
Abstract: *A rhodium-catalyzed hydroformylation of 1,1-disubstituted allenes is reported. Using a Rh^{I}/6-DPPon catalyst system, one can obtain β,γ-unsaturated aldehydes in high regio- and chemoselectivity. The Z-configured product is formed with up to >95% selectivity when unsymmetrically 1,1-disubstituted allenes are submitted to the reaction conditions. This is the first time that these interesting building blocks are accessible by hydroformylation of allenes. The utility of this methodology is demonstrated by further transformations of one of the obtained products.*

Hydroformylation is one of the most important industrial processes applying homogeneous catalysis.[1] In 2008 more than 10 million tons of oxoproducts have been produced.[2] Whereas hydroformylation of alkenes is highly developed, only little is known about the corresponding reactions with other π-unsaturated species such as alkynes,[3] 1,3-dienes,[4] and allenes.[5]

Especially reports about the hydroformylation of allenes are elusive, mainly due to the fact that one has to control chemo-, regio-, and stereoselectivity in this cumulated unsaturated system. The C–C bond formation may occur at three different positions resulting in several α,β- or β,γ-unsaturated aldehydes (Scheme 1). By π-bond isomerization, alkene and/or aldehyde hydrogenation, or a second hydroformylation an even more complex array of products might be formed. As an alternative to hydroformylation, reductive couplings with formaldehyde have been reported[6] regiodivergently for internal alkynes,[6b] 2-substituted 1,3-dienes,[6c] and allenes.[6d,e] However, these methodologies require stoichiometric amounts of reducing agents whereas the reducing agent in hydroformylation (hydrogen) is incorporated in the product making it an atom-economic reaction.[7] Furthermore, reductive couplings of allenes to formaldehyde have only been reported with a C1-selectivity. C–C bond formation at the C2-sp-atom of an allene has been reported for Ni-catalyzed reductive couplings with higher aldehydes.[8]

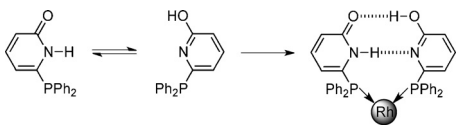


Scheme 1. The hydroformylation of allenes.

Reports about the hydroformylation of allenes suggest that it has the potential to deliver the missing equivalent at the C3-position. In 1976 Fell and Beutler performed studies on the hydroformylation of allene and found complex mixtures of mono- and dialdehydes.[5a] DFT calculations by Jiao, Beller, and co-workers suggested that coupling at the terminal sp^2-carbon of allene should be thermodynamically and kinetically favored over the reaction at the sp-center.[5b] The only chemoselective hydroformylation of allenes is in agreement with this theory and converts a 1,2-allenyl-phosphine oxide into the corresponding linear saturated aldehyde (aldehyde **3** in Scheme 1).[5c] However, maintaining one of the double bonds during allene hydroformylation would yield synthetically more interesting products. In particular β,γ-unsaturated aldehydes **2** could be highly attractive building blocks for organic synthesis.

In our group we developed the 6-DPPon ligand[9] which can self-assemble[10] through complementary hydrogen bonding (Scheme 2) and proved to form excellent catalysts in Rh-catalyzed hydroformylation of terminal alkenes and alkynes.[3f]

We were interested in applying this catalyst system to the hydroformylation of allenes because of its unique properties of flexibility combined with structural integrity that allow for the adoption of different coordination geometries together with maintaining the regiodiscriminating properties of a chelating ligand.[9d]



Scheme 2. The self-assembling 6-DPPon catalyst system.

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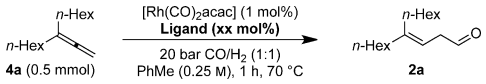
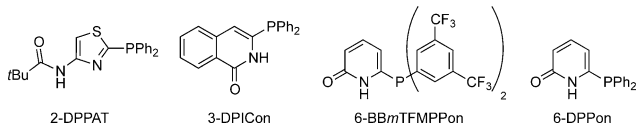
Initial studies focused on the hydroformylation of the symmetrically 1,1-disubstituted allene **4a**. The substitution pattern would allow for the optimization of the reaction conditions omitting stereoselectivity issues. To identify a catalyst system that is able to provide β,γ-unsaturated aldehydes in a chemo- and regioselective manner we screened different ligands (Table 1). Besides PPh_3, Xantphos and BIPHEPHOS,

Table 1: Ligand screening.[a]



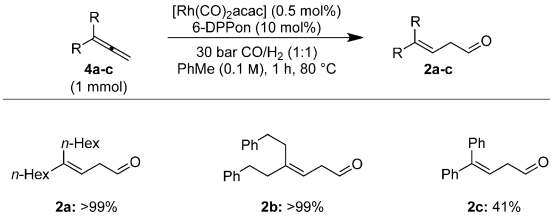
Entry	Ligand (mol%)	Selectivity [%][b]	Yield [%][c]
1	PPh_3 (10)	n.d.	12
2	Xantphos (5)	65	36
3	BIPHEPHOS (5)	89	52
4	2-DPPAT/3-DPICon (5 each)	77	69
5	6-BB*m*TFMPPon (10)	85	50
6	6-DPPon (10)	>95	76
7	6-DPMePon (10)	27	20
8	2-MeODPP (10)	43	20
9	Ph_2PPy (10)	37	14

[a] see SI for details; [b] selectivity toward **2a** among all aldehydes, determined by ^{1}H NMR analysis of the crude product; [c] ^{1}H NMR yield of all aldehydes formed, trimethoxybenzene as internal standard.
n.d. = not determined.



we also tested different self-assembling ligands such as the 2-DPPAT/3-DPICon system[10] and the 6-BB*m*TFMPPon-ligand, which was successfully applied in alkyne hydroformylation.[3f] To our delight it was the parent 6-DPPon ligand, which was superior to all other tested ligands in regard to both reactivity and selectivity toward the desired β,γ-unsaturated aldehyde. *O*- and *N*-methylated analogues of 6-DPPon as well as Ph_2PPy were examined proofing the importance of the hydrogen-bond interaction of the ligand (entries 7–9).

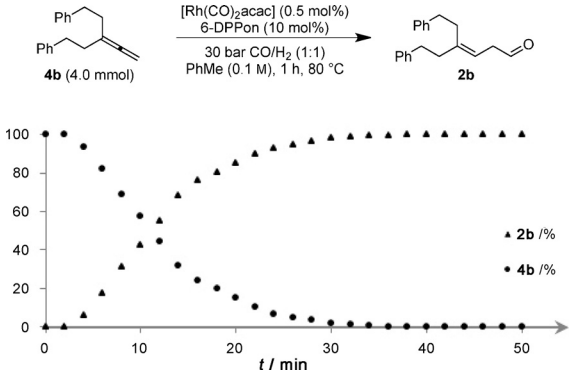
With this catalyst system in hand, the reaction conditions were adjusted in terms of solvent, pressure, temperature, and concentrations (see the Supporting Information (SI) for details). The optimal conditions and a substrate scope for the hydroformylation of symmetrically 1,1-disubstituted allenes are shown in Scheme 3. The β,γ-unsaturated aldehydes **2a** and **2b** could be obtained in excellent yields and selectivity. As a limitation, the hydroformylation product of



Scheme 3. Hydroformylation of symmetrically 1,1-disubstituted allenes. Yields are of isolated products (see SI for details).

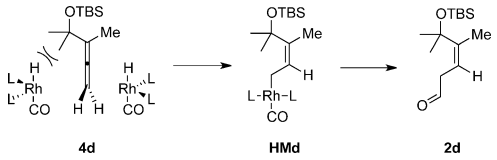
diphenylallene **2c** could only be isolated in moderate yields due to degradation of the allene starting material under the reaction conditions.[12]

To get further insights into the reaction, the kinetics were monitored (Scheme 4). After a short period of catalyst preformation the conversion linearly increases up to 60–70% in less than 15 min. Within this range a turnover frequency of 761 h^{-1} can be determined.



Scheme 4. Reaction kinetics for the hydroformylation of **4b**. The conversion was determined by ^{1}H NMR analysis (see SI for details).

With these results in hand, we wondered whether it was possible to induce stereoselectivity in unsymmetrically 1,1-disubstituted allenes. We envisioned that sterically demanding substituents at the C1-position of an allene should reach into one half room of the allene moiety thereby hindering the hydrometalation step from this side (Scheme 5). This suggests that the *Z*-product should be formed predominantly.

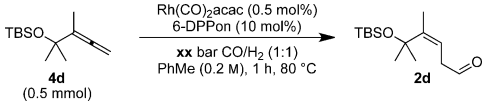


Scheme 5. Proposed reason for stereoinduction.

Indeed, when we optimized the conditions for the hydroformylation of unsymmetrically 1,1-disubstituted allenes we found that the expected stereoinduction is possible. Interestingly, the stereoselectivity showed a significant dependence on the syngas pressure (Table 2). Gradually going from 20 to 50 bar led to an increasing preference for the *Z*-configured product. This proposes that the stereoselectivity is determined kinetically. In contrast to low syngas pressures that are applied in isomerizing hydroformylation of internal alkenes to linear aldehydes[13] to facilitate reversible hydrometalation by β-H-elimination in the 16-valence-electron complex **HMd**, high pressures should accelerate the coordination of CO to form an 18-valence-electron complex thereby suppressing isomerization.

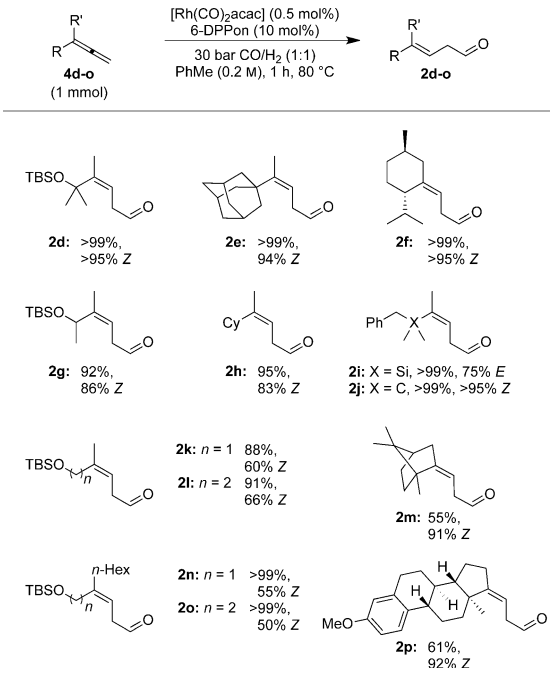
With these conditions in hand we screened more 1,1-disubstituted allenes (Scheme 6). Gratifyingly, the reaction

Table 2: Dependency of the *Z*/*E*-selectivity on the pressure of CO/H_2.[a]



Entry	*p* [bar]	*Z*:*E*[b]	Yield [%][c]
10	20	5:1	85
11	30	20:1	97
12	40	22:1	92
13	50	30:1	89

[a] see SI for details; [b] determined by ^{1}H NMR analysis of the crude product; [c] ^{1}H NMR-yield of **2d**, trimethoxybenzene as internal standard.

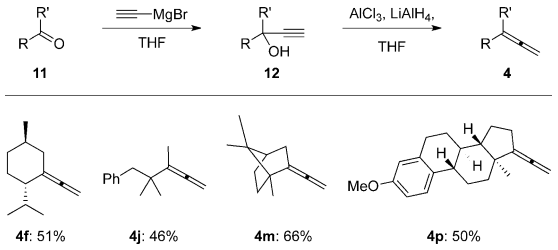


Scheme 6. Hydroformylation of unsymmetrically disubstituted allenes. *Z*/*E*-selectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures and confirmed by NOE experiments. Yields are of isolated products (see SI for details).

conditions proved to be very general and yielded the corresponding aldehydes in very good to excellent yield. Expectedly, the diastereoselectivity of alkene formation is a function of the differentiation of the sterical demand of the two substituents at the allene terminus: the larger the difference the higher the stereoselectivity (see **2d**,**g**,**k**,**l**,**n**,**o**).

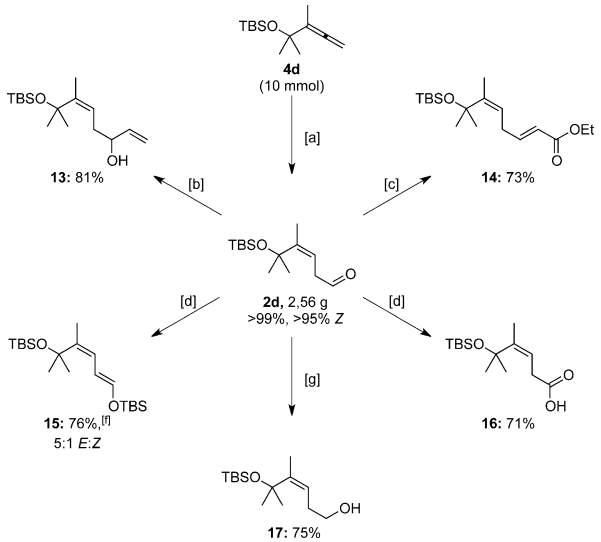
Next, the hydroformylation of allenes was applied to more complex substrates and high stereoselectivities could be reached for all of them (**2f**,**m**,**p**). A (−)-menthone derived allene provided the corresponding β,γ-unsaturated aldehyde **2f** in quantitative yield, a (+)-camphor and an estrone 3-methyl ether derived product could be isolated in satisfying yield.[14] Interestingly, the hydroformylation of 1-(benzyldimethylsilyl)-1-methylallene (**4i**) gave the *E*-configured product predominantly. To limit the reason for this switch of stereoselectivity to the properties of the silicon atom, the analogous substrate with a carbon at this position (**4j**) was hydroformylated to yield the *Z*-configured product as a single stereoisomer.[15] The BDMS-group is one of the most potent substrates for Hiyama couplings[16] which can potentially be used for derivatization at this position.

Since allene substrates are, with a few examples, not commercially available, their accessibility determines the synthetic utility of this methodology. Interestingly, allenes can be readily prepared over a two-step sequence consisting of alkynyl-Grignard addition and propargylic S_N2' reduction potentially from any ketone (Scheme 7).



Scheme 7. Two-step synthesis of allenic substrates from ketones (see SI for details).

Furthermore, the reaction can be performed on a 10 mmol scale with excellent yield, chemo-, regio-, and stereoselectivity (Scheme 8). To demonstrate the synthetic utility of the obtained β,γ-unsaturated aldehydes, a small scope of further transformations was performed. Under Horner–Wadsworth–



Scheme 8. Synthesis and chemical transformations of **2d** (see SI for details). [a] $Rh(CO)_2acac$ (0.5 mol%), 6-DPPon (10 mol%), PhMe (0.2 M), CO/H_2 (1:1, 30 bar), 80 °C, 1.5 h; [b] **2d** (0.5 mmol), $BrMgCHCH_2$ (4.0 equiv), THF (0.2 M); [c] **2d** (1.0 mmol), $EtO_2CCH_2P(=O)(OEt)_2$ (1.1 equiv), NaH (1.1 equiv), THF (0.33 M); [d] **2d** (2.0 mmol), NEt_3 (1.5 equiv), THF (1.0 M), TBSTf (1.1 equiv); [e] **2d** (0.5 mmol), *t*BuOH (0.6 M), 2-methyl-2-butene (6.6 equiv), $NaClO_2$ (1.3 equiv), KH_2PO_4 (1.3 equiv), H_2O (0.9 M); [f] ^{1}H NMR yield, trimethoxybenzene as internal standard; [g] **2d** (0.5 mmol), $LiAlH_4$ (1.0 equiv), THF (0.5 M). acac = acetylacetonate, 6-DPPon = 6-diphenylphosphanyl-2-pyridone, TBSTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.

Emmons (HWE) reaction conditions 1,4-dienes can be obtained, namely the α,β-δ,ε-unsaturated ester **14**. Applying a Pinnick oxidation, the aldehyde could be converted to the corresponding acid **16**. β,γ-Unsaturated acids have been hydrogenated asymmetrically.[17] Reduction of the aldehyde to the homoallylic alcohol **17** leads to structures that have recently been used for enantioselective Heck-type reactions in order to construct quaternary stereocenters.[18] Furthermore, **2d** is readily transformed into the corresponding dienolsilylether **15**. Such building blocks could potentially be used for Diels–Alder[19] or vinylogous Mukaiyama aldol reactions.[20] The addition of vinyl-Grignard to the aldehyde results in a substitution pattern (**13**) which is prone to an oxy-Cope rearrangement.[21]

In summary, applying the self-assembling Rh^{I}/6-DPPon catalyst system the hydroformylation of 1,1-disubstituted allenes to β,γ-unsaturated aldehydes was achieved in excellent chemo- and regioselectivity with high yields. When unsymmetrical 1,1-disubstituted allenes are converted, stereoselectivities of more than 95% for the *Z*-configured product can be reached. Furthermore, it was shown that the used allenes can be obtained in a short two-step synthesis starting from simple ketones. The hydroformylation products are interesting and useful building blocks as shown by further transformations of the obtained β,γ-unsaturated aldehydes.

Keywords: aldehydes · allenes · hydroformylation · rhodium · self-assembly

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[12] The hydroformylation of differently substituted allenes was not as successful under these conditions: 5-Phenyl-1,2-pentadiene was converted to a complex mixture of more than five aldehydes (32% selectivity for the β,γ-unsaturated aldehyde as the main product, 13% selectivity for the fully saturated linear aldehyde); as an example for an internal allene, 1,7-diphenylhepta-3,4-diene could be reisolated quantitatively.

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[14] **21** and **2o** were formed with 80% selectivity for the desired aldehyde. During isolation some of the material was lost due to the acidity of the CH_2-group in α-position of the aldehyde.
[15] The reason for this switch in stereoselectivity is not clear yet, but one could propose that the electronic properties of the silicon substituents might accelerate isomerization of the complex **HMd** thereby enabling generation of the thermodynamically more favored *E*-aldehyde.
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