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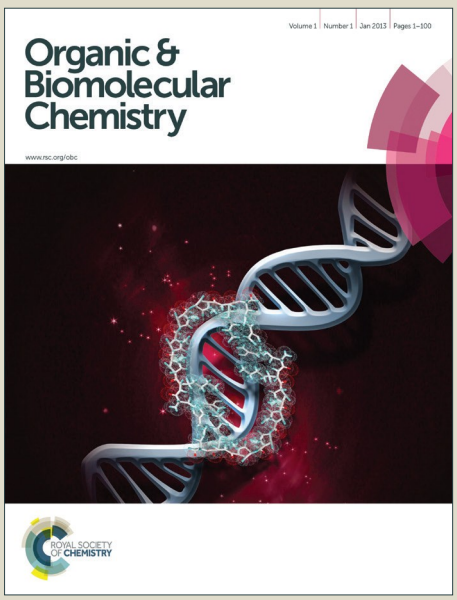

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Accessible protocol for asymmetric hydroformylation of vinylarenes using formaldehyde

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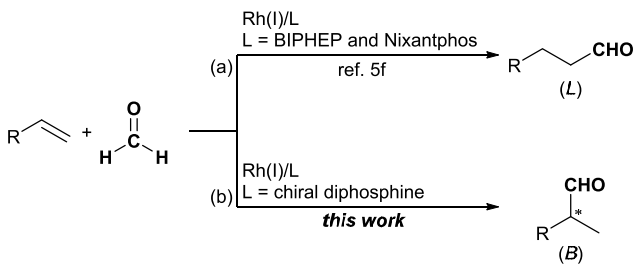
We report herein on an accessible protocol for the asymmetric hydroformylation of vinylarenes using formaldehyde as a substitute for syngas. The regioselectivity (branched/linear = up to 96/4) and enantioselectivity (up to 95%ee) can be attributed to the use of chiral Ph-bpe as a ligand.

Asymmetric hydroformylation has attracted the interest of numerous synthetic organic researchers because it can produce versatile chiral aldehydes which have intrinsic value as synthetically useful intermediates.[1] The products are easily converted to enantiomerically enriched alcohols, carboxylic acids and their derivatives, amines, and imines.[2] Since the pioneering discovery of a highly effective ligand for rhodium-catalyzed hydroformylation, BINAPHOS,[3] numerous efforts to achieve a higher degree of enantioselectivity have been focused on the discovery of novel ligands.[4]

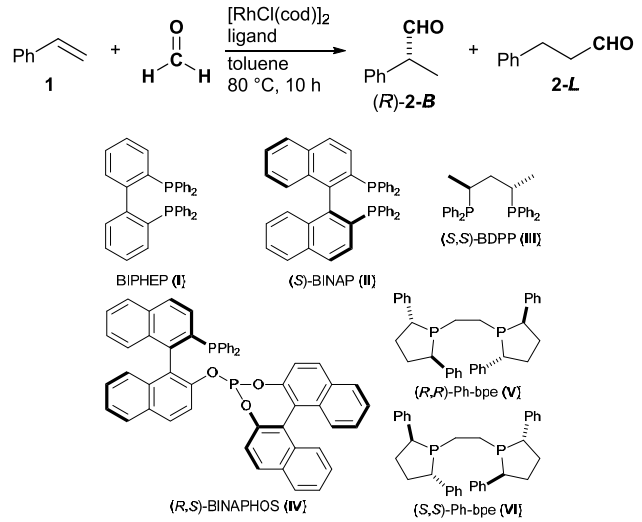


Scheme 1 Selective Hydroformylation Using Formaldehyde.

For the next-stage progress in asymmetric hydroformylation methodology, we investigated the use of formaldehyde as a substitute for synthesis gas ($CO + H_2$, syngas). Using formaldehyde is highly attractive, because it is constructed from the same elements (one carbon, one oxygen and two hydrogen atoms) as syngas, thus making it atom-economical. The success of using formaldehyde would lead to operational simplicity and convenience for the transformation. To our knowledge,[5–9] to date, asymmetric hydroformylation without the direct use of syngas has never been reported. We describe here the first asymmetric hydroformylation of vinylarenes with formaldehyde (Scheme 1b). This represents a promising synthetic tool for producing chiral aldehydes and derivatives thereof.

We recently developed a new method for the highly *linear*-selective hydroformylation of 1-alkenes using formaldehyde as a syngas-substitute (Scheme 1a).[5f] This report revealed that, in the rhodium-catalyzed reaction of 1-alkenes with formaldehyde, the simultaneous use of two types of phosphine ligands, BIPHEP and Nixantphos, led to a highly linear-selective hydroformylation (*L*/*B* = >95/5). The findings showed that BIPHEP and Nixantphos are responsible for the decarbonylation and the hydroformylation processes, respectively, totally resulting in a *linear*-selective hydroformylation. In developing the method, we first examined the simultaneous use of two phosphines, BIPHEP for decarbonylation and a chiral phosphine for the *branched*- and enantioselective hydroformylation, in the rhodium-catalyzed reaction of styrene with formaldehyde. When styrene (**1**) was treated with formalin (37wt% aqueous solution of formaldehyde) in the presence of 0.5 mol% $[RhCl(cod)]_2$, 0.6 mol% BIPHEP, and 0.6 mol% (*S*)-BINAP[10] in toluene at 80 °C for 10 h, the hydroformylation proceeded *branched*-selectively (**2-*B*/2-*L*** = 84/16) to give a mixture of *branched* and *linear* aldehydes in 28 % yield with a low enantioselectivity (18 %ee (*R*)) (Table 1, entry 1). The use of (*S*,*S*)-BDPP[11] instead of (*S*)-BINAP led to more smooth reaction with moderate regioselectivity (**2-*B*/2-*L*** = 78/22), although the enatioselectivity was still moderate (52 %ee (*R*)) (entry 2). When (*R*,*S*)-BINAPHOS[3] was used for the asymmetric hydroformylation process, the regioselectivity and enantioselectivity were very low (entry 3). The simultaneous use of BIPHEP and (*R*,*R*)-Ph-bpe[4b] proceeded much more smoothly to give the aldehydes in extremely high yield (96 %) with higher *branched*- and enantioselectivities (**2-*B*/2-*L*** = 90/10, 81 %ee (*R*)) (entry 4). Contrary to our expectation, when (*R*,*R*)-Ph-bpe was used alone, a higher regio- and enantioselectivities was observed: >99% yield with a 93% *branched* aldehyde-selectivity and 90 %ee (*R*) (entry 5).[12] Thus, (*R*,*R*)-Ph-bpe was found to be sufficiently effective for both of the decarbonylation and stereoselective hydroformylation processes. Furthermore, when paraformaldehyde was used as a source of formaldehyde under the above conditions, the conversion of styrene decreased, but the branched aldehyde was produced more predominantly with a higher enantioselectivity (93 %ee (*R*)).

Table 1 The Rh(I)-catalyzed asymmetric hydroformylation of styrene using formaldehyde[a]

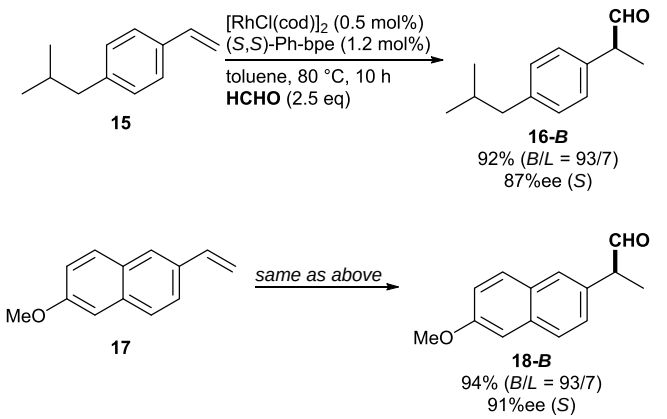


Entry	**I** (mol%)	Chiral ligand (mol%)	Conv.[b] (%)	Yield[b] (%)	**2-*B*/2-*L*[b]**	ee of **2-B** (%)[c]
1	0.6	**II** 0.6	39	28	84/16	18 (*R*)
2	0.6	**III** 0.6	71	69	78/22	52 (*R*)
3	0.6	**IV** 0.6	60	54	47/53	37 (*R*)
4	0.6	**V** 0.6	93	96	90/10	81 (*R*)
5	–	**V** 1.2	>99	>99 (92)	93/7	90 (*R*)
6	–	**VI** 1.2	>99	>99	94/6	90 (*R*)
7[d]	–	**V** 1.2	75	73	95/5	93 (*R*)

[a] Reaction conditions: styrene (1 mmol), formalin (37 wt% aqueous solution, 0.19 mL, 2.5 mmol), $[RhCl(cod)]_2$ (0.5 mol%), ligands (1.2 mol% totally) in toluene (5 mL) at 80 °C for 10 h. [b] Determined by GC using n-dodecane as an internal standard; yield of isolated product in parentheses. [c] Determined by HPLC after conversion to the corresponding alcohol. The absolute configurations were determined from specific optical rotation measurement. [d] Paraformaldehyde (5 equivs) was used instead of formalin, and the reaction was run for 20 h.

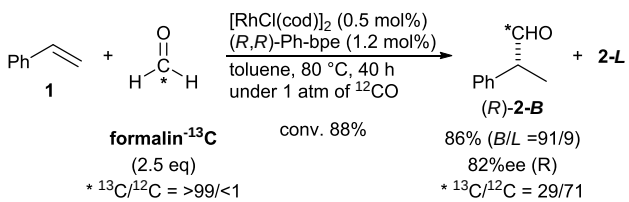
Various vinylarenes were converted to the corresponding *branched*-aldehydes with high enantioselectivity using the following reaction protocol: vinylarene (1 mmol), formaldehyde (for formalin, 2.5 mmol (A); for paraformaldehyde, 5 mmol (B)), $[RhCl(cod)]_2$ (0.5 mol%), (*R*,*R*)-Ph-bpe (1.2 mol%), and toluene (5 mL) at 80 °C in a 10 mL of screw-capped vial. The results are summarized in Table 2. Vinylarenes with electron-donating groups, 4-MeO- (**3**), 4-Me- (**5**), and 3-Me- (**7**), were hydroformylated to give the corresponding *branched*-aldehydes more highly enantioselectively, although the reaction efficiencies were slightly lower compared to the reaction of styrene (entries 1 and 3). On the other hand, the reactions of compounds with electron-withdrawing groups, 4-F- (**9**), 4-Cl- (**11**), and 4-CF_3- (**13**), proceeded more smoothly, however the regio- and enantioselecivities decreased (entries 7, 9, and 11). In the reactions of all of the vinylarenes examined, the use of paraformaldehyde led to the higher *branched*- and enantioselectivities, predominantly giving the corresponding *branched*-aldehydes (entries 2, 4, 6, 8, 10, and 12).

We next applied the present protocol to the synthesis of some pharmaceutical precursors. Under the standard conditions (Table 1, entry 6), 4-Isobutylstyrene (**15**) and 2-methoxy-6-vinylnaphthalene (**17**) reacted smoothly with formalin to give the corresponding branched aldehydes, **16-*B*** and **18-*B***, in high yields with both high regio- and enantioselectivities (Scheme 2). These aldehydes can easily be converted by classical oxidation methodology to the non-steroidal anti-inflammatory drugs, (*S*)-(+)-Ibuprofen and Naproxen, respectively.



Scheme 2 Synthesis of Pharmaceutical Precursors.

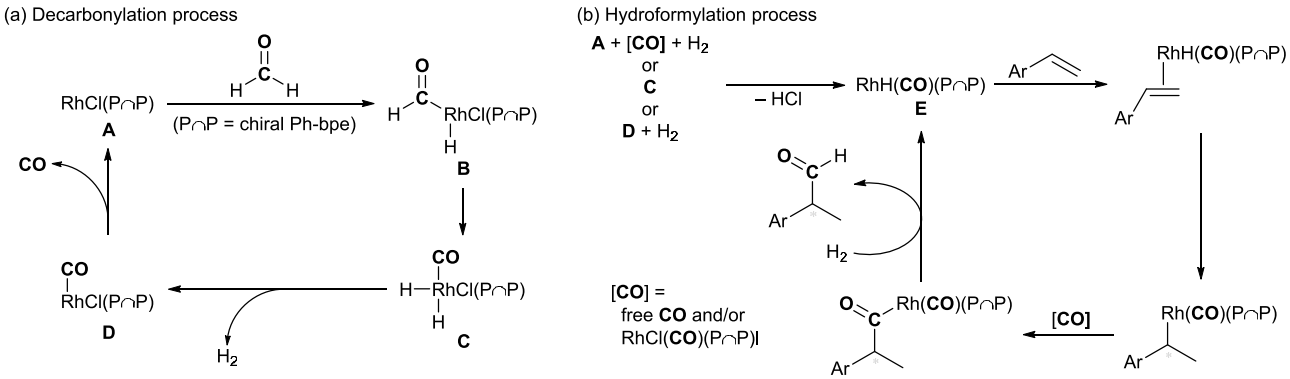
Lastly, we investigated whether the hydroformylation system developed here involves the decarbonylative degradation of formaldehyde to a carbonyl moiety and H_2. Using catalytic conditions similar to those for entry 5 in Table 1, the reaction of styrene with ^{13}C-labeled formaldehyde (>99% of ^{13}C) under ^{13}C-unlabeled carbon monoxide at atmospheric pressure was examined. Although the complete consumption of the substrate required a somewhat longer reaction time mainly due to the presence of external CO, the corresponding aldehydes were obtained with regio- and enantioselectivities similar to those for entry 5 in Table 1 (Scheme 3). A ^{13}C NMR analysis of the alcohol which was produced by reduction with $NaBH_4$ revealed that only 29% of the ^{13}C was introduced into the $–CH_2–OH$ group (originally, –CHO). This suggests that the pathway for the present hydroformylation reaction involves the incorporation of a carbonyl unit in the form of a CO ligand; thus, the carbonyl group of formaldehyde is transformed once to a CO ligand, which can be easily exchanged with external CO, on the rhodium center. It also means that rhodium-hydride species, which is essential for the hydroformylation, is also generated as well as a carbonyl moiety.



Scheme 3 Reaction of styrene with formaldehyde-^{13}C in the presence of ^{12}CO.

A possible reaction pathway is as follows (Scheme 4). The reaction begins with the decarbonylation of formaldehyde to produce formally a carbonyl moiety and two hydrogen moieties (left cycle). It includes the oxidative addition of formaldehyde to a rhodium center of **A** (**B**), the migratory extrusion of the carbonyl moiety (**C**), and the subsequent reductive elimination of H_2 (**D**), followed by the release of CO along with the regeneration of the decarbonylation catalyst **A**. The vinylarene is then enantioselectively hydroformylated using the resulting carbonyl, free CO and/or a CO ligand ([CO] in Scheme 4), and the resulting hydrogen, free H_2 and/or a hydride ligand (right

cycle). The hydroformylation cycle is catalysed by the rhodium(I)-hydride species (**E**), which is generated from (i) **A**, [CO] and H_2, (ii) **D** and H_2, and/or **C**. Although it is, at present, unclear in what form the carbonyl and hydrogen are introduced into the hydroformylation process (free CO or a carbonyl ligand and free H_2 or a hydride ligand, respectively), these two processes are catalyzed by a singly-loaded rhodium catalyst precursor, Rh(I)/chiral Ph-bpe. The results for the reaction using ^{13}C-labeled formaldehyde supports the conclusion that the hydroformylation pathway may not involve the direct addition of a formyl-rhodium-H species **B**,[13] which is generated from the oxidative addition of formaldehyde to the rhodium center.[14] Thus, formaldehyde acts as if it was syngas in the present protocol. Consequently, the sequence of events leads to a highly regio- and enantioselective hydroformylation without the direct use of syngas.



Scheme 4 Possible reaction pathway.

In conclusion, we report on the asymmetric hydroformylation of vinylarenes using formaldehyde as a syngas-substitute. The regioselectivity (*branched*/*linear* = up to 96/4) and enantioselectivity (up to 95%ee) can be attributed to the use of chiral Ph-bpe as a ligand. Both the decarbonylative degradation of formaldehyde to a CO moiety and hydrogen and the subsequent hydroformylation of vinylarenes are catalyzed by a singly-loaded catalyst, Rh(I)/chial Ph-bpe. Although further efforts will be necessary for improving the reaction from the standpoint of the amount of the catalyst loading and reaction efficiency, the present protocol has the potential to be a more practical synthesis of enantiomerically enriched aldehydes and their derivatives because all of the reagents used, except for vinylarenes, are readily commercially available. The mechanistic details of the reaction, including the origin of the enantioselectivity, are currently unclear but will be a subject of a future study.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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13 Seok's group proposed that the direct addition of a formyl-rhodium species, which are formed via the oxidative addition of the formyl C-H bond of formaldehyde to the rhodium center, to a C=C bond (formylrhodation) is included in $RhH(CO)(PPh_3)_3$-catalyzed hydroformylation of allyl alcohol with paraformaldehyde. See ref. 5c.

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Table 2 Asymmetric reactions of various vinylarenes with formaldehyde[a]

Entry	Vinylarene	HCHO[b]	Conversion (%)[c]	Time (h)	Yield (%)[c]	*B*/*L*[c]	ee of *B* (%)[d]
1	**3** 4-MeO-C_6H_4-CH=CH_2	A	97	15	**4** 93	94/6	91 (*R*)
2	**3**	B	64	40	**4** 63	96/4	95 (*R*)
3	**5** 4-Me-C_6H_4-CH=CH_2	A	>99	15	**6** >99	93/7	86 (*R*)
4	**5**	B	76	40	**6** 76	96/4	91 (*R*)
5	**7** 3-Me-C_6H_4-CH=CH_2	A	98	15	**8** 95	94/6	89 (*R*)
6	**7**	B	82	40	**8** 78	96/4	94 (*R*)
7	**9** 4-F-C_6H_4-CH=CH_2	A	94	10	**10** 93	94/6	92 (*R*)
8	**9**	B	69	20	**10** 69	96/4	95 (*R*)
9	**11** 4-Cl-C_6H_4-CH=CH_2	A	>99	10	**12** >99	91/9	80 (*R*)
10	**11**	B	80	20	**12** 80	96/4	92 (*R*)
11	**13** 4-CF_3-C_6H_4-CH=CH_2	A	>99	10	**14** 96	86/14	62 (*R*)
12	**13**	B	>99	20	**14** 96	88/12	67 (*R*)

[a] Reaction Conditions: vinylarene (1 mmol), formaldehyde, $[RhCl(cod)]_2$ (0.5 mol%), (*R*,*R*)-Ph-bpe (1.2 mol%) in toluene (5 mL) at 80 °C. [b] A = formalin(37 wt% aqueous solution, 0.19 mL, 2.5 mmol); B = paraformaldehyde (5 mmol). [c] Determined by GC using *n*-dodecane as an internal standard. [d] Determined by HPLC after conversion to the corresponding alcohol. The absolute configurations were determined from specific optical rotation measurement.

