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Transition-Metal-Catalyzed Carbonylation Reactions of Olefins and Alkynes: A Personal Account

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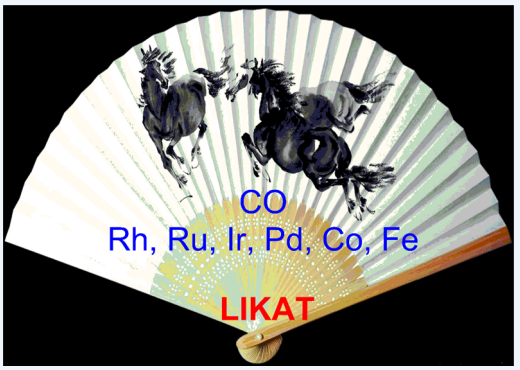
ABSTRACT: Carbon monoxide was discovered and identified in the 18th century. Since the first applications in industry 80 years ago, academic and industrial laboratories have broadly explored CO's use in chemical reactions. Today organic chemists routinely employ CO in organic chemistry to synthesize all kinds of carbonyl compounds. Despite all these achievements and a century of carbonylation catalysis, many important research questions and challenges remain.

Notably, apart from academic developments, industry applies carbonylation reactions with CO on bulk scale. In fact, today the largest applications of homogeneous catalysis (regarding scale) are carbonylation reactions, especially hydroformylations. In addition, the vast majority of acetic acid is produced via carbonylation of methanol (Monsanto or Cativa process). The carbonylation of olefins/alkynes with nucleophiles, such as alcohols and amines, represent another important type of such reactions.



In this Account, we discuss our work on various carbonylations of unsaturated compounds and related reactions. Rhodium-catalyzed isomerization and hydroformylation reactions of internal olefins provide straightforward access to higher value aldehydes. Catalytic hydroaminomethylations offer an ideal way to synthesize substituted amines and even heterocycles directly. More recently, our group has also developed so-called alternative metal catalysts based on iridium, ruthenium, and iron.

What about the future of carbonylation reactions? CO is already one of the most versatile C1 building blocks for organic synthesis and is widely used in industry. However, because of CO's high toxicity and gaseous nature, organic chemists are often reluctant to apply carbonylations more frequently. In addition, new regulations have recently made the transportation of carbon monoxide more difficult. Hence, researchers will need to develop and more frequently use practical and benign CO-generating reagents. Apart from formates, alcohols, and metal carbonyls, carbon dioxide also offers interesting options. Industrial chemists seek easy to prepare catalysts and patent-free ligands/complexes. In addition, non-noble metal complexes will interest both academic and industrial researchers. The novel Lucite process for methyl methacrylate is an important example of an improved catalyst. This reaction makes use of a specific palladium/bisphosphine catalyst, which led to the successful implementation of the technology. More active and productive catalysts for related carbonylations of less reactive olefins would allow for other large scale applications of this methodology. From an academic point of view, researchers continue to look for selective reactions with more functionalized olefins. Finally, because of the volatility of simple metal carbonyl complexes, carbonylation reactions today remain a domain of homogeneous catalysis. The invention of more stable and recyclable heterogeneous catalysts or metal-free carbonylations (radical carbonylations) will be difficult, but could offer interesting challenges for young chemists.

INTRODUCTION

Carbon monoxide (CO) was discovered in the 18th century by de Lassone who reacted zinc oxide with coke. Soon after, it was first identified by W. C. Cruikshank.[1] Nowadays, this gas is used as an inexpensive and easily available C1 source for all kinds of carbonylation reactions. Already at the beginning of the 20th century, the first work on transition metal-catalyzed carbonylations has been performed. Since then, impressive progress has been achieved in this area. Notably, apart from academic developments, carbonylation reactions with CO are applied on bulk scale in industry. For example, the vast majority of acetic acid is produced via carbonylation of methanol (Monsanto or Cativa process).[2] Furthermore, the carbonylation of olefins/alkynes with nucleophiles, for example, alcohol and amine, constitute another important type of such reactions. As shown in Scheme 1, a range of carboxylic acids, esters, and amides can be easily prepared by this and related transition metal-catalyzed carbonylations.

From the point view of reaction mechanism, despite the differences in catalysts, substrates, and nucleophiles, the general accepted reaction mechanism is as shown in Scheme 2. The reaction starts with the corresponding metal-hydride species, which is primarily formed by the reaction of the precatalyst

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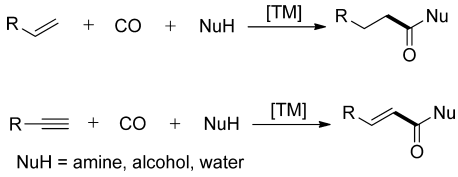
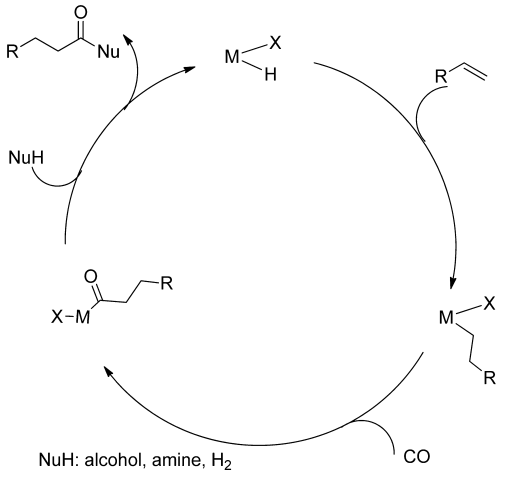
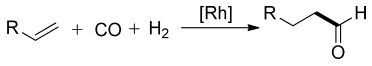
Scheme 1. Carbonylation of Unsaturated Compounds



Scheme 2. General Reaction Mechanism: Pd-Catalyzed Carbonylation of Olefins



with acid additives (TsOH, HBF_4, etc.) or from the reaction of a suitable acylmetal complex with nucleophiles during the catalytic cycle. Subsequent coordination, insertion of the unsaturated substrates, followed by further insertion of carbon monoxide leads to the acyl metal complex. Finally, the catalytic cycle is finished by the nucleophilic attack of the nucleophile on the acylmetal species and the metal-hydride is regenerated. To be clear, the alternative carbomethoxy mechanism was provided



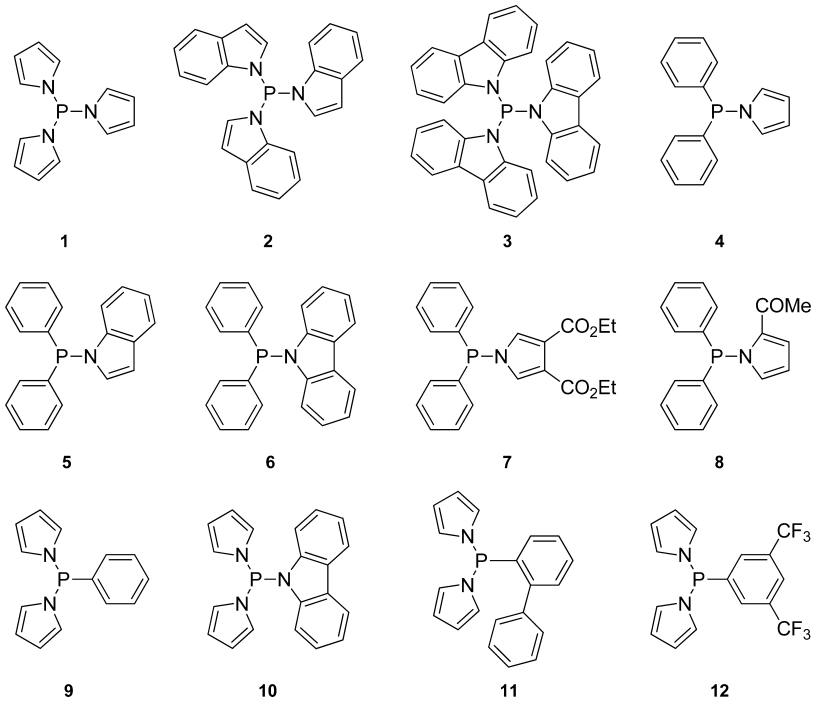
in the copolymerization of alkenes with CO and carbonylation of alkynes as well.

A special case of the carbonylation of unsaturated substrates is the so-called hydroformylation, which makes use of hydrogen as nucleophile.[3] With respect to scale this process represents the most important homogeneous catalytic reaction. At the beginning of industrial homogeneous catalysis, nickel and cobalt catalysts prevailed in alkoxycarbonylations and hydroformylations. Due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylation) and palladium (for alkoxycarbonylations) as base metals. More recently, there is an increasing interest to develop less expensive and environmentally benign catalysts for these reactions. In this Account, a brief overview on our developments as well as important work of other research groups in the area of carbonylations of olefins and alkynes will be given. In addition, related reactions such as the carbonylative Heck reaction will be discussed, too.

RHODIUM-CATALYZED HYDROFORMYLATION REACTIONS

After the work developed in the industry from 1991 to 1995 on rhodium-catalyzed hydroformylations, this topic was started and pursued in the research group at the TUM (eq 1). From the beginning on, the focus of the work was on the development of industrially relevant catalysts. For the bulk chemical industry, a key issue for any larger scale application is the price of starting materials. Hence, it is not surprising that there exist a continuing interest to substitute terminal olefin feedstock by cheaper olefins mixtures. Typical examples of this strategy are the use of mixtures of butenes to give valeraldehyde as well as C8-olefins to yield nonanals. In order to obtain the

Scheme 3. Pyrrolyl-, Indolyl-, and Carbazoylphosphines Ligands for Domino-Isomerization-Hydroformylation Processes



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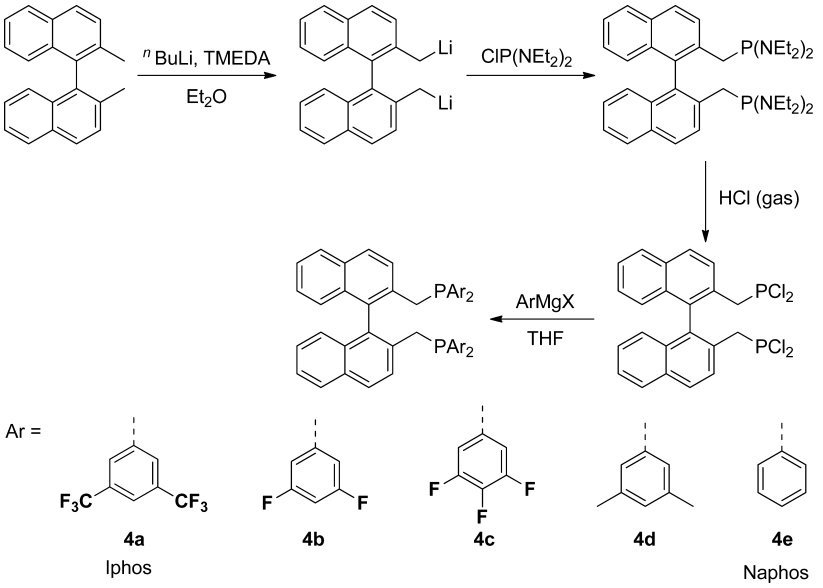
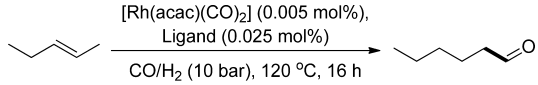
Scheme 4. Modular Synthesis of Substituted Naphos Derivatives



desired linear aldehyde from the corresponding internal olefins, isomerization of internal olefins must occur faster than the hydroformylation reaction. In addition, there should be a reasonable difference in the rate of hydroformylation of internal and terminal olefins and finally the catalyst should be highly *n*-selective for the hydroformylation step of the terminal olefin. It is well-known that coordinatively unsaturated rhodium species with less electron-rich ligands exhibit significant activity toward isomerization of the substrate. Such active catalysts are formed in the presence of sterically demanding phosphites or phosphines. After establishing the research group in Rostock, we started working on this topic in the late 1990s. Since then, several groups including us reported excellent regioselectivities for the rhodium-catalyzed hydroformylation of internal olefins with chelating bulky phosphites or phospines as ligands.[4] While phosphites often can be prepared more easily, phosphines offer advantages in terms of stability (hydrolysis). In general, the regioselectivity of the hydroformylation is influenced by π-acceptor and σ-donor properties of the respective ligand. Hence, we were curious to investigate the electronic properties of heterocyclic phosphine ligands and their influence on the *n*/*iso* ratio of the hydroformylation of internal olefins. More specifically, a number of phosphines containing pyrrol-, indol-, and carbazol units were synthesized by reaction of phosphorus chloride and *N*-heteroarenes or by the reaction of di(*N*-pyrrolyl)chlorophosphine with Grignard reagents (Scheme 3). The application of these ligands in the rhodiue-catalyzed hydroformylation of 2-pentene was also demonstrated. Although the observed regioselectivities were not fully satisfactory, the results show that domino-isomerization-hydroformylation processes of internal olefins proceed in the presence of specific pyrrolyl phosphines in good to very good total yield of all aldehydes. As expected increasing π-acidity of the ligand resulted in an increased yield of the linear hydroformylation product. The best *n*/*iso* ratios of about 60:40 were obtained at low synthesis gas pressure (10 bar) in the presence of the simple P(pyrrolyl)$_3$ (**1**) ligand.[5]

Another class of ligands, which we studied for such reactions is based on the ligand Naphos with a binaphthyl backbone. Our group developed a simple procedure for the synthesis of various substituted Naphos derivatives on multigram scale (Scheme 4). For the first time, these Naphos-derivatives were used in the hydroformylation of internal olefins to linear aldehydes. Notably, good yields with excellent regioselectivities were obtained (Scheme 5).[6] However, in order to be applied in industrial hydroformylation reactions, the activity and long-term stability of the catalyst system needs to be improved further.

Scheme 5. Hydroformylation of 2-Pentene with Naphos-type Ligands



Ligand = **4a,**	**4b,**	**4c,**	**4d,**	**4e**
Yield: 68%	59	61	11	22
n/*iso*: 91:9	94:6	93:7	78:22	89:11
TOF: 425 h^{-1}	369 h^{-1}	381 h^{-1}	69 h^{-1}	138 h^{-1}

Sulfonated Naphos (so-called BINAS) was synthesized first in 1996 and used for the highly selective rhodium-catalyzed hydroformylation of propene.[7] Later on, we successfully applied a mixture of the different sulfonated ligand isomers in hydroformylations of internal olefins in a biphasic water system (Scheme 6).[8] Apart from the ligand, also the pH value and CO partial pressure are important factors for the success of this reaction. Notably, the resulting water-soluble rhodium catalyst led to significantly higher regioselectivity compared to similar rhodium complexes soluble in organic solvents. At that time, the obtained *n*-selectivities exceeded all known literature data and the catalyst was easily reused several times without decrease of product yield and selectivities.

With respect to ligands, phosphites are easily prepared from inexpensive PCl_3 and alcohols. In fact, from an industrial point of view creating a P−O bond is more economical to a P−C bond due to the lower costs for such a transformation. Although they might hydrolyze more easily, they are less sensitive to air and other oxidizing agents than phosphines. Hence, in the past decades, several companies but also academic groups continuously synthesize novel phosphite

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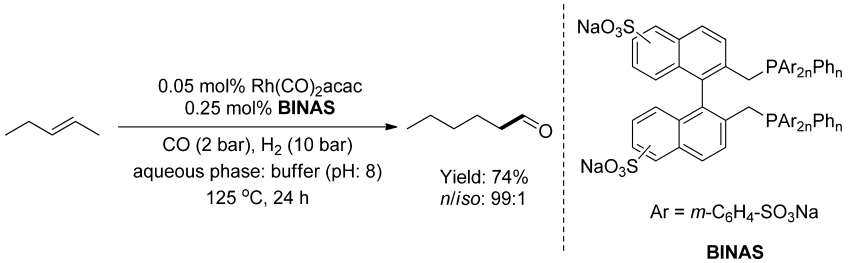
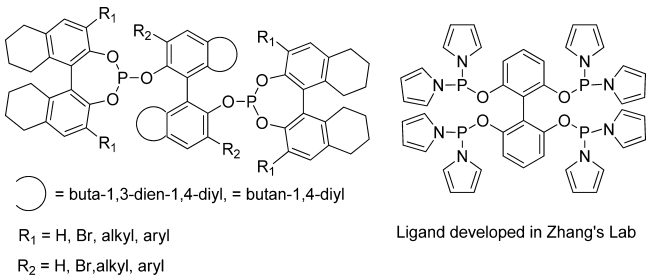
Scheme 6. Hydroformylation of 2-Pentene with BINAS



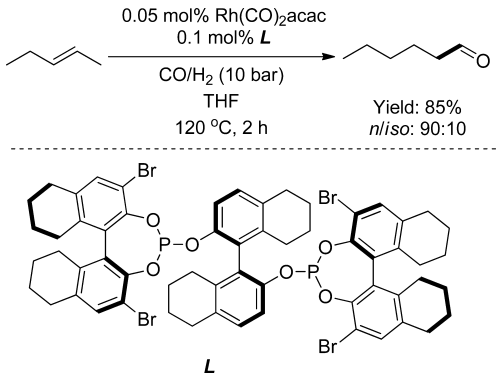
ligands for hydroformylation reactions (Scheme 7).[9] In this context, our H_8-BINOL-based phosphite ligands displayed

Scheme 7. Novel Bisphosphite Ligands



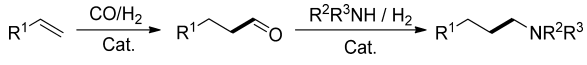
excellent activity in the hydroformylation of internal and terminal olefins with high selectivities for the linear aldehydes (Scheme 8).[10] From a mechanistic point of view, the active catalysts have been characterized by in situ NMR studies.[11]

Scheme 8. Isomerization-Hydroformylation of 2-Pentene with Novel Bisphosphite Ligand



After the move of the research group from Munich to Rostock in 1998, the development of synthetic methodologies for the selective formation of C−N bonds was attractive. In consequence, we started to investigate an extension of the hydroformylation technology, the so-called hydroaminomethylation reaction (Scheme 9). Obviously, this transformation represents an environmentally benign (one-pot, atom efficient) synthesis of amines from easily available olefins. This domino reaction consists of an initial hydroformylation of olefins to the corresponding aldehyde, subsequent formation of an enamine

Scheme 9. Hydroaminomethylation of Olefins



(or imine) followed by hydrogenation. The challenge of this reaction sequence is to obtain high chemo- and regioselectivity to achieve efficiently the expected amine.

Using the hydroformylation of olefins in the presence of diethylamine as a model system, we developed an efficient catalyst system, consisting of a cationic rhodium precursor together with Xantphos as ligand. Terminal olefins are regioselectively hydroaminomethylated to produce synthetically important linear amines in excellent yield and selectivity (Scheme 10).[12] Aliphatic olefins gave the corresponding linear products with excellent regioselectivities > 98:2. Notably, the catalyst system is tolerant to a variety of reactive functional groups, thereby making the procedure valuable for the synthesis of interesting organic building blocks.

During our studies of the hydroformylation of internal olefins to linear aldehydes, Naphos-type ligands with electron-withdrawing substituted aryl groups such as Iphos showed high activity for isomerizations. Hence, we introduced these ligands also for the hydroaminomethylation of internal olefins. Gratifyingly, we found that the combination of a cationic rhodium precursor $[Rh(cod)_2]BF_4$ with Iphos as ligand allows for highly selective hydroaminomethylation of internal olefins (Scheme 11).[13] Different aliphatic internal olefins gave for the first time the corresponding linear products in general with good regioselectivities (Table 1).

In addition to Naphos and Iphos ligands, also Xantphos derivatives were tested for the hydroaminomethylation of aliphatic alkenes. Best results were obtained using Xantphenoxaphos (Scheme 12), which showed excellent selectivities in this reaction. The steric hindrance and the large bite angle of the Xantphos ligands is particularly adapted to produce linear aldehydes in the hydroformylation step, even starting from internal alkenes, owing to the isomerization reaction of the carbon−carbon double bond. Very high regioselectivities were achieved, not only starting from terminal olefins (*n*/*iso* > 98:2), but also from internal olefins (Scheme 13) or even from an industrial mixture of octene isomers. In this latter case, the chemo- and regioselectivities attained were 85% and 81%, respectively. Extension to aromatic olefins gave also satisfactory regioselectivities, as n/iso values ranging between 80:20 and 99:1 were reached.[14]

Testing various combinations of $[Rh(cod)_2]BF_4$ with bisphosphine ligands, we found that 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) in the presence of tetrafluoroboric acid provided the best result in the reaction between styrene and aniline (96%, and 12:88, respectively) (Scheme 14). Different arylethylenes with various substituted anilines gave the corresponding secondary amines in high yields with good regioselectivities toward the branched product. An attractive feature of this catalytic system lies in the mild pressure and low temperature used. This procedure showed to

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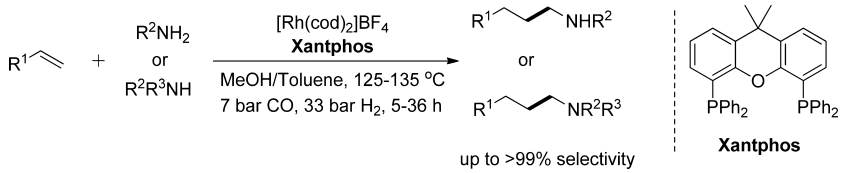
Scheme 10. Hydroaminomethylation of Terminal Olefins



Scheme 11. Hydroaminomethylation of 2-Butene

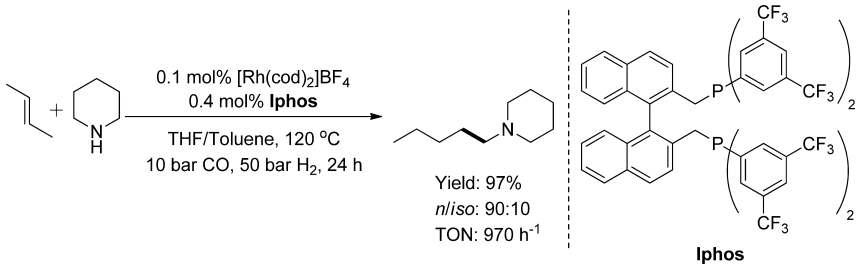
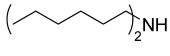
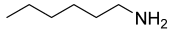
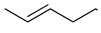
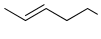
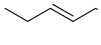


Table 1. Hydroaminomethylation of Internal Olefins[a]

Olefin	Amine	Conv. (%)	Total amine selectivity (%)	Linear amine selectivity (%)	*n*:*iso*	TON
		100	97	88	90:10	970
		88	98	82	82:18	862
		71	69	53	72:28	490
		78	90	83	91:9	702
		100	65	74	78:22	650
		80	87	62	71:29	696
		77	91	76	78:22	701
		60	96	90	94:6	576
		88	96	68	71:29	563*

[a]Reaction conditions: olefin/amine (15 mmol), $[Rh(cod)_2]BF_4$ (0.1 mol %), Iphos (0.4 mol %), toluene (15 mL), THF (15 mL), P_{CO} (10 bar), P_{H_2} (50 bar), temperature (120 °C), time (24 h). *10 mmol of both 3-hexene and piperidine.

be useful for the synthesis of a wide variety of amphetamine derivatives.[15]

N-Heterocyclic carbene (NHC) ligands bound to transition metals have been proven to be effective in a wide variety of catalytic reactions. Hydroaminomethylations with N-heterocyclic carbene ligands were first reported by our group.[16] The rhodium monocarbene complex [RhCl(cod)(Imes)] (Imes = 1,3-dimesitylimidazol-2-ylidene) was successfully tested for the hydroaminomethylation of several aliphatic and cyclic olefins or aryethylenes (Scheme 15). Using this catalyst most of the time good activity was achieved. Obviously, starting from 1,1-diarylethenes the regioselectivity toward the linear amines is excellent because of the steric hindrance of the two aryl substituents. In the presence of 0.1 mol % of [RhCl(cod)(Imes)] the corresponding arylpropylamines are obtained in high yield and selectivity. This procedure gave for the first time

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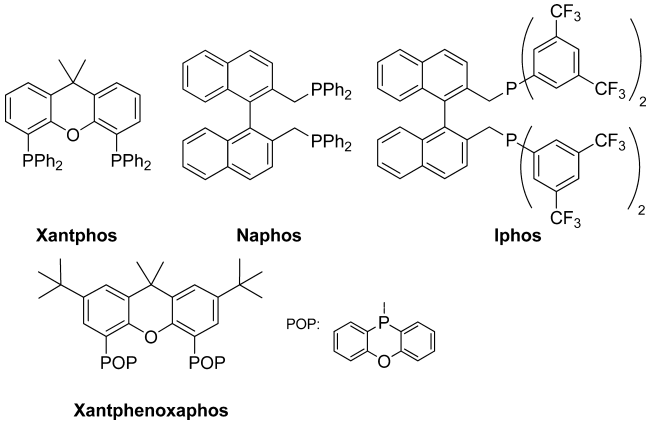
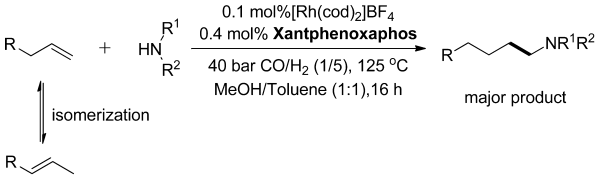
Scheme 12. Selected Bisphosphine Ligands for Hydroaminomethylation of Olefins



Scheme 13. Hydroaminomethylation of Internal Olefins with Secondary Amines Using Xantphenoxaphos as Ligand

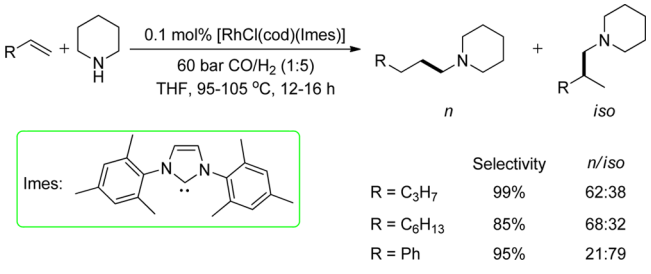


R = C_5H_{11}, C_3H_7, C_2H_5, or substituted aliphatic chains, only the 2-alkene is represented
HNR^1R^2 = various secondary amines

biologically active pheniramines in a single reaction step with high catalyst activity (Scheme 16).

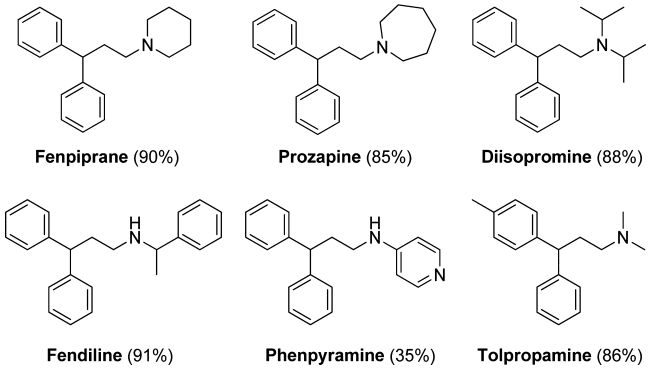
During our studies on the improvement of tailor-made catalyst systems for hydroaminomethylations, we noted that the reaction steps of the sequence [(1) hydroformylation, (2) imine/enamine formation, and (3) hydrogenation] are influenced by the ligand in different ways. Among the ligands tested in the model reaction of 1-pentene with piperidine, Naphos and its derivatives provided the corresponding enamine (*N*-1-hexenylpiperidine). After careful optimization, we discovered a highly selective catalyst system for the hydroaminomethylenation of olefins to enamines (Scheme 17).[17] Such a domino reaction has advantages compared to the stepwise procedure. Key to the success is the use of a catalyst system consisting of a neutral rhodium precursor together with Naphos as ligand under mild conditions (CO/H_2 = 10 bar; 65 °C). As shown in Scheme 17, aliphatic olefins gave the corresponding linear products with regioselectivities of 99:1. Interestingly, this catalyst system is also tolerant to a variety of potentially reactive functional groups making the procedure valuable for the synthesis of interesting organic building blocks, including chiral enamines.

Scheme 15. Hydroaminomethylation with Rhodium-Carbene Complexes



	Selectivity	n/iso
R = C_3H_7	99%	62:38
R = C_6H_{13}	85%	68:32
R = Ph	95%	21:79

Scheme 16. Pheniramines Synthesized Using Rhodium-Carbene Complexes

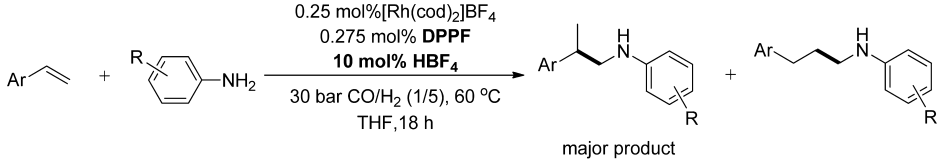


Moreover, we were interested in the reactivity of other *N*-nucleophiles under hydroformylation conditions, such as hydrazines. Based on our previous work of hydroformylation reactions, we easily found a suitable catalyst system for the selective synthesis of hydrazones from various olefins (Scheme 18). Here, the optimal catalyst system consisted of a neutral rhodium precursor together with Iphos as ligand (CO/H_2 = 10 bar; 65 °C). Based on this catalyst system, we also realized the synthesis of indoles by combination of this method with the Fischer indole synthesis (Scheme 19).[18]

IRIDIUM-CATALYZED HYDROFORMYLATION OF OLEFINS

As mentioned earlier on apart from cobalt and rhodium, other metals have only been scarcely applied in these transformations so far. The main reasons for this were the low activity of the corresponding metal carbonyl complexes as well as the tendency to undergo increased side reactions such as hydrogenations. On the other hand, alternative metals might display new reactivity in the presence of suitable ligands and offer also easier patent strategies. In this regard, the use of iridium catalysts provides an interesting option. Unfortunately, the activity of iridium complexes for the synthesis of aldehydes

Scheme 14. Hydroaminomethylation of Styrenes with Anilines Using DPPF as Ligand



Ar = C_6H_5, *p*-ClC_6H_4, *p*-$MeOC_6H_4$
R = H, -OMe, $-CF_3$, -CN

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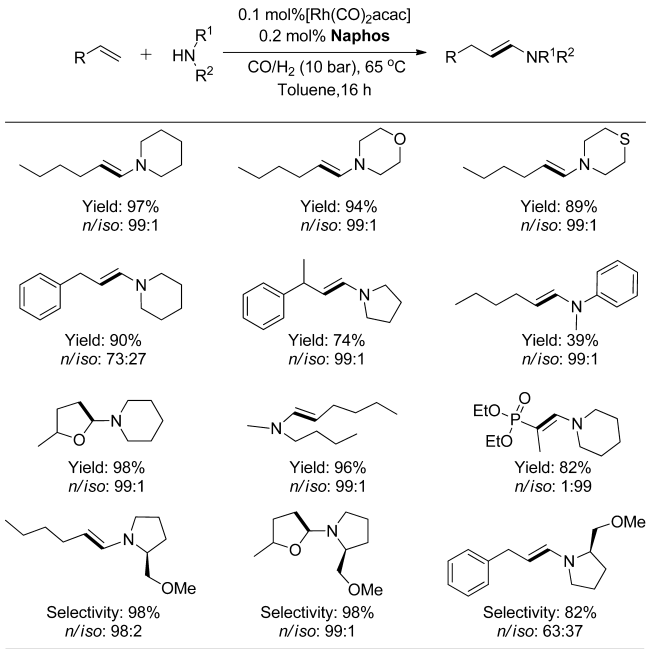
Scheme 17. Hydroaminomethylenation of Olefins to Enamines with Rh/Naphos

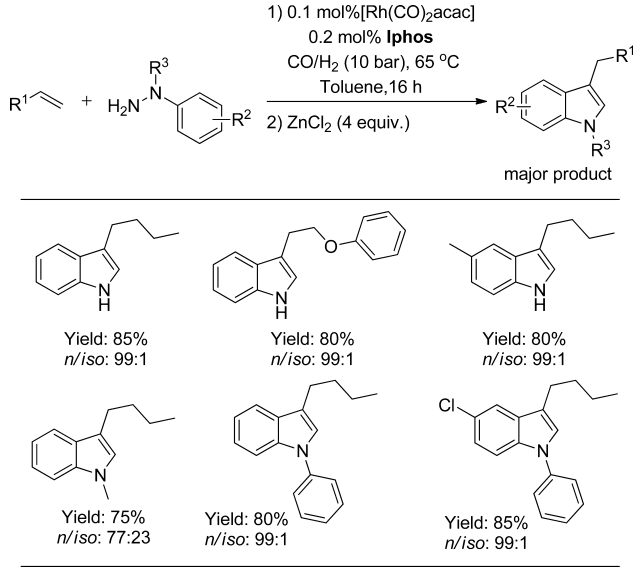


or alcohols from olefins was only moderate compared to similar rhodium and cobalt systems. Moreover, hydrogenations to the unwanted alkanes constitute a serious side reaction. Noteworthy, our group developed a general and efficient protocol for iridium-catalyzed hydroformylation of olefins, which proceeded under mild conditions with commercially available iridium precursors and phosphine ligands.[19] The competing hydrogenation side reaction is significantly reduced by careful control of the reactions conditions. Key to the success is the use of an excess of carbon monoxide (partial pressures $CO/H_2 = 2/1$) and the introduction of CO pressure before heating. The catalyst system was applied successfully to various aliphatic and aromatic olefins. Aldehyde yields ranging from 62 to 90% have been achieved for different olefins (Scheme 20).[20] Interestingly, when the reaction mixture was allowed to stand at 0−10 °C for several hours, precipitation of $[Ir_2(CO)_6(PPh_3)_2]$ was observed. The use of this complex as a catalyst in the hydroformylation of 1-octene gave *n*-nonanal in 46% yield with a regioselectivity of 74:26. Hence, this complex readily forms the "real" active species.

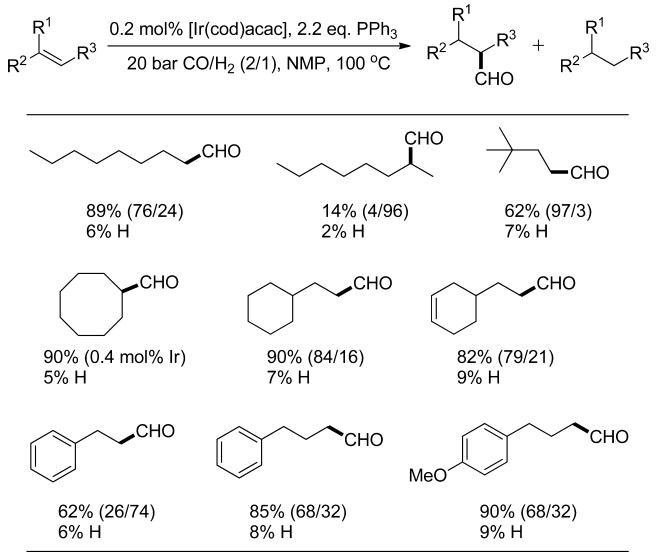
RUTHENIUM-CATALYZED HYDROFORMYLATION AND RELATED REACTIONS

Among all the available noble metal catalysts used for carbonylation reactions, ruthenium is the least expensive metal, and is also becoming increasingly important in homogeneous catalysis.[21] The relative activity of ruthenium carbonyl complexes is assumed to be lower by a factor of 10^5

Scheme 19. One-Pot Synthesis of Indoles from Olefins

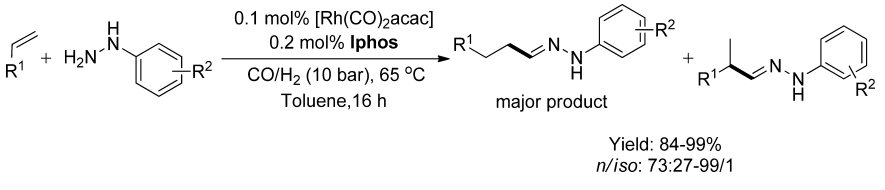


Scheme 20. Iridium-Catalyzed Hydroformylation of Various Olefins



compared with similar rhodium complexes for hydroformylation reactions. Although pioneering work for the application of ruthenium catalysts in hydroformylation reactions were reported by Wilkinson and co-workers already in 1965, only a few selective ruthenium-based catalysts have been described in the decades since then. Similar to iridium, in general only a narrow substrate scope was realized with these systems and the reactions were often carried out under harsh conditions with high catalyst loadings. Typically, mixtures of aldehydes and

Scheme 18. Synthesis of Hydrazones from Various Olefins



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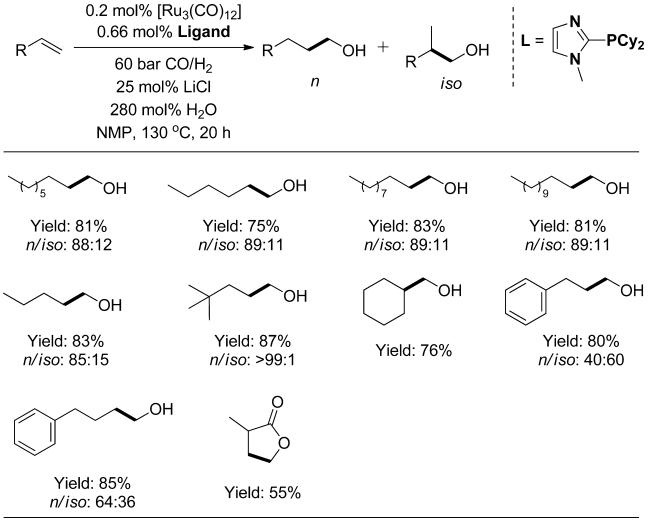
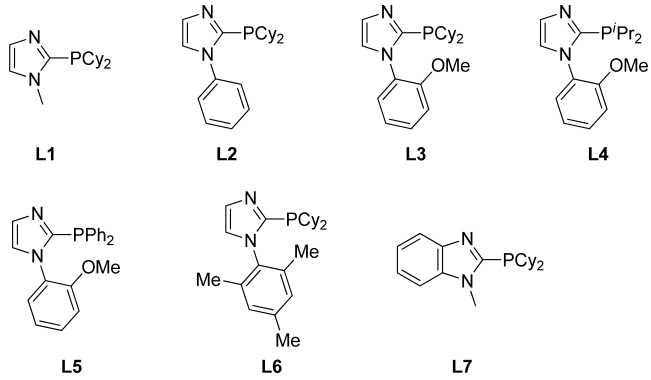
alcohols were obtained, with higher temperatures preferred for obtaining the alcohols. In addition, hydrogenation and/or isomerization of the substrate occurred as side reactions. Very recently, our group developed efficient ruthenium catalyst systems based on $[Ru_3(CO)_{12}]$ and imidazole-substituted monophosphine ligands.[22] This catalyst allows for hydroformylation/hydrogenation of olefins to provide selectively linear aliphatic alcohols. Notably, water is employed as an additive, which is believed to facilitate the formation of a catalytically active ruthenium hydride species. To suppress unwanted hydrogenation of the alkene, 0.25 equiv of LiCl is added to the reaction mixture. The catalyst system was applied to various aliphatic and aromatic olefins providing the corresponding alcohols in good to excellent yields and with high chemo- and regioselectivities (Scheme 21). The more challenging internal alkene, 2-octene, was transformed to C9-alcohols in 59% yield and 66:34 n/iso selectivity.

Scheme 21. Ruthenium-Catalyzed Hydroxymethylation of Olefins



Similar to hydroformylations, the hydroaminomethylation of olefins was mainly performed in the presence of rhodium catalysts and the application of alternative metals has received only scarce attention. In this area, only few examples have been reported including the ruthenium-catalyzed hydroaminomethylation reaction of propene by Keim and Schaffrath using carbon monoxide and the $Ru_3(CO)_{12}$-catalyzed hydroaminomethylation using carbon dioxide under reverse water-gas-shift-reaction (WGSR) conditions by Eilbracht and co-workers.[23] Due to the narrow substrate scope as well as the required high catalyst loading and harsh reaction conditions, more general ruthenium-catalyzed hydroaminomethylation reactions are desired. As mentioned above, we found that imidazole-substituted monophosphine ligands showed good activity and regioselectivity for ruthenium-catalyzed hydroformylation of olefins. Based on this observation, several imidazole-based monophosphine ligands were synthesized and tested for the hydroaminomethylation of olefins in the presence of $Ru_3(CO)_{12}$ (Scheme 20). To our delight, **L3** (Scheme 22) was identified as a promising ligand. As shown in Scheme 21, various types of olefins and amines were smoothly transformed to the corresponding linear amines in good to excellent yields and regioselectivities using catalytic amounts of triruthenium dodecacarbonyl and **L3** (Scheme 23).

Scheme 22. Different Imidazole-Substituted Monophosphine Ligands



More interestingly, this system also showed promising activity in the challenging hydroaminomethylation of enamides and internal olefins.[24]

PALLADIUM-CATALYZED HYDROFORMYLATION REACTIONS

Among all transition metals, palladium forms probably the most general and versatile catalysts which are widely used for all kinds of CC-bond formation. Regarding industrially important carbonylation reactions of olefins, in the last two decades especially cationic palladium cis-chelating diphosphine complexes proved to be versatile catalyst precursors. On the other hand, only few studies on palladium-catalyzed hydroformylations are reported in the literature. Based on our general interest in less common catalytic systems, we recently applied palladium complexes with phenylpyrrole-substituted bisphosphine ligands, which showed a high efficiency and selectivity in hydroformylation of aliphatic and aromatic olefins.[25] The presence of acid (*p*-TsOH) added to the catalyst led to extremely fast isomerization of 1-octene, even at room temperature and without any hydrogen pressure: After 10 min more than 90% of 1-octene is converted to internal olefins. Under optimized conditions of temperature, pressure and acid, the system was successfully applied to various substrates providing good to excellent selectivity (Scheme 24). Indeed, *N*-vinylphthalimide was hydroformylated in 95% of yield with regioselectivity up to 98% for the linear aldehyde, which is the highest value so far reported for this substrate.

Moreover, a less reactive substrate such as cyclooctene was converted in 57% of yield without further optimization.

Compared to the well-known hydroformylation of olefins using Rh or Co catalysts, the corresponding reaction of alkynes has received only scarce attention. In these cases, the formation of the corresponding saturated aldehydes and alkenes was hardly suppressed. A recent improvement was reported by Breit and co-workers who used a rhodium-based catalyst system employing a self-assembling ligand for the selective hydroformylation of alkynes.[26] Most recently, we demonstrated the palladium-catalyzed general hydroformylation of alkynes, too.[27] Notably, competing hydrogenation side reactions were almost completely suppressed. Various alkynes were smoothly transformed to the corresponding α,β-unsaturated aldehydes in good to excellent yields with good stereoselectivities. As shown in Scheme 25, representative examples of unsymmetrical alkynes having different functional groups gave the correspond-

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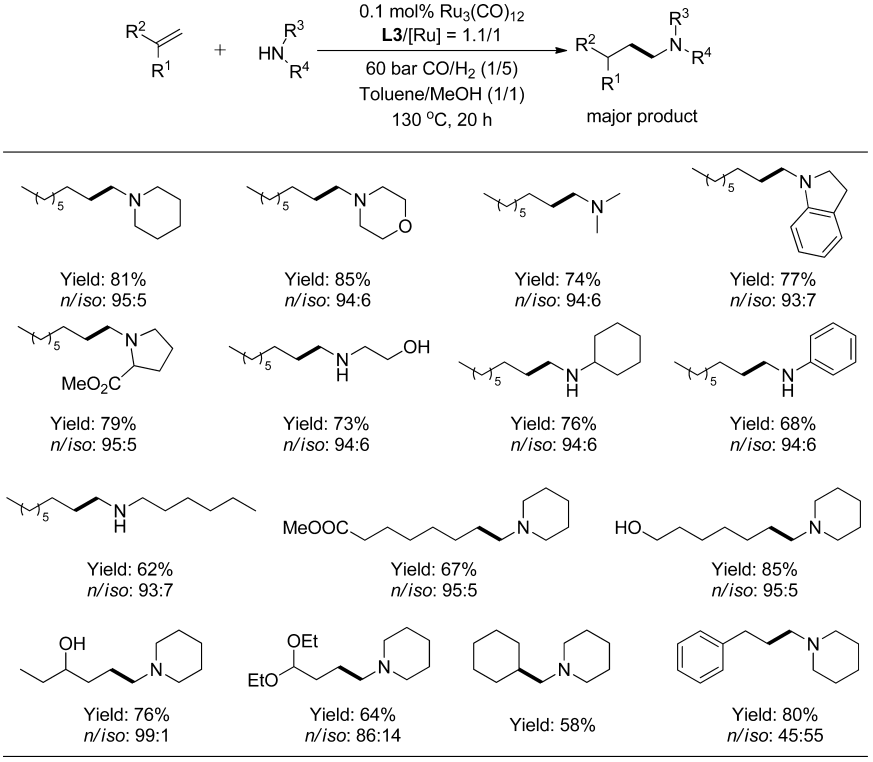
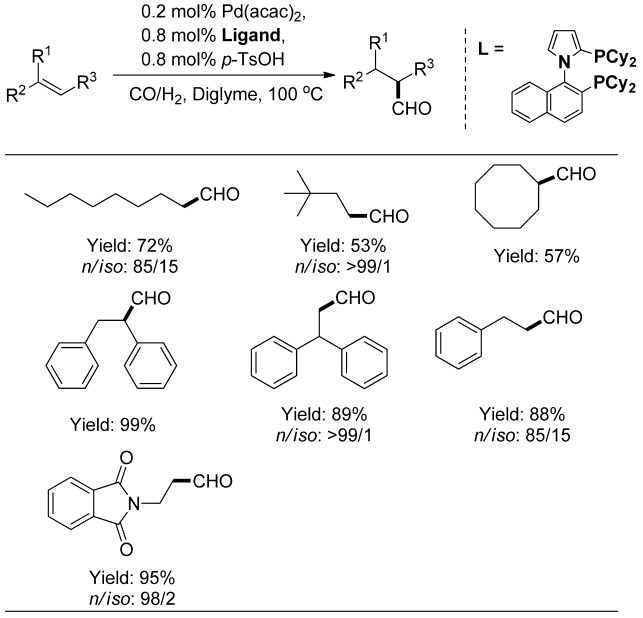
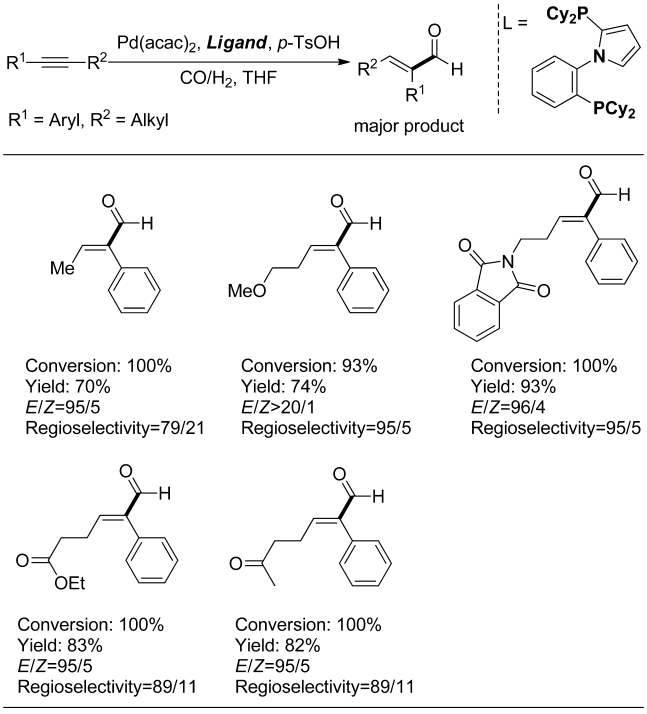
Scheme 23. Ruthenium-Catalyzed Hydroaminomethylation of Olefins with Amines



Scheme 24. Palladium-Catalyzed Hydroformylation of Olefins



Scheme 25. Palladium-Catalyzed Hydroformylation of Unsymmetrical Alkynes



ing α,β-unsaturated aldehydes in high yields with good regio- and stereoselectivities.

PALLADIUM-CATALYZED CARBONYLATION OF ALKENES AND RELATED REACTIONS

Alkoxycarbonylations, also called hydroesterifications, represent a straightforward method for the conversion of olefins, CO and alcohols to the corresponding esters. Nickel-based catalysts were originally employed, as described in the seminal work by Reppe and Vetter.[28] However, nowadays palladium catalysts are generally used for this transformation because they work under milder conditions and allow for a broader substrate scope. So far, the vast majority of catalytic alkoxycarbonylations employs CO as source of the carbonyl group. Clearly, CO is a versatile and inexpensive C1 building block; however, its toxicity and physical properties (gaseous form, flammability) make it less convenient to handle and transport. Hence, there exists

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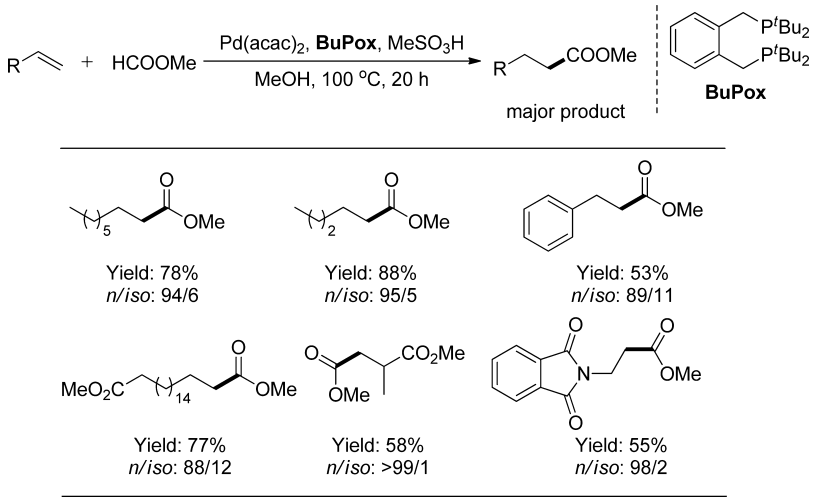
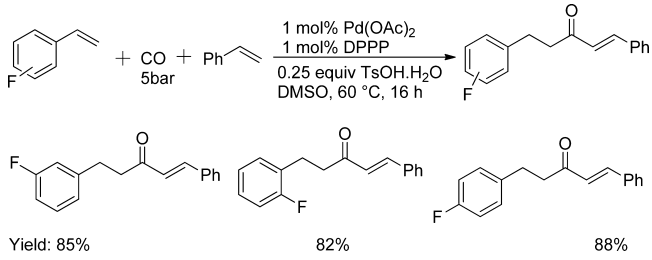
Scheme 26. Palladium-Catalyzed Methoxycarbonylation of Olefins Using Methyl Formate



significant interest in easier-to-handle, less toxic synthetic equivalents of carbon monoxide. In this regard, formic acid derivatives are especially promising alternatives, because of their low price and availability. The first hydroesterifications of olefins with formates were reported in 1983 by Sneeden, Cognion, and their co-workers.[29] They used a ruthenium complex for the conversion of ethylene to methyl propionate at high temperature (190 °C). Since then, few catalyst modifications, using ruthenium, iridium, or palladium have been developed.[30] However, the reported reactions require harsh conditions (T > 150 °C), and/or additional CO pressure. Furthermore, the obtained chemo- and regioselectivities were poor and the reported substrate scope was narrow, very often limited solely to ethylene. Based on our interest in the synthesis and use of formates for organic synthesis and energy applications, we developed a more general catalyst system based on Pd with the so-called BuPox ligand for the catalytic alkoxycarbonylation of olefins using formates instead of CO.[31] As shown in Scheme 26, various types of olefins were smoothly transformed to the corresponding linear esters in good yields with good *n*-selectivities under relatively mild conditions. More interestingly, the present system was able to transform the seven different octene isomers into the corresponding linear methyl nonanoate with a yield of 80% and with 94% *n*-selectivity.

Based on our interest in industrially relevant carbonylation reactions, we performed a systematic study on the alkoxycarbonylation of 1,3-butadiene,[32] which is produced on an enormous scale (about 12 × 10^6 metric tons annually) and offers the possibility to produce 3-pentenoic acid esters. It was proved that the first step of the catalytic cycle, the formation of crotylpalladium complexes from 1,3-butadiene, proceeds even at room temperature. Examination of the influence of different reaction parameters on product yield and selectivity demonstrated the importance of chelating phosphine ligands and benzoic acids as additive in order to get good results. During our studies on the oxidative carbonylation of arylboronic acids and alkenes to the corresponding chalcones,[33] we observed the carbonylative dimerization of alkenes, which occurred due to the decomposition of the corresponding boronic acid.[34] From a mechanistic point of view, the active palladium hydride species is crucial for this transformation. Hence, quantitative yield was obtained by using 0.25 equiv of TsOH·H_2O as additive, while no desired dimerization product was observed in the absence of acid additives. The reaction proceeded in a highly selective manner, and can also be carried out with two different aromatic olefins. As an example, the nonsymmetrical dimerization of fluorinated styrenes with excess of styrene proceeded well (Scheme 27).[35]

Scheme 27. Carbonylative Dimerization of Two Styrenes



IRON-CATALYZED AMINOCARBONYLATION OF ALKYNES

The transition metal-catalyzed aminocarbonylation reaction provides an easy and practical method for the synthesis of amides, which are valuable products for the bulk and fine chemical industries.[36] Applying this methodology α,β-unsaturated amides can be prepared directly from alkynes in the presence of amines. As usual, most of the known catalysts are based on complexes of precious metals such as palladium, rhodium, iridium, and ruthenium. Among the various biorelevant metals especially iron is an attractive alternative compared to precious metals. Obviously, iron is cheap, benign, readily available, and ecologically friendly. Hence, we are interested for a long time in the development of iron-catalyzed transformations. In order to achieve catalytic carbonylations based on iron, we started to investigate the reaction of alkynes with carbon monoxide and different nucleophiles. The main reason choosing this class of substrates was the increased reactivity compared to more common olefins. In fact, we realized the first iron-catalyzed synthesis of succinimides by double carbonylation of different terminal and internal alkynes with ammonia or amines in good selectivity and high activity (Scheme 28).[37] Shortly after, the synthetic usefulness of the

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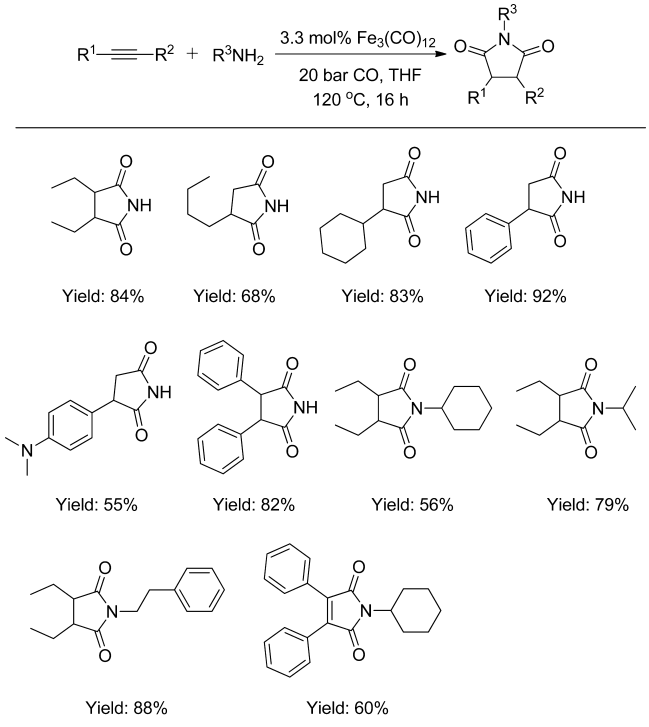
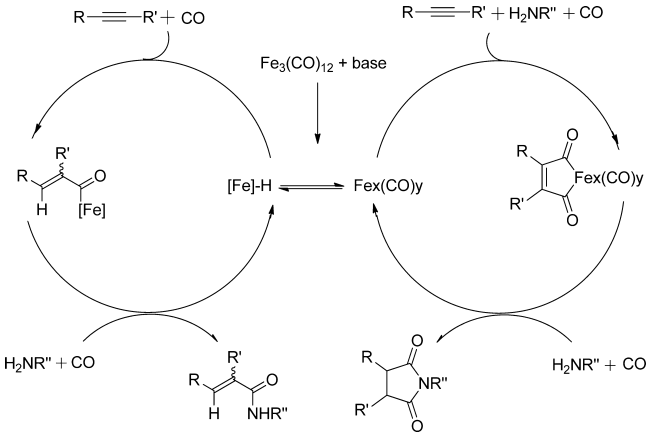
methodology was demonstrated in the synthesis of biologically active himanimide A and B in our group.

Scheme 28. Iron-Catalyzed Carbonylative Synthesis of Succinimides



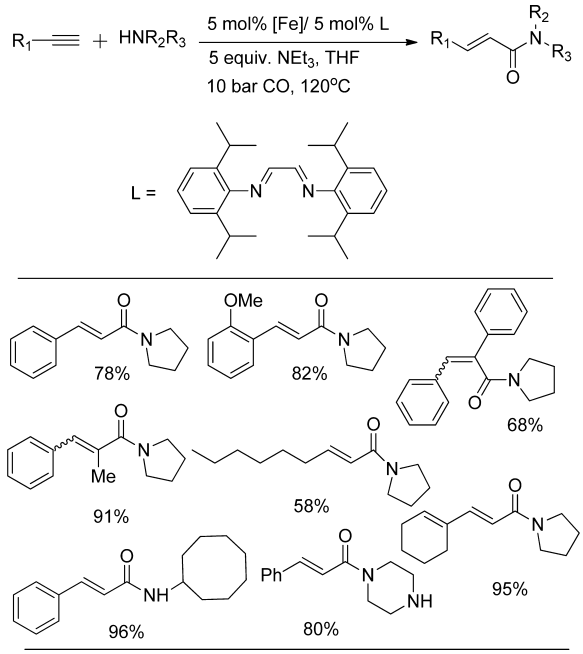
Regarding the reaction mechanism, the formation of the cyclic iron complex is believed to be the key intermediate (Scheme 29). From a synthetic point of view, it was also

Scheme 29. Proposed Mechanism for Fe-Catalyzed Carbonylation of Alkynes



interesting to realize the synthesis of α,β-unsaturated amides as the terminal product by insertion of only one molecule of CO. Gratifyingly, this idea was realized by a slight change of the reaction conditions.[38] Starting from commercially available amines and alkynes, a range of structurally diverse cinnamides and acrylamides are obtained smoothly in the presence of catalytic amounts of $Fe_3(CO)_{12}$ and *N,N′*-(butane-2,3-diylidine)bis(diisopropylaniline) (Scheme 30). Notably are the high chemo- and regioselectivity of the processes and no expensive catalyst is required for this novel environmentally friendly reaction.

Scheme 30. Iron-Catalyzed Carbonylative Synthesis of Cinnamides



SUMMARY AND OUTLOOK

In conclusion, in this Account, the selected developments of our groups in Rostock in the area of transition metal-catalyzed carbonylative transformations of unsaturated compounds have been summarized. Industrially relevant rhodium-catalyzed hydroformylation and hydroaminomethylation reactions of internal alkenes allow for the conversion of cheap alkenes or even alkene mixtures to more valuable functionalized products in a selective manner. More recently, we have shown that these reactions can also be catalyzed by less expensive ruthenium as well as iridium catalysts. On the other hand, palladium-catalyzed carbonylations of alkenes and alkynes offers an atom economic procedure for the preparation of carboxylic acid derivatives and alkenones. In special cases, basic triiron dodecacarbonyl can be applied in carbonylations of alkynes. By slightly changing the reaction conditions, the selectivity of this reaction can be modified to give either succinimides or cinnamides as the terminal products.

What about the future of carbonylation reactions? Clearly, carbon monoxide is a versatile C1 building block for synthesis and widely used in industry. However, due to its physical properties (high toxicity and gaseous nature) organic chemists are reluctant to apply carbonylations more often. In this context, it should be also noted that transportation of carbon monoxide is becoming more difficult. In fact, in Germany an industrial CO-pipeline was not realized due to public protests.[39] Hence, in the future, the development of carbon monoxide surrogates is an important topic. Here, practical and benign CO-generating reagents should be developed and applied. Apart from formates, alcohols, and metal carbonyls, also CO_2 offers interesting options.

Regarding the catalyst systems, easy to prepare and patent-free ligands/complexes are still highly desired by various

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companies. Particularly, non-noble metal complexes will be interesting for both academic and industrial researchers. As an example for the importance of improved catalysts, the novel Lucite process for methyl methacrylate makes use of a specific palladium/bisphosphine catalyst, which was crucial for the successful implementation of the technology. More active and productive catalysts for related carbonylations of less reactive olefins would allow for other large scale applications of this methodology.

From an academic point of view, selective reactions of more functionalized olefins still constitute a significant challenge. Apart from the obvious question of stereoselectivity, also regioselectivity cannot always be controlled in the desired manner. For example, simple alkoxycarbonylation or amino-carbonylation reactions of terminal olefins to the branched product are not possible with high selectivity. Finally, it should be mentioned that carbonylation reactions constitute today a domain of homogeneous catalysis due to the volatility of simple metal carbonyl complexes. The invention of more stable and recyclable heterogeneous catalysts or metal-free carbonylations (radical carbonylations) will be difficult, but should be investigated in more detail. Despite more than 80 years of carbonylation catalysis, this area continues to provide important questions and challenges for research. Hence, we encourage more young chemists to look after these interesting methodologies.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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Xianjie Fang works as a Ph.D. student in LIKAT with Matthias Beller.

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Ralf Jackstell is group leader at LIKAT.

Helfried Neumann is group leader at LIKAT.

Matthias Beller is director of LIKAT.

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