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Selective Rhodium-Catalyzed Hydroformylation of Alkynes to α,β-Unsaturated Aldehydes with a Tetraphosphoramidite Ligand

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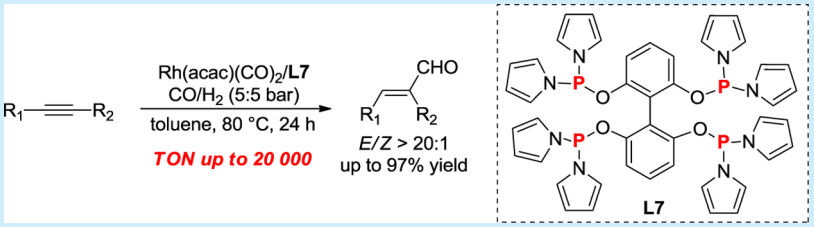
Supporting Information

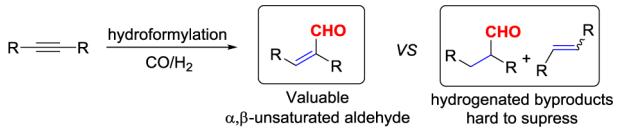


ABSTRACT: A tetraphosphoramidite ligand was successfully applied to a Rh-catalyzed hydroformylation of various symmetrical and unsymmetrical alkynes to afford corresponding α,β-unsaturated aldehyde products in good to excellent yields (up to 97% yield). Excellent chemo- and regioselectivities and high activities (up to 20 000 TON) were achieved. The corresponding α,β-unsaturated aldehyde products can be transformed into many useful and important organic molecules, such as indenamine derivatives and lukianol pyrroles. This great performance makes the hydroformylation of alkynes highly practical with great potential.

The hydroformylation of alkenes is one of the most important and efficient methods to access aldehydes.[1] Since it was first discovered by Otto Roelen in 1938,[2] this transformation has been widely explored and has made great progress in recent decades. Compared with the well-developed hydroformylation of alkenes, the corresponding hydroformylation of alkynes to produce α,β-unsaturated aldehydes in a perfect atom economic manner has received little attention.[3] The generated α,β-unsaturated aldehyde products and their derivatives are very valuable intermediates in organic synthesis for the construction of building blocks for agrochemicals, pharmaceuticals, and fine chemicals.[4] The early research on the hydroformylation of alkynes demonstrated that this transformation was extremely challenging owing to the poor reactivity and selectivity.[5] The byproducts of hydrogenated products and saturated aldehydes were difficult to suppress (Scheme 1).[6] After decades of strenuous effort, several relatively efficient catalytic systems have been developed. In 1995, Buchwald and co-workers applied Rh-Biphephos into the hydroformylation of some symmetric and unsymmetric alkynes with moderate results.[7] Subsequently, Hidai and co-workers developed a heterobimetallic $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$ catalytic system for this transformation under very harsh reaction conditions, yet chemoselectivity and *E*/*Z*-selectivity problems remain unresolved.[8] Alper and Van den Hoven introduced a zwitterionic Rh-PPh_3 complex to realize the hydroformylation of thiophenyl substituted alkynes.[9] In 2013, Breit and Beller respectively developed a Rh/self-assembling ligand system[10] and Pd/*N*-phenylpyrrole-based bisphosphine system[11] for the hydroformylation of alkynes with excellent chemo- and stereoselectivities. Despite the great progress that has been made, these catalytic systems did not exhibit high activity and showed a low turnover number (TON), which limited their practical application. To date, there has been no effective catalytic system for achieving excellent chemo- and stereoselective hydroformylations of various alkynes with a high TON. Herein, we present our electron-deficient tetraphosphoramidite ligand providing a highly active rhodium catalytic system for excellent chemo- and regioselective hydroformylation of symmetrical and unsymmetrical alkynes to furnish various α,β-unsaturated aldehydes with good to excellent yields and up to a 20 000 TON under mild reaction conditions.

It is well-known that a ligand is one of the most crucial factors to achieve high activity and selectivity for hydroformylation. We have successfully developed a variety of efficient and privileged ligands for Rh-catalyzed hydroformylation of alkenes with excellent selectivities in recent

Scheme 1. Challenges for the Hydroformylation of Alkynes



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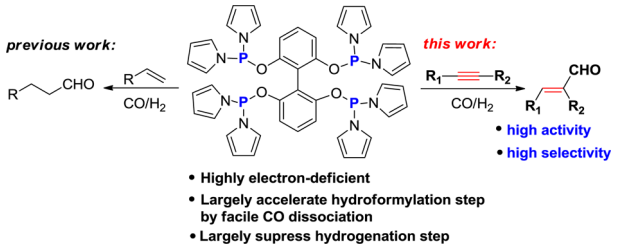
decades, such as phosphite ligands,[12] phosphorus ligands,[13] and phosphoramidite ligands.[14] Based on our ongoing research interest in this field, we made efforts to improve the selectivity and activity of hydroformylation of alkynes. Highly electron-deficient phosphine ligands contribute to largely accelerating the hydroformylation step by facile CO dissociation and suppressing the hydrogenation step in the hydroformylation of alkynes (Scheme 2).

Scheme 2. Features of Tetraphosphoramidite Ligand and the Application for the Hydroformylation of Alkenes and Alkynes



We began our initial investigation by evaluating a series of phosphine ligands in our laboratory (Figure 1) in the

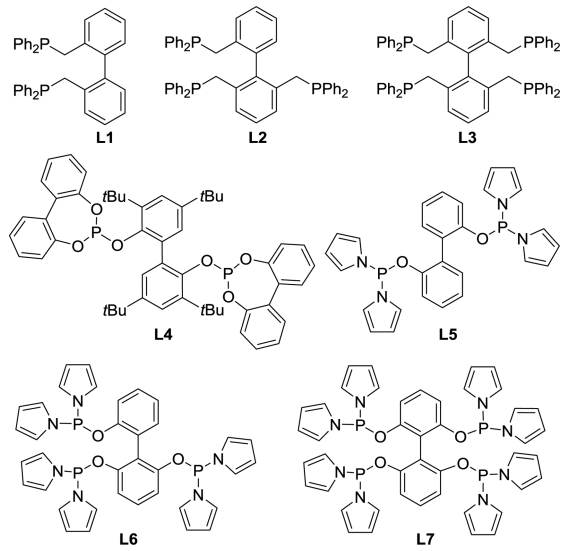
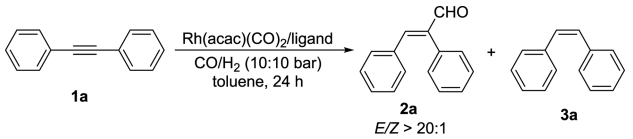


Figure 1. A series of phosphine ligands in our laboratory.

hydroformylation of diphenylacetylene (**1a**)[15] as the model substrate with the catalyst generated *in situ* by mixing Rh(acac)$(CO)_2$ and ligands in toluene (S/C = 2000). As shown in Table 1, biphosphorus, triphosphorus, and tetraphosphorus ligands (**L1**−**L3**) were applied, and low conversions and little hydrogenation product (*Z*)-**3a** were observed (Table 1, entries 1−3). This is probably due to the electron-rich properties of these ligands that tend to slow down the hydroformylation step. The phosphite ligand **L4** also obtained a similar result with them (Table 1, entry 4 vs entries 1−3). However, the highly electron-deficient biphosphoramidite, triphosphoramidite, and tetraphosphoramidite ligands (**L5**−**L7**) worked well and provided moderate to excellent yields of hydroformylation product **2a** and little hydrogenation product (*Z*)-**3a** (Table 1, entries 5−7). To our delight, the tetraphosphoramidite ligand **L7** was revealed as the best ligand (Table 1, entry 7). This

Table 1. Screening Conditions for Hydroformylation of Diphenylacetylene 1a[a]



entry	L	L/Rh	S/C	temp (°C)	conv (%)[b]	**2a** yield (%)[c]	**3a** yield (%)[b]
1	**L1**	1	2000	80	23.8	11.7	1.4
2	**L2**	1	2000	80	30.7	20.9	1.8
3	**L3**	1	2000	80	32.7	22.0	1.6
4	**L4**	1	2000	80	57.1	23.4	14.2
5	**L5**	1	2000	80	87.4	55.8	10.2
6	**L6**	1	2000	80	93.8	66.7	9.7
7	**L7**	1	2000	80	98.2	85.6	7.5
8	**L7**	1	5000	80	98.4	86.2	8.9
9	**L7**	2	5000	80	98.8	91.2	6.1
10	**L7**	3	5000	80	99.1	90.8	6.4
11	**L7**	4	5000	80	99.0	90.9	7.1
12	**L7**	8	5000	80	98.3	88.3	8.3
13	**L7**	2	5000	60	37.5	36.0	0.7
14[d]	***L7***	***2***	***5000***	***80***	***99.4***	***93.3***	***5.9***

[a][Rh(acac) $(CO)_2$] = 0.1 μM, toluene as solvent, diphenylacetylene **1a** as the substrate, reaction time was 24 h, reaction temperature was 80 °C, decane as internal standard, **L** = ligand. [b]Determined on the basis of GC analysis. [c]Yield was isolated yield. [d]CO/H_2 = 5/5.

result corresponded to the hypothesis we made that the highly electron-deficient catalytic system can largely facilitate the hydroformlation step by facile dissociation of CO via the *trans* effect and at the meantime largely suppress the hydrogenation step; as a result, excellent activity and selectivity were observed. When the ratio of substrate and catalyst (S/C) was increased from 2000 to 5000, a similar result was observed (Table 1, entry 8). Then we investigated the effect of the ratio of ligand **L7**/metal. Increasing the ratio from 1:1 to 2:1 led to an excellent yield of **2a** and trace hydrogenation product (*Z*)-**3a** (Table 1, entry 9). The yield became lower when the ligand/metal ratio was gradually increased to 8:1 resulting in no improvement (Table 1, entries 10−12). In addition, decreasing the reaction temperature from 80 to 60 °C provided extremely low reactivity (Table 1, entry 9 vs 13). We further found that syngas pressure played an important role in the result. When the pressure of CO/H_2 was decreased from 10:10 to 5:5, excellent reactivity and yield were obtained (93.3% yield, Table 1, entry 14).

Subsequently, a study of the reaction with S/C = 5000 in various solvents was carried out. These results are summarized in Table 2. Trace hydrogenation product (*Z*)-**3a** was observed in these solvents. The reactions proceeded well in toluene and CH_2Cl_2 with excellent results, but CH_2Cl_2 provided a slightly lower yield of hydroformylation product **2a** (Table 2, entries 1−2). The reactions displayed poor reactivities in polar solvents, such as THF, *i*-PrOH, and CH_3CN (Table 2, entries 3, 5, 7). In addition, ethyl acetate, *n*-hexane, and 1,4-dioxane furnished moderate to good yields of hydroformylation product **2a** (Table 2, entries 4, 6, 8). Therefore, solvents screening showed that toluene was identified as the best choice.

Encouraged by these excellent results, we turned our attention to the scope and generality of the hydromylation of various alkynes under the optimized reaction conditions. As shown in Scheme 3, a variety of diaryl alkynes proceeded

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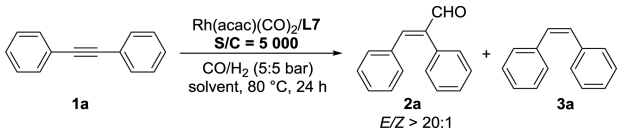
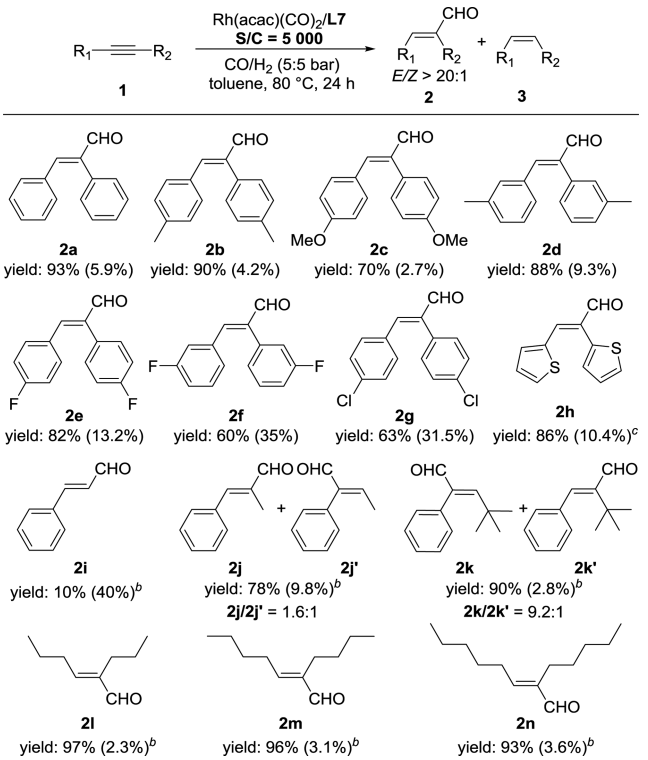
Table 2. Screening Solvents for Hydroformylation of Diphenylacetylene 1a Catalyzed by Rh(acac)(CO)$_2$/L7[a]



entry	solvent	conv (%)[b]	2a yield (%)[c]	3a yield (%)[b]
1	***toluene***	***99.4***	***93.3***	***5.9***
2	CH_2Cl_2	99.6	90.3	7.8
3	THF	46.7	36.7	4.7
4	ethyl acetate	97.3	81.8	8.1
5	*i*-PrOH	44.4	35.4	4.7
6	*n*-hexane	>99	84.3	10.7
7	CH_3CN	7.9	6.3	1.2
8	1,4-dixoane	92.5	62.9	9.3

[a][Rh(acac) $(CO)_2$] = 0.1 μM, diphenylacetylene **1a** as the substrate, **L7** as the ligand, reaction temperature was 80 °C, reaction time was 24 h, decane as internal standard. [b]Determined on the basis of GC analysis. [c]Yield was isolated yield.

Scheme 3. Study Scope for Hydroformylation of Various Alkynes 1 Catalyzed by Rh(acac)(CO)$_2$/L7[a]

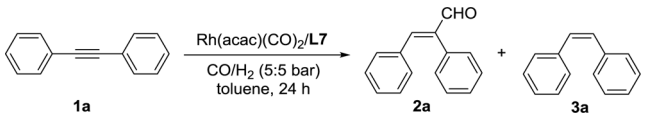


[a][Rh(acac) $(CO)_2$] = 0.1 μM, toluene as solvent, reaction temperature was 80 °C, reaction time was 24 h, S/C = 5 000. Yield of **2** was isolated yield. The yields of **3** are in parentheses, and *E*/*Z* selectivities were determined by ^{1}H NMR. [b]S/C = 1000, reaction temperature was 100 °C. [c]S/C = 100.

smoothly and formed the desired corresponding diaryl-substituted α,β-unsaturated aldehyde products (**2a**–**2g**) in good to excellent yields (60%–93% yields) with high *E* stereoselectivity (*E*/*Z* > 20:1) with S/C = 5000. In addition, although electron-deficient diaryl alkynes with different substitution patterns on the aromatic ring were tolerated in these reactions with 60%–82% yields of the corresponding α,β-unsaturated aldehyde products (**2e**–**2g**), we found a small amount of hydrogenation products (**3e**–**3g**) in the reaction systems. It was probably due to the electron-deficient properties of these substrates that tend to slow down the hydroformylation step. Remarkably, the heteroaromatic dithiophene alkyne (**2h**) also worked well in this catalytic system with a good yield. When phenylacetylene was used as a substrate, the reaction system did not produce good results. The terminal alkyne was easily hydrogenated, and we only obtained a 10% yield of the hydroformylation product (**2i**). It is noteworthy that when we changed the alkyl group of the unsymmetric aryl-alkyl alkynes from a methyl group (**2j**) to a bulky *tert*-butyl group (**2k**), the regioselectivity was improved to 9.2:1. This is mainly due to the steric effect, as it preferred to produce an aldehyde group on the less steric side. In addition, dialkyl alkynes (**2l**–**2n**) performed efficiently with excellent results (93%–97% yields).

As we expected, the Rh–**L7** complex was very stable and highly active. When the catalyst loading was decreased to 0.01 mol % (S/C = 10 000), the hydroformylation product **2a** was obtained in 99% conversion and 90% yield within 24 h. When the catalyst loading was further lowered to 0.005 mol % (S/C = 20 000), the reaction still proceeded well and provided **2a** in 99% conversion and 85% yield within 24 h (Scheme 4). And

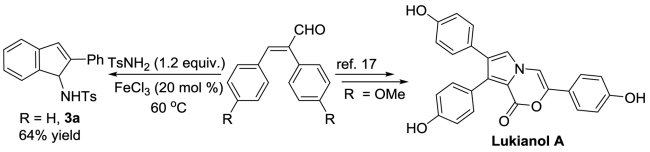
Scheme 4. Hydroformylation of Diphenylacetylene 1a with High S/C



traces of the hydrogenation product (*Z*)-**3a** were found in these reaction systems. This efficient performance contributes toward this transformation being used in industrial application with great potential.

To our delight, indenamine derivative **3a** can be obtained through condensation of the readily accessible cinnamylaldehyde **1a** via our excellent catalytic system and sulfonylamine under mild conditions (Scheme 5).[16] In addition, the

Scheme 5. Synthetic Transformation



corresponding products can be applied to synthesize lukianol pyrroles, such as lukianol A, which have been found to have activity against human epidermatoid carcinoma.[17]

In summary, we successfully developed the Rh-catalyzed hydroformylation of various symmetrical and unsymmetrical alkynes to afford corresponding α,β-unsaturated aldehyde products in good to excellent yields utilizing our previously developed highly electron-deficient tetraphosphoramidite ligand **L7**. It was possible that the highly electron-deficient feature of **L7** can largely accelerate the hydroformylation step and suppress the hydrogenation step. As a result, excellent chemo- and regioselectivities and high activities (up to 20 000

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TON) were achieved by our catalytic system. The great performance of this hydroformylation makes the preparation for α,β-unsaturated aldehydes practical and should broaden its utility in organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01605.

Experimental details and NMR data (PDF)

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Author Contributions

§Z.Z. and Q.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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