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Highly selective synthesis of hydrazones and indoles from olefins

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Abstract—Reaction of aliphatic olefins with synthesis gas and hydrazines in the presence of rhodium phosphine catalysts leads directly to the corresponding hydrazones. Applying Iphos as ligand good to excellent yields and high chemo- and regioselectivities were obtained in toluene under mild conditions. In case of aromatic hydrazines in situ Fischer indole synthesis can be combined with the new hydrazone preparation to give substituted indoles directly from olefins.
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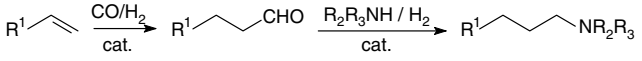
Hydroamination[1] and hydroaminomethylation[2] represent elegant, atom-economic and efficient methods for the synthesis of various amines from aliphatic olefins. From both economic and environmental points of view, these direct preparation routes for nitrogen-containing compounds from inexpensive feedstock are advantageous compared to classic laboratory procedures such as nucleophilic substitution reactions. While general methods for direct hydroamination of olefins are still in their infancy, the hydroaminomethylation is applicable on a broader scale. As shown in Scheme 1, this domino reaction consists of hydroformylation of an olefin to yield the corresponding aldehyde, subsequent formation of an enamine (or imine) followed by hydrogenation to give the desired amine.

In spite of the advantages of this one pot reaction, for example, easy availability of starting materials and atom efficiency, until recently comparatively few preparative applications were known.[3] Here, the work of Eilbracht and co-workers, who developed elegant domino reactions with an initial hydroformylation step, is of special importance.[4] For some time we have been interested in improving hydroaminomethylation reactions. As an example the first selective hydroaminomethylation reaction of aliphatic olefins using ammonia was achieved.[5] More recently, we developed the first rhodium phosphine catalyst systems for highly selective hydroaminomethylation reactions of internal and terminal olefins to give linear amines.[6] Based on this work we became interested in the use of other *N*-nucleophiles instead of amines in domino-hydroformylation–amination sequences. Here, especially the use of hydrazines attracted our interest. In the present paper, we describe for the first time a rhodium-catalyzed one pot synthesis of hydrazones from terminal olefins. In addition, the combination of this new method with the classic Fischer indole synthesis[7] to give substituted indoles directly from olefins is demonstrated. In this respect the work of Eilbracht et al. is also noteworthy, who developed parallel to our work a novel tandem hydroformylation/Fischer indole synthesis starting from olefins and aryl hydrazines.[8]



Scheme 1. Hydroaminomethylation of olefins.

Clearly, the development of a high-yielding hydrazone synthesis from olefins requires a tailor-made catalyst system, which provides the desired chemo- and regioselectivity. On the one hand the catalyst system should be sufficiently active for hydrogenation of the intermediate acylrhodium complex, but not active for reduction of the resulting hydrazone. On the other hand the catalyst should provide a high regioselectivity for the desired linear or branched isomer. Surprisingly, little is known about the influence of different phosphine

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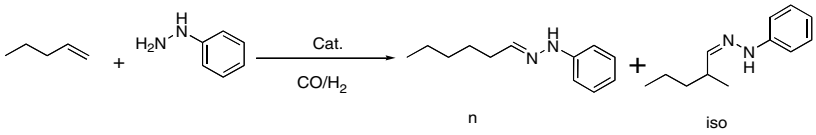
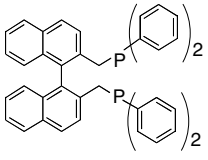
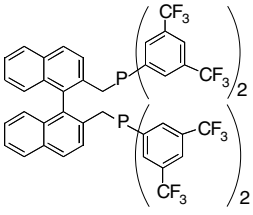
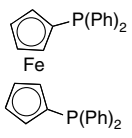
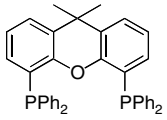
ligands on both chemo- and regioselectivity in hydroaminomethylation reactions.[6b]

In order to get an impression of the effect of various ligands on the chemo- and regioselectivity of the hydroformylation step in the presence of hydrazines, we studied the reaction of 1-pentene with phenylhydrazine at different conditions as a model system.[9] As shown in Table 1 (entries 1–8, 12) 2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthyl (Naphos),[10] 2,2′-bis[di(3,5-trifluoromethyl-phenyl)phosphinomethyl]-1,1′-binaphthyl (Iphos)[6a,11] and Xantphos[12] proved to be excellent ligands for the desired transformation. Other bidentate ligands, for example, dppe and dppf were less active and/or selective (Table 1, entries 10 and 11). Also the standard ligand PPh_3 gave a significantly lower regioselectivity (*n*:*iso* = 76:24) compared to Naphos, Iphos and Xantphos. Among the latter three ligands Iphos leads to the most active catalyst system (>99% yield of *N*-hexenyl-*N*′-phenylhydrazone) at low temperature (65 °C). The regioselectivity of the model reaction is highly dependant on the temperature and the partial pressure of carbon monoxide (see Table 1, entries 1–5). A slight increase from 65 to 80 °C decreases the *n*:*iso*-selectivity from 88:12 to 77:23. Also an increase of the synthesis gas pressure from 10 to 20 bar gave a decrease in selectivity from 88:12 to 75:25. Among the three solvents (toluene, methanol, tetrahydrofurane) tested, toluene gave the best results (Table 1, entries 6–8). It is important to note that the achieved high regioselectivity in the initial hydroformylation reaction is the key for the successful methodology development. Otherwise product isolation from the different regioisomers is often extremely difficult.

Next, we were interested in the compatibility of our new procedure with a number of aliphatic and aromatic olefins (Table 2). Apart from *N*-phenylhydrazine, *N*,*N*-dimethylhydrazine, *N*-methyl-*N*-phenylhydrazine, *N*-4-chlorophenylhydrazine and *N*-4-methylphenylhydrazine

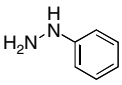
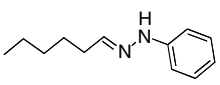
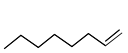
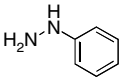
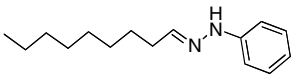
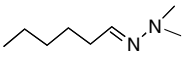
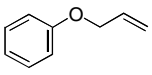
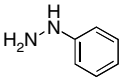
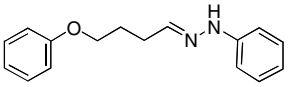
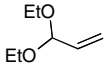
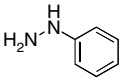
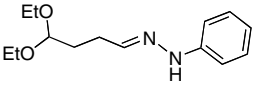
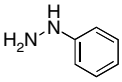
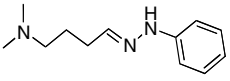
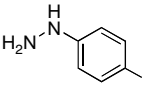
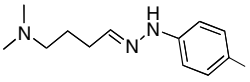
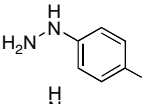
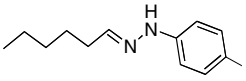
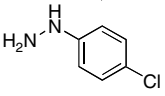
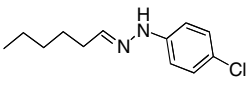
Table 1. Reaction of 1-pentene, phenylhydrazine and synthesis gas in the presence of different ligands[a]



Entry	Ligand	$P_{CO/H2}$ (bar)	Solvent	Temperature (°C)	Conversion[b] (%)	Hydrazone yield (%)[b]	*n*:*iso*[c]
1		10	Toluene	65	84	83	88:12
2		10	Toluene	80	100	99	77:23
3		10	Toluene	100	100	99	78:22
4		20	Toluene	65	100	99	75:25
5		40	Toluene	65	100	99	61:39
6		**10**	**Toluene**	**65**	**100**	**99**	**>99:1**
7		10	MeOH	65	94	91	98:2
8		10	THF	65	91	89	93:7
9	PPh_3	10	Toluene	65	100	99	76:24
10	dppe	10	Toluene	65	32	31	48:52
11		10	Toluene	65	100	98	71:29
12		10	Toluene	65	79	76	98:2

[a] Reaction conditions: 1-pentene (10 mmol), phenylhydrazine (10 mmol), solvent (30 mL), $Rh(CO)_2acac$ (0.1 mol %), ligand (0.2 mol %), time (16 h).
[b] Conversion and yields were determined by GC using bis(methoxyethyl)ether as an internal standard.
[c] Minor amount of the corresponding azo compound were observed by GC.

Table 2. Rhodium-catalyzed synthesis of hydrazones from various olefins[a]

Entry	Olefin	Hydrazine	Major product	Conversion (%)	Hydrazone selectivity (%)	Hydrazone yield[b] (%)	*n:iso*
1				100	99	99	>99:1[c]
2				99	98	97	>99:1
3				100	99	99	73:27
4				100	98	98	98:2[c]
5				98	95	93	78:22[c]
6				99	85	84	88:12
7				98	87	85	88:12
8				99	95	94	>99:1[c]
9				95	98	93	>99:1

[a] Reaction conditions: olefin (10 mmol), hydrazin (10 mmol), $Rh(CO)_2acac$ (0.1 mol%), Iphos (0.2 mol%), toluene (30 mL), CO/H_2 (1:1, 10 bar), temperature (65 °C), time (16 h).

[b] Yields were determined by GC using bis(methoxyethyl)ether as an internal standard.

[c] Minor amount of the corresponding azo compound were observed by GC.

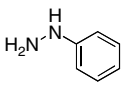
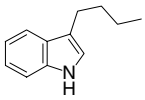
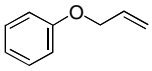
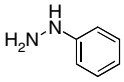
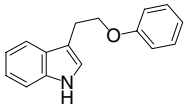
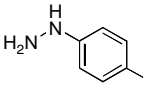
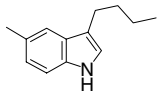
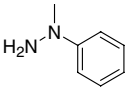
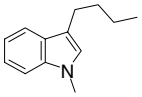
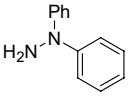
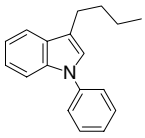
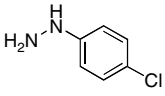
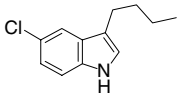
have been employed as *N*-nucleophile. In addition to simples aliphatic olefins also functionalized alkenes such as allyl phenyl ether, *N*,*N*-dimethylallylamine and 1,1-dimethoxy-3-propene were used as substrates. In all cases the conversion was >95% and the yield and selectivity for hydrazones was good to excellent (85–99%). In general, the corresponding hydrazone was isolated as the sole product in excellent yield, however in some cases (Table 2, entries 1, 4, 5 and 8) minor amounts of the respective azo compound were also detected spectroscopically. With regard to the regioselectivity it is interesting to note that *N*-arylhydrazines gave a significantly higher selectivity for the linear isomer compared to *N*,*N*-dimethylhydrazine (Table 2, entry 3) due to steric reasons. Using nonfunctionalized aliphatic olefins the regioselectivity for the linear isomer was typically >99:1 (Table 2, entries 1–2, 8 and 9). In case of the functionalized substrates somewhat lower selectivities in between 78:22 and 98:2 were observed (Table 2, entries 4–7).

Having a reliable method for the synthesis of hydrazones from olefins in hand we turned our interest to the combination of this new method with the classic Fischer indole synthesis, which is still one of the most important approaches to indoles.[7] Due to their biological importance even today the development of new syntheses of indoles is subject of considerable efforts.[13]

Indeed cooling of the crude reaction mixture to room temperature, addition of an excess (4 equiv) of $ZnCl_2$ and heating for several hours provided substituted indoles in a one pot reaction from olefins. As shown in Table 3 various indoles have been isolated in yields from 75% to 85%. Except for the reaction of *N*-methyl-*N*-phenylhydrazine (Table 3, entry 4) all transformations proceeded highly selective (regioselectivity >99:1), which is remarkable compared to mechanistically related hydroaminomethylation reactions. Clearly the key to success here is the use of our Rh/Iphos catalyst system.

In summary, we have developed the first general synthesis of hydrazones directly from olefins. Good to excellent chemo- and regioselectivity are achieved under mild reaction conditions. Further refinement of the produced hydrazones via the Fischer indole synthesis leads to a one pot synthesis of indoles from olefins. Compared to known stepwise procedures the method is

Table 3. One pot synthesis of indoles from olefins[a]

Entry	Olefin	Hydrazine	Indol	Yield[b]	*n*:*iso*
1				85	99:1
2				80	99:1
3				80	99:1
4				75	77:23
5				80	99:1
6				85	99:1

[a] Reaction conditions: olefin (10 mmol), hydrazine (10 mmol), $Rh(CO)_2acac$ (0.1 mol%), Iphos (0.2 mol%), toluene (30 mL), CO/H_2 (1:1, 10 bar), temperature (65 °C), time (16 h), then 4 equiv of $ZnCl_2$ are added, and reaction is heated until conversion is complete.
[b] Isolated yield based on hydrazine.

advantageous and environmentally friendly because waste generation during work-up steps is minimized. In addition, time and energy is saved.

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References and notes

1. Reviews: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703; (b) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579–1594; (c) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813; (d) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983; (e) Brunet, J.-J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001.
2. Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329–3365.
3. Selected examples: (a) Törös, S.; Gemes-Pesci, I.; Heil, B.; Maho, S.; Tubar, Z. *Chem. Commun.* **1992**, 585–589; (b) Baig, T.; Kalck, P. *Chem. Commun.* **1992**, 1373–1374; (c) Baig, T.; Molinier, J.; Kalck, P. *J. Organomet. Chem.* **1993**, *455*, 219–224; (d) Brunet, J. J.; Neibecker, D.; Agbossou, F.; Srivastav, R. S. *J. Mol. Catal.* **1994**, *87*, 223–230; (e) Breit, B. *Tetrahedron Lett.* **1998**, *39*, 5163–5166; (f) Schaffrath, H.; Keim, W. *J. Mol. Catal.* **1999**, *140*, 107–113.
4. (a) Rische, T.; Bärfacker, L.; Eilbracht, P. *Eur. J. Org. Chem.* **1999**, *3*, 653–660; (b) Rische, T.; Kitsos-Rzychon, B.; Eilbracht, P. *Tetrahedron* **1998**, *54*, 2723–2742; (c) Kranemann, C. L.; Eilbracht, P. *Synthesis* **1998**, *1*, 71; (d) Rische, T.; Eilbracht, P. *Synthesis* **1997**, *11*, 1331–1337.
5. Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2372–2375.
6. (a) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676–1678; (b) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311–10318.
7. For reviews see: (a) Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: Chichester, 1982; (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607–623.
8. Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *18*, 3213–3216.
9. General procedure: All carbonylation experiments were carried out in a Parr stainless steel autoclave (100 mL). In

a typical experiment (Table 1, entry 6), the autoclave was charged with $Rh(CO)_2acac$ (0.1 mol%), Iphos (0.2 mol%), olefin (10.0 mmol), hydrazine (10.0 mmol) and toluene (30 mL) under argon atmosphere. The autoclave was pressurized with CO (5 bar) and hydrogen (5 bar) and the reaction was carried out at 65 °C for 16 h. Then, the autoclave was cooled to room temperature and depressurized. The reaction mixture was transferred to a Schlenk flask under argon atmosphere, dried over $MgSO_4$ and analyzed by gas chromatography using bis(methoxyethyl)ether as internal standard. *N*-Hexenyl-*N*′-phenylhydrazone was identified by comparison with an authentic sample by GC (HP5890 series; column: HP5 (Crosslinked 5% PH ME Siloxane) 30 m, 0.25 mm, 0.25 μm). The product was also confirmed by GC–MS, HRMS and NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 6.89–7.35 (m, 5H), 6.60 (t, $J = 5$ Hz, 1H), 2.23–2.35 (m, 6H), 1.59–1.70 (m, 2H), 1.06 (t, $J = 7$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 141.6, 129.0, 119.2, 112.3, 32.01, 31.31, 26.65, 22.40 13.92. GC–MS (EI, 70 eV): $m/z = 190$ [M^+], 175, 161, 147, 133, 118, 106, 93, 77, 65, 51, 39, 29. HRMS calcd for $C_{11}H_{21}N$ [M^+]: 190.14700, found: 190.14510.

10. (a) Beller, M.; Krauter, J. G. E. *J. Mol. Catal.* **1999**, *143*, 31–39; (b) Herrmann, W. A.; Schmid, R.; Kohlpaintner, C. W.; Priermeier, T. *Organometallics* **1995**, *14*, 1961–1968; (c) Bahrmann, H. B.; Bergrath, K.; Kleiner, H.-J.; Lapper, P.; Naumann, C.; Peters, D.; Regnat, D. *J. Organomet. Chem.* **1996**, *520*, 97–100; (d) Rampf, F. A.; Spiegler, M.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *582*, 204–210.
11. Klein, H.; Jackstell, R.; Wiese, K.-D.; Röttger, D.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3408–3411.
12. For an excellent review see: (a) Kamer, P. C. J.; van Leeuwen, P. W. N.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904; (b) Kranenburg, M.; van der Bugt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081–3083.
13. (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045; (b) Verspui, G.; Elbertse, G.; Sheldon, F. A.; Hacking, M. A. P. J.; Sheldon, R. A. *Chem. Commun.* **2000**, 1363–1364.