Asymmetric Catalysis

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Highly Regio- and Enantioselective Asymmetric Hydroformylation of Olefins Mediated by 2,5-Disubstituted Phospholane Ligands**

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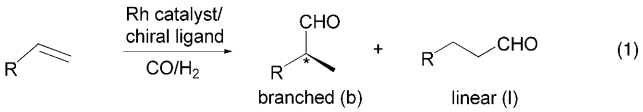
Asymmetric hydroformylation (AHF) is a powerful synthetic methodology that allows conversion of olefins into optically active aldehydes in a single step [Eq. (1)].[1] The aldehyde



(1)

group is one of the most versatile functional groups and can be readily transformed into a variety of high-value-added chiral chemicals, such as amines, imines, alcohols, and acids.[2] Even though AHF offers great promise to the fine-chemical industry, this reaction has not been utilized on a commercial scale because of several remaining technical challenges; among the most important to overcome are a) low reaction rates at low temperatures for reactions in which good selectivities are usually observed, b) difficulties in controlling the regio- and enantioselectivities simultaneously, and c) limited substrate scope for any single ligand.

The reaction rates of Rh-catalyzed hydroformylations are commonly slower than those of asymmetric hydrogenations that are conducted near ambient temperature. Commercially viable rates in AHF can be achieved at 80–120 °C (turnover rates of several thousand per hour); however, lower regio- and enantioselectivities are usually observed at these high temperatures. Thus, the most desired characteristic of the new generation of AHF ligands should be the ability to produce optically active aldehydes at high temperatures without compromising product selectivity.

Only a few chiral ligands have been successfully applied in AHF reactions (Scheme 1). Among the most effective are (2*R*,4*R*)-chiraphite (**1**)[3] and its analogues,[4] which exhibit enantioselectivities of up to 90 % *ee* for the hydroformylation of styrene at low temperatures; (*R*,*S*)-binaphos (**2**),[5] which shows high enantioselectivities for the hydroformylation of many structurally diverse olefins; (*S*,*S*)-kelliphite (**3**), which is effective for the hydroformylation of allyl cyanide[6] and vinyl acetate;[7] and (*S*,*S*)-esphos (**5**), which displays a high enantioselectivity for the hydroformylation of vinyl acetate.[8] Together with Landis and co-workers, we recently reported[9] the application of diazaphospholane ligands **4** in AHF reactions which showed outstanding hydroformylation rates and very high enantioselectivities for reactions with styrene and allyl cyanide substrates. Diazaphospholane **4** is especially selective for vinyl acetate at 80 °C (96 % *ee*, b/l = 35). This ligand family is structurally related to 1,2-bis(2,5-dialkylphospholano)benzene (duphos; **6**–**8**), 1,2-bis(2,5-dialkylphospholano)ethane[10] (bpe; **9**–**11**), and especially the recently reported (*R*,*R*)-1,2-bis(2,5-diphenylphospholano)ethane ((*R*,*R*)-Ph-bpe; **12**) Scheme 2).[11] The duphos and bpe ligands[12] have been proven to be exceptional ligands for the asymmetric hydrogenation[13] of dehydroamino acids and mono- and disubstituted itaconates, among numerous other applications, but their use has not been reported for AHF reactions.

Herein, we report that **12** is an excellent ligand for the rhodium-catalyzed AHF of styrene, allyl cyanide, and vinyl acetate at high temperatures (80–100 °C). (*R*,*R*)-Ph-bpe (**12**) displays the best regio- and enantioselectivities reported to date for the hydroformylation of styrene and allyl cyanide and the second best for the hydroformylation of vinyl acetate. The reaction rates obtained at these elevated temperatures render this catalytic system amenable to industrial applications.

The hydroformylation reactions were carried out at 80 °C and 1.034 MPa CO/H_2 pressure with substrate/catalyst molar ratios of 5000:1 and a catalyst concentration of 0.37 mM. Phospholane and phosphetane ligands **6**–**16** (Scheme 2) and previously reported ligands **1**–**4** were evaluated under identical conditions for comparison. Active catalysts were prepared by combining $[Rh(acac)(CO)_2]$ (acac = acetylacetonate) with 1.2 equivalents of each bidentate ligand (2.1 equiv for **16**) in toluene followed by pressurizing the resulting solution with syngas (CO/H_2, molar ratio of 1:1). Styrene, allyl cyanide, and vinyl acetate underwent simultaneous hydroformylation under constant pressure, with the gas uptake being monitored continuously. Olefin conversion, together

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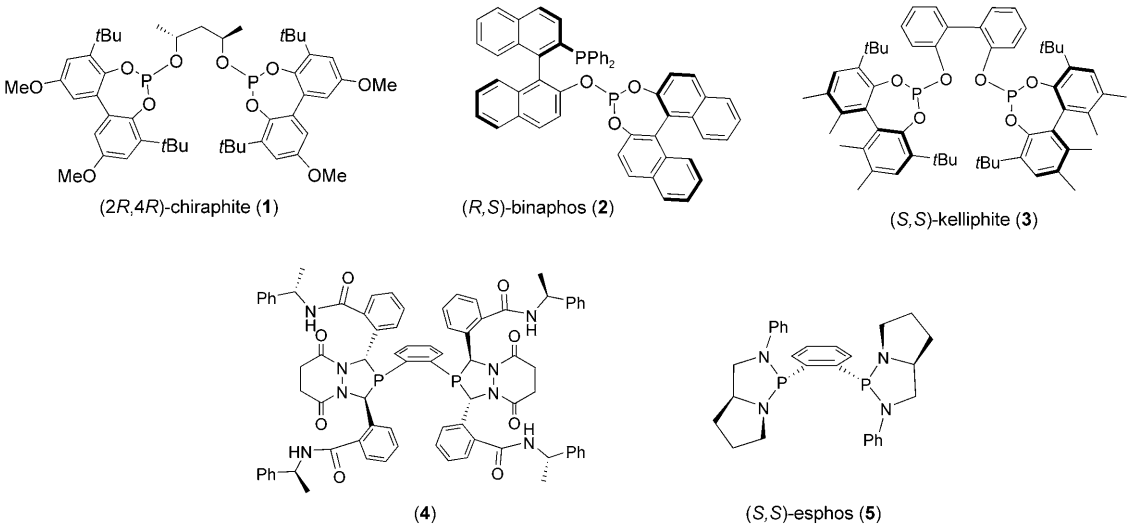
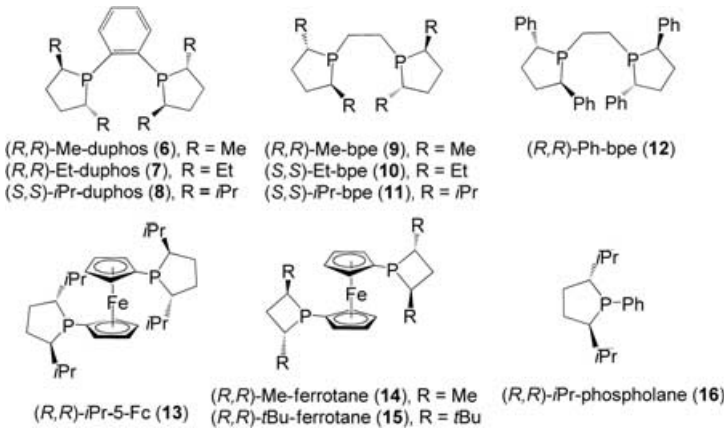
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Chiral ligands that have been successfully applied in AHF reactions.



Scheme 2. Phospholane and phosphetane ligands.

with the regio- and enantioselectivities of the products, was determined by using gas chromatography on a chiral stationary phase, as previously described.[7] The syngas uptake curves demonstrate that all the phospholane ligands screened exhibited low hydroformylation rates except for **12** (Figure 1). The lowest hydroformylation rates were observed for the ferrocenyl phospholane and phosphetane[14] ligands **13**–**15** (Table 1, entries 12–14). (*R*,*R*)-Ph-bpe (**12**) exhibits an average turnover frequency of 1139 h^{-1}, which is about five times more active than the second fastest phospholane **11** and only about two times slower than **1** and **2**. The most likely reason for the increased activity of **12** compared with the other phospholane ligands is the presence of the electron-withdrawing phenyl rings that reduce the overall basicity of the phosphine moiety. The IR spectroscopic data ν_{CO} obtained for [Mo(CO)$_4${(*S*,*S*)-Me-bpe}], [Mo(CO)$_4${(*S*,*S*)-*i*Pr-bpe}], and [Mo(CO)$_4${(*R*,*R*)-Ph-bpe}] (2012, 2011, and 2015 cm^{-1}, respectively)[15] support the assertion that (*R*,*R*)-Ph-bpe is the least basic phosphine amongst the bpe ligands. It is well established that electron-poor phosphines lead to more active catalysts in Rh-catalyzed hydroformylation.[1a]

The olefin conversion and regio- and enantioselectivity data for the ligands investigated in this study are summarized in Table 1. The olefin conversion data are in close agreement with the syngas uptake curves and clearly demonstrate that **12** exhibits the fastest hydroformylation rates of all the phospholane and phosphetane ligands in this study (Table 1, entry 11 versus entries 6–10 and 12–15). The enantioselectivity data show that bpe and duphos ligands with larger substituents in the 2,5-positions of the phospholane rings (*i*Pr and Ph versus Me and Et) lead to noticeably higher enantioselectivities. Importantly, the selectivities observed for styrene, allyl cyanide, and vinyl acetate are comparable for a given phospholane ligand, thus suggesting the potential for broad applicability of phospholane ligands to a wide range of substrates. Monodentate ligand **16** has a very poor activity and selectivity, which indicates that the bidentate nature of the ligand is necessary for achieving high regio- and enantioselectivities. Phospholane **12** is the most enantioselective ligand in this study giving 94, 90, and 82% *ee* for the

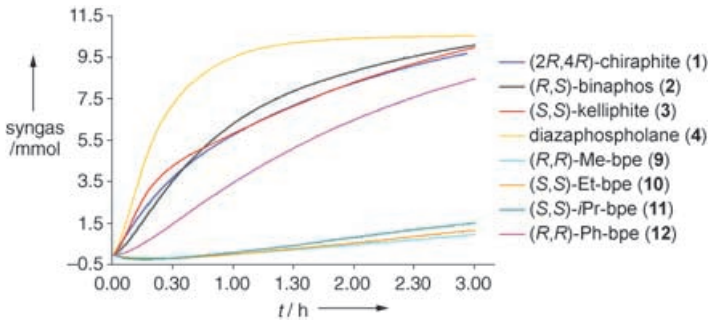


Figure 1. Syngas-uptake curves for reactions performed with a olefin/catalyst ratio of 5000:1 (at 80 °C in toluene with 1.034 MPa of CO/H_2 (1:1) and a L/Rh ratio of 1.2:1).

Table 1: Percentage conversion (conv.), branched/linear ratio (b/l), and enantioselectivities of the hydroformylation reactions of styrene, allyl cyanide, and vinyl acetate.

Entry	Ligand	Styrene			Allyl cyanide			Vinyl acetate		
		conv. [%]	b/l	*ee* [%]	conv. [%]	b/l	*ee* [%]	conv. [%]	b/l	*ee* [%]
1	(2*R*,4*R*)-chiraphite (**1**)	89	9.1:1	50 (*R*)	98	5.8:1	14 (*R*)	76	246:1	49 (*R*)
2	(*R*,*S*)-binaphos (**2**)	96	4.5:1	82 (*R*)	98	2.1:1	72 (*R*)	72	8.2:1	48 (*S*)
3	(*S*,*S*)-kelliphite (**3**)	82	8.4:1	3 (*S*)	98	9.9:1	68 (*S*)	83	65:1	72 (*R*)
4	diazaphospholane **4**	100	6.6:1	82 (*R*)	100	4.1:1	87 (*R*)	100	37:1	96 (*S*)
5	(*R*,*R*)-Me-duphos (**6**)	10	15.7:1	44 (*S*)	42	6.6:1	32 (*S*)	26	176:1	51 (*R*)
6	(*R*,*R*)-Et-duphos (**7**)	14	13.7:1	52 (*S*)	49	7.8:1	35 (*S*)	27	371:1	66 (*R*)
7	(*S*,*S*)-*i*Pr-duphos (**8**)	15	11.3:1	83 (*S*)	55	7.2:1	82 (*S*)	29	322:1	74 (*R*)
8	(*R*,*R*)-Me-bpe (**9**)	8	14.0:1	43 (*S*)	36	5.8:1	37 (*S*)	23	97:1	59 (*R*)
9	(*S*,*S*)-Et-bpe (**10**)	10	11.3:1	55 (*R*)	40	6.2:1	49 (*R*)	23	152:1	66 (*S*)
10	(*S*,*S*)-*i*Pr-bpe (**11**)	11	9.5:1	82 (*S*)	48	6.7:1	83 (*S*)	28	142:1	70 (*R*)
11	(*R*,*R*)-Ph-bpe (**12**)	57	45.0:1	94 (*R*)	96	7.1:1	90 (*R*)	52	340:1	82 (*S*)
12	(*R*,*R*)-*i*Pr-5-Fc (**13**)	9	3.2:1	15 (*R*)	28	3.9:1	49 (*R*)	22	94:1	29 (*R*)
13	(*R*,*R*)-*t*Bu-ferrotane (**14**)	10	1.7:1	55 (*R*)	31	5.3:1	73 (*R*)	23	29:1	27 (*R*)
14	(*R*,*R*)-Me-ferrotane (**15**)	9	3.6:1	18 (*S*)	28	2.3:1	53 (*S*)	22	8.5:1	39 (*R*)
15	(*R*,*R*)-*i*Pr-phospholane (**16**)	11	4.4:1	11 (*R*)	30	3.5:1	7 (*R*)	17	21:1	8 (*S*)

[a] All the reactions were performed at 80 °C in toluene with 1.034 MPa of CO/H_2 (1:1), L/Rh = 1.2:1 (2.1:1 for **16**), substrate/Rh = 5000:1, catalyst concentration of 0.037 mol %, and a reaction time of 3 h.

reactions of styrene, allyl cyanide, and vinyl acetate, respectively.[16] Phospholane **12** is not only the most enantioselective ligand for the hydroformylation of styrene (including previously reported ligands **1**–**4**), but it also gives an unprecedented high regioselectivity (b/l = 45:1). Under identical conditions, **2**, for example, exhibits a significantly lower regioselectivity (b/l = 4.5:1). The ability of a ligand to give high regioselectivities in AHF (high ratio of branched to linear isomers) is a very important attribute as any amount of achiral linear isomer can be regarded as an additional impurity that must be separated from the desired chiral product. To put the regioselectivities of the styrene products into perspective, the amount of the undesired linear isomer formed with (*R*,*R*)-Ph-bpe (**12**) is 2.2 % (b/l = 45:1), whereas with (*R*,*S*)-binaphos (**2**) it is 18.2 % (b/l = 4.5:1; Table 1, entries 11 and 2). Phospholane **12** also gives the highest enantioselectivity (90 % *ee*, b/l = 7.1:1) in the case of the hydroformylation of allyl cyanide. Under the same conditions, diazaphospholane **4** gives a similar enantioselectivity (87 % *ee*) but a noticeably lower regioselectivity (b/l = 4.1:1). For ligands **1**–**4**, only **3** gives a higher regioselectivity for the hydroformylation of allyl cyanide (b/l = 9.9:1), although with a much lower enantioselectivity (68 % *ee*). Phospholane **12** gives the second best enantioselectivity (82 % *ee*) for the hydroformylation of vinyl acetate but with a high regioselectivity (b/l = 340:1) that is unprecedented. The only ligand that shows higher enantioselectivity for the hydroformylation of vinyl acetate is the recently reported diazaphospholane **4** (96 % *ee*, b/l = 37:1).[9]

A second set of hydroformylation reactions was conducted to compare ligand **12** with ligands **1**–**4** using mixtures of neat olefins at 80 °C and 1.034 MPa pressure of syngas with substrate/catalyst molar ratios of 30000:1 and a catalyst concentration of 0.062 mM. At these very low catalyst loadings, the rate of hydroformylation with **12** (an average turnover frequency of 4467 h^{-1}) was virtually identical to those of **1** and **2** and only slower than **3** and **4** (see Figure 2). The regio- and enantioselectivities achieved under these conditions were comparable to those obtained at the substrate/catalyst ratio of 5000:1 (see Table 2).

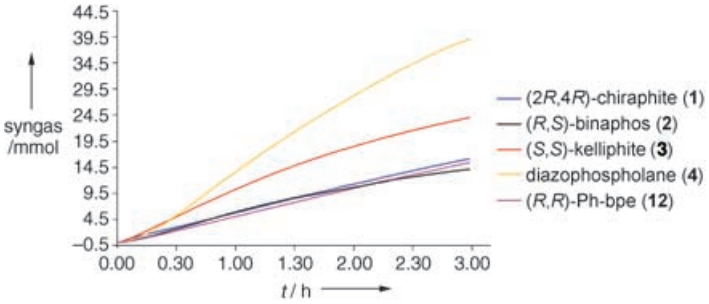


Figure 2. Syngas-uptake curves for reactions were performed with a ratio of olefin/catalyst = 30000:1 (at 80 °C in toluene with 1.034 MPa of CO/H_2 (1:1) and a L/Rh ratio of 1.2:1).

Hydroformylation experiments conducted with the isolated rhodium complex [Rh(acac){(*R*,*R*)-Ph-bpe}], prepared by the reaction of **12** and [Rh(cod)(acac)] (cod = cyclooctadiene), gave identical results to experiments in which the rhodium complex was prepared in situ prior to the hydroformylation reaction. The solid-state structures of **12** and [Rh(acac){(*R*,*R*)-Ph-bpe}] were determined by single-crystal X-ray analysis (Figures 3 and 4).[17]

A preliminary investigation into the reaction conditions (olefin concentration, CO and H_2 pressures, and temperature) reveals that the hydroformylation rate with **12** is first order in olefin concentration, zero order in ligand concentration (ligand/Rh = 1:1–5:1), zero order in H_2 pressure, and negative first order in CO pressure. These observations are consistent with the dissociation of CO from a five-coordinate rhodium dicarbonyl complex as a pre-equilibrium step prior to the rate-limiting insertion of the olefin into the Rh–H bond.[18] Interestingly, the enantioselectivities of all the products were

Table 2: Percent conversion (conv.), branched/linear ratio (b/l), and enantioselectivities of the hydroformylation reactions of styrene, allyl cyanide, and vinyl acetate.

Entry	Ligand	Styrene			Allyl cyanide			Vinyl acetate		
		conv. [%]	b/l	*ee* [%]	conv. [%]	b/l	*ee* [%]	conv. [%]	b/l	*ee* [%]
1	(2*R*,4*R*)-chiraphite (**1**)	32	10.8:1	51 (*R*)	74	5.8:1	13 (*R*)	34	204:1	50 (*R*)
2	(*R*,*S*)-binaphos (**2**)	35	4.6:1	81 (*R*)	58	2.1:1	68 (*R*)	23	7.1:1	58 (*S*)
3	(*S*,*S*)-kelliphite (**3**)	32	9.2:1	3 (*S*)	99	10.1:1	66 (*S*)	32	100:1	75 (*R*)
4	diazaphospholane (**4**)	73	5.7:1	80 (*R*)	100	3.9:1	80 (*R*)	92	47:1	95 (*S*)
5	(*R*,*R*)-Ph-bpe (**12**)	33	45.0:1	92 (*R*)	67	7.6:1	90 (*R*)	34	263:1	82 (*S*)

[a] All the reactions were performed at 80 °C in toluene at 1.034 MPa of CO/H_2 (1:1) with L/Rh = 1.2:1, substrate/Rh = 30000:1, a reaction time of 3 h, and 4.43 mL of a mixture of styrene/allyl cyanide/vinyl acetate/dodecane (1:1:1:0.3 molar ratio).

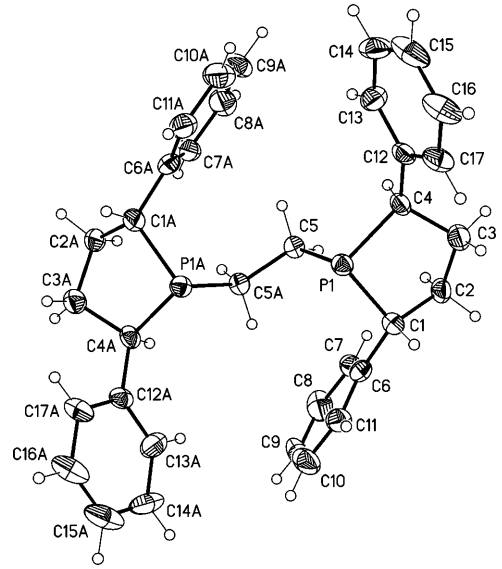


Figure 3. Molecular structure of (*R*,*R*)-Ph-bpe (**12**), with the thermal ellipsoids set at 40% probability.

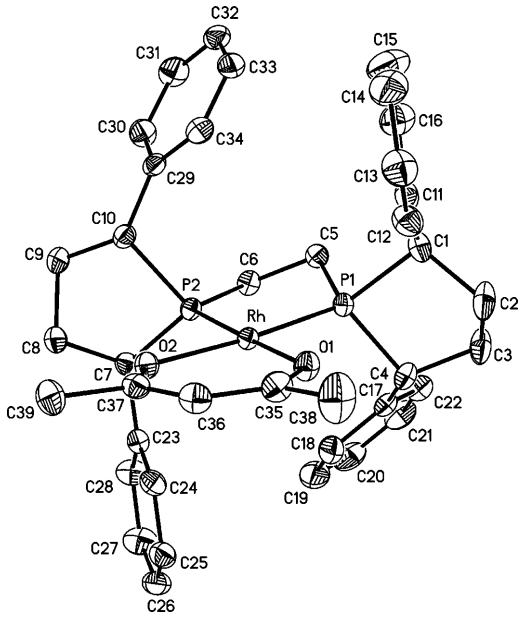


Figure 4. Molecular structure of [Rh(acac){(*R*,*R*)-Ph-bpe}], with the thermal ellipsoids set at 40% probability.

unaffected by variations in the syngas pressure (0.345–3.102 MPa), whereas the regioselectivities were dependent upon pressure, with b/l ratios of 40:1– 45:1 for the styrene products and b/l ratios of 1060:1–155:1 for the vinyl acetate products being observed over these pressures.

In conclusion, (*R*,*R*)-Ph-bpe (**12**) was identified as an excellent ligand for asymmetric hydroformylation which gives state-of-the-art regio- and enantioselectivities for styrene, allyl cyanide, and vinyl acetate, while maintaining commercially viable turnover rates over 4000 h^{-1} at 80 °C. The remarkable ability of phospholane-based ligands **12** and **4** to yield very high enantioselectivities at high temperatures renders these ligands suitable for large-scale industrial applications.

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[16] Hydroformylation experiments conducted with individual olefins gave the same selectivities for all three substrates as those obtained from simultaneous hydroformylations of these olefins, except for the regioselectivity for the reaction of vinyl acetate, which was lowered to b/l = 260:1.
[17] X-ray diffraction data for **12**: $M_r = C_{34}H_{36}P_2$, $T = 173$ K, $\lambda = 0.71073$ Å, monoclinic, $C2$, $a = 19.394(1)$, $b = 18.956(1)$, $c = 24.752(2)$ Å, $\beta = 104.717(1)°$, $Z = 12$, no. reflections = 14755 ($7283 > 2\sigma(I)$), refinement on $F2$, $R1(>2\sigma(I)) = 0.0363$, $R1$(all data) = 0.086, GOF = 0.756; [Rh(acac){(*R*,*R*)-Ph-bpe}]: $M_r = C_{80}H_{89}NO_4P_4Rh_2$, $T = 173$ K, $\lambda = 0.71073$ Å, monoclinic, $P2_1$, $a = 10.3863(6)$, $b = 19.9915(12)$, $c = 17.8855(10)$ Å, $\beta = 105.370(1)°$, $Z = 2$, no. reflections = 14572 ($13725 > 2\sigma(I)$), refinement on $F2$, $R1(>2\sigma(I)) = 0.0209$, $R1$(all data) = 0.0229, GOF = 1.000. CCDC-270008 and -270009 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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