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A Mild Chemoselective Ru-Catalyzed Reduction of Alkynes, Ketones, and Nitro Compounds

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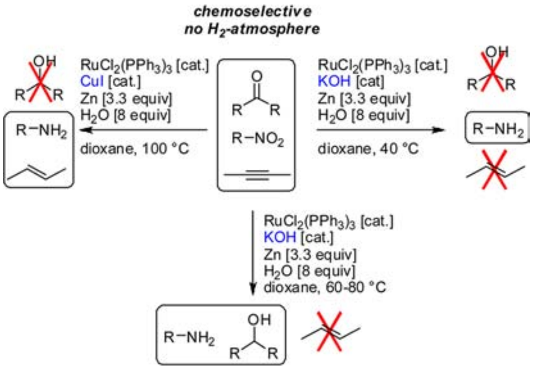
ABSTRACT



The chemoselective reduction of alkyne, ketones, or nitro groups using $(Ph_3P)_3RuCl_2$ as an inexpensive catalyst and Zn/water as a stoichiometric reductant is reported. Depending on the nature of the additive and the temperature, good chemoselectivities were observed allowing, e.g., for the selective reduction of a nitro group in the presence of a ketone or an alkyne.

The development of environmentally benign catalytic reactions is without a doubt a focus of current chemical research.[1] Apart from lowering the energy consumption of a chemical transformation using catalysts, the chemoselective transformation of only one out of many functional groups within a more complex molecular framework allows the reduction of byproducts (and hence waste) and streamlines synthetic pathways by eliminating tedious protecting group operations.[2] Within the catalytic portfolio hydrogenations play a pivotal role. Although well-established and performed on multi-ton scale this type of chemical reaction suffers from different problems such as chemoselectivity. To date only three protocols for the chemoselective reduction of, e.g., a nitro group in the presence of a carbonyl group or an alkyne using either hydrazine[3] or formic acid/Et_3N[4] as a stoichiometric reductant has been developed. Recently, our group and others became interested in transition-metal catalyzed reduction of alkynes under transfer hydrogenation conditions using formic acid as a H_2-surrogate.[5] In furtherance of these investigations we were wondering whether it could be possible to develop a protocol that addresses two important questions: (a) Is it possible to develop a protocol in which H_2O, the most stable and abundant H_2-surrogate, is employed in a

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[†] Both authors contributed equally.

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(2) Sarmah, P. P.; Dutta, D. K. *Green Chem.* **2012**, *14*, 1086.

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stoichiometric manner?[6] and (b) Can we address the open question of chemoselectivity in transition-metal catalyzed hydrogen transfer reactions by utilizing addivitives? Here, we present the results of our studies which led to the discovery of a Ru-catalyzed reduction by which, depending on the additive and temperature, alkynes are reduced to olefins in the presence of carbonyl groups and vice versa. Stoichiometric amounts of Zn-powder and water are used as a hydrogen source.

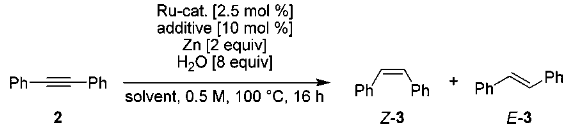
At the outset of our studies we choose the reduction of diphenylacetylene as a starting point and evaluated the influence of solvent, catalyst, and temperature (Table 1). Commercially available $RuCl_2(Ph_3P)_3$ (**1**) in dioxane *in the presence of only 8 equiv of water* showed a promising conversion rate in favor of the *Z*-configured substitution product (entry 1, Table 1). However at a certain point the conversion stopped. In order to circumvent problems associated with the passivation of the Zn-surface, catalytic amounts of CuI were added.[7] This additive had a beneficial influence on both reaction rate and *Z*/*E*-selectivity. The desired *Z*-stilbene (*Z*-**3**) was obtained in almost quantitative conversion and a *Z*/*E*-selectivity of $>8:1$ (entry 7, Table 1). Various Ru(+II)-complexes were subsequently screened for their catalytic activities (entries 10–22, Table 1). Strong ligand and anion effects were observed. Whereas three basic ligands allow for good to excellent conversion rates, complexes that are coordinated by four N- or P-ligands turned out to be nonactive. Apart from complex **1** Murai's catalyst **7** showed good reactivity; however it led to the formation of the *E*-configured olefin predominantely. Complex **1** on the other hand proved to be more active in the reduction and less active for π-bond isomerization. The isomerization was complete within 36 h (entry 7, Table 1). For reasons of practicality and with regard to the stereodivergence option, we chose the readily available $(Ph_3P)_3RuCl_2$ as the catalyst for this study. Importantly, no conversion was observed in the absence of the Ru-catalyst (entries 23 and 24, Table 1).

Having in hand a practical catalytic protocol for the semireduction of alkynes, we subsequently tested the scope of this transformation using various internal alkynes (Table 2). The reaction proved to be broadly applicable toward the reduction of arylacetylenes. After 36 h at 100 °C good to excellent *E*/*Z* selectivities and yields were obtained (*protocol A*, Table 2).

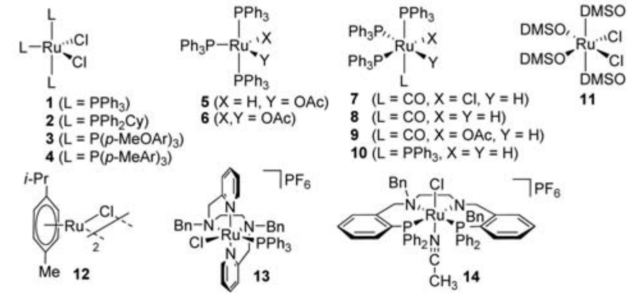
Functional groups such as amides, esters, alcohols, halides, and nitriles are compatible with the reaction conditions (Table 2). In the presence of a nitro group, however, rapid reduction of the nitro group was observed. The reduction of the triple bond was significantly slower. However, in all cases no overreduction to the saturated C–C bond was observed. Stopping the reaction after 16 h using only 2.5 mol % of catalyst **1** led to the formation of the desired olefin in good to excellent yields albeit at moderate to good stereoselectivities in favor of the *Z*-configured double bond. Aliphatic alkynes are also reactive under the given reaction conditions; however π-bond migration and hence product mixtures were obtained.[8]

The use of Murai's catalyst (**7**) led to the direct formation of the *E*-configured alkenes within just 16 h (entry 15, Table 1). However, this protocol proved to be very sensitive toward the functional group as compared to the use of $(Ph_3P)_3RuCl_2$ (Table 2). Careful control of *E*/*Z* selectivity vs conversion and time indicated this catalyst to be active both for the reduction to the *Z*-configured olefin and for its isomerization into the thermodynamically more favorable *E*-product. The fact that even ketones are not reduced at 100 °C after 36 h attracted our attention. We were wondering whether we could extend the method to the reduction of

Table 1. Ru-Catalyzed Semireduction of Alkynes: System Development[a]



entry	cat.[b]	add	solvent	t [°C]	Z/E[c]	conv [%][c]
1	**1**	---	dioxane	100	5.3/1	38
2	**1**	---	DMF	100	2/1	22
3	**1**	---	toluene	100	2.7/1	23
4	**1**	---	EtOAc	100	5.3/1	30
5	**1**	---	CH_3CN	100	---	---
6	**1**	---	H_2O	100	3.1/1	43
7	**1**	CuI	dioxane	100	8.3/1 (1/20)	98 (98)[d]
8	**1**	CuI	dioxane	80	8.3/1	56
9	**1**	CuI	dioxane	60	8.3/1	26
10	**2**	CuI	dioxane	100	2.3/1	45
11	**3**	CuI	dioxane	100	7.3/1	75
12	**4**	CuI	dioxane	100	8.1/1	72
13	**5**	CuI	dioxane	100	3.3/1	99
14	**6**	CuI	dioxane	100	5.7/1	65
15	**7**	CuI	dioxane	100	1/20	99
16	**8**	CuI	dioxane	100	5.7/1	75
17	**9**	CuI	dioxane	100	3.3/1	39
18	**10**	CuI	dioxane	100	5.3/1	51
19	**11**	CuI	dioxane	100	1.9/1	36
20	**12**	CuI	dioxane	100	1.5/1	27
21	**13**	CuI	dioxane	100	7.3/1	20
22	**14**	CuI	dioxane	100	3.2/1	15
23	---	CuI	dioxane	100	---	~5
24	---	---	dioxane	100	---	---



1 (L = PPh_3)
2 (L = PPh_2Cy)
3 (L = P(*p*-MeOAr)$_3$)
4 (L = P(*p*-MeAr)$_3$)
5 (X = H, Y = OAc)
6 (X,Y = OAc)
7 (L = CO, X = Cl, Y = H)
8 (L = CO, X = Y = H)
9 (L = CO, X = OAc, Y = H)
10 (L = PPh_3, X = Y = H)
11
12
13
14

[a] The reactions were performed on a 0.5-mmol scale using 2.5 mol % Ru cat. at 100 °C in dry solvent (1 mL) for 16 h under a N_2 atmosphere. [b] Catalyst structures shown above. [c] Determined by ^1H NMR or GC integration. [d] *E*/*Z* selectivity and yield after a reaction time of 36 h are given in parentheses.

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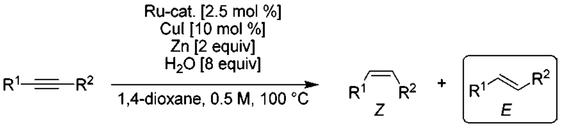
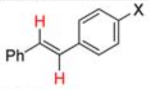
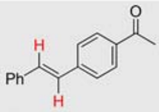
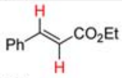
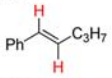
(8) (a) Yue, C. J.; Liu, Y.; He, R. *J. Mol. Catal. A* **2006**, *259*, 17–23. (b) Lastra-Barreira, B.; Crochet, P. *Green Chem.* **2010**, *12*, 1311–1314.

Table 2. Ru-Catalyzed Semireduction of Alkynes



entry	product	protocol[a]	$Z:E$[b,d]	yield [%][c,d]
1	 **3** (X = H)	A	>1:20	98
2			(8:1)	(98)
3		B	> 1:20	98
4		A	>1:20	88
5	**15** (X = OMe)		(4:1)	(82)
6		B	>1:4.7	71
7		A	>1:20	77
8	**18** (X = CH_2OH)		(5:1)	(91)
9		B	>1:4.1	65
10		A	>1:20	85
11	**19** (X = CO_2Me)		(3:1)	(97)
12		B	>1:1.1	82
13		A	>1:20	79
14	**20** (X = NHAc)		(1.3:1)	(96)
15		B	>1:20	76
16		A	>1:20	81
17	**21** (X = Cl)		(3.5:1)	(98)
18		B	>1:20	43
19		A	1.2:1	79
20	**22** (X = CN)		(2:1)	(93)
21		B	1:1	32
22		A	1:10	97
23	**16** (X = NH_2)		(6.5:1)	(90)
24		B		
25	 **17**	A	>1:20	95
26			(2:1)	(86)
27		B	>1:3.2	81
28	 **23**	A	>1:20	97
29			(1.5:1)	(97)
30		B	>1:20	94
31	 **24**	A	>1:20	98
32		B	>1:20	96

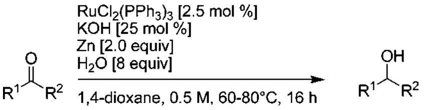
[a] The reactions were performed on a 0.5-mmol scale using 2.5 mol % $RuCl_2(PPh_3)_3$ (**1**) at 100 °C in dry dioxane (1 mL) for 36 h under a N_2 atmosphere (*protocol A*) or using 2.5 mol % $(Ph_3P)_3Ru(CO)HCl$ (**7**) at 100 °C for 36 h under a N_2 atmosphere (*protocol B*). [b] E/Z selectivity was determined by ^1H NMR or GC integration. [c] Isolated yields. [d] Values in brackets refer to the Z/E selectivity and yields for the same reaction conditions using 2.5 mol % $RuCl_2(PPh_3)_3$ (**1**) and a 16 h reaction time.

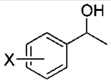
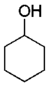
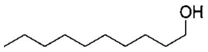
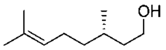
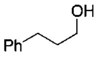
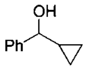
carbonyl or nitro groups and were hoping to invert the course of the chemoselectivity. Since the initial steps within the reduction of carbonyl and nitro groups are identical we assumed a transfer of the known literature conditions for reductive dimerizations of nitro arenes to the corresponding diazocompounds using a Zn/KOH combination to be possible.[9] Indeed by exchanging the additive from CuI to KOH and lowering the reaction temperature down to 60−80 °C, a variety of functionalized ketones and aldehydes were reduced to the corresponding alcohols (Table 3).

A variety of ketones proved to be reactive under the given conditions. At temperatures of ~80 °C good to excellent yields of the corresponding alcohols were observed. However, whereas both aromatic and aliphatic ketones are suitable substrates, aromatic aldehydes undergo a fast noncatalytic pinacol-type coupling and proved to be a limitation of this method.[10] In sharp contrast aliphatic aldehydes are highly reactive and give rise to the expected products in good to excellent isolated yields. Even an aqueous formalin solution can be employed giving methanol in high yield (entry 8, Table 3). Importantly, no conversion was observed in the absence of catalyst **1**. Moreover, nitro groups proved to be more reactive. Increasing the amount of the Zn powder and base allowed for a reduction of *p*-aminoacetophenone to the corresponding aminoalcohol **29** with formation of significant amounts of *p*-aminoacetophenone as the side product (Table 3, entry 5).

Subsequently we extended this method to the reduction of nitroarenes[4,11−13] (Table 4). Nitro groups are known

Table 3. Ru-Catalyzed Reduction of Aldehydes/Ketones[a]



entry	product	t [°C]	yield [%][b]
		80	
1	**25** (X = H)	80	93
2	**26** (X = *p*-CH_3)	80	85
3	**27** (X = *m*-CF_3)	80	63
4	**28** (X = *p*-OCH_3)	80	81
5[d]	**29** (X = *p*-NH_2)	80	41 (55)[c]
6	 **30**	80	95
7	 **31**	60	82
8	 **32**	60	73
9	CH_3OH **33**	60	98
10	 **34**	60	77
11	 **35**	80	46

[a] All reactions were performed on a 0.5-mmol scale using 2.5 mol % $RuCl_2(PPh_3)_3$ (**1**), 25 mol % KOH powder, 2 equiv of Zn-powder, and 8 equiv of H_2O at the given temperature in dry 1,4-dioxane (1 mL) for 16 h under a N_2 atmosphere. [b] Isolated yields. [c] Starting from *p*-nitroacetophenone. Yield of *p*-aminoacetophenone is given in parentheses. [d] The reaction was performed on a 0.5-mmol scale using 5 mol % $RuCl_2(PPh_3)_3$ (**1**), 1 equiv of KOH powder, 4 equiv of Zn-powder, and 16 equiv of H_2O at 80 °C in dry 1,4-dioxane (1 mL) for 16 h under a N_2 atmosphere.

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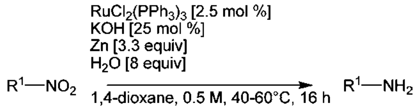
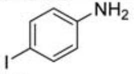
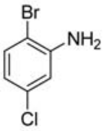
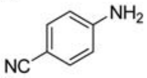
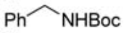
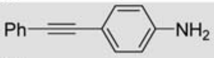
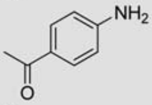
(9) Robinson, B. *Org. Synth.* **1942**, *22*, 28.

(10) (a) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1990**, *55*, 2981–2983. (b) Oller-Lopez, J. L.; Campana, A. G.; Cuerva, J. M.; Oltra, J. E. *Synthesis* **2005**, *15*, 2619–2622. (c) Arai, S.; Sudo, Y.; Nishida, A. *Chem. Pharm. Bull.* **2004**, *52*, 287–288. (d) Khan, R. H.; Mathur, R. K.; Ghosh, A. C. *Synth. Commun.* **1997**, *27*, 2193–2196.

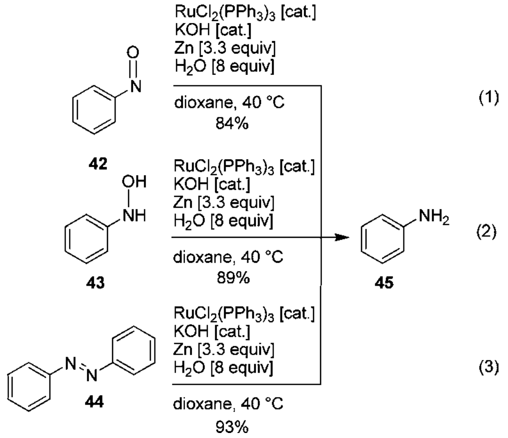
Table 4. Ru-Catalyzed Reduction of Nitro Groups[a]



entry	product	t [°C]	yield [%][b]
1	 **36**	40	96
2	 **37**	rt	74
3	 **38**	60	56
4	 **39**	80	28
5	 **40**	rt	91
6	 **41**	rt	97

[a] All reactions were performed on a 0.5-mmol scale using 2.5 mol % $RuCl_2(PPh_3)_3$ (**1**), 25 mol % KOH powder, 3.3 equiv of Zn-powder, and 8 equiv of H_2O at the given temperature in dry 1,4-dioxane (1 mL) for 16 h under a N_2 atmosphere. [b] Isolated yields.

Scheme 1. Ru-Catalyzed Reduction of Nitroso Groups, Oximes, and Diazobenzene



to be reduced by elemental zinc in the presence of base to the corresponding nitroso group, oximes, or even diazocompounds.[9] However, in the presence of catalyst **1** neither of these products was observed. *Instead a very selective reduction of the nitro group even in the presence of a ketone(entry 6, Table 4) or an alkyne (entry 5, Table 4) was observed.* Whereas nitroarenes are reactive under the given conditions, aliphatic or benzylic nitro groups were giving no or very low yields (entry 4, Table 4).

In the absence of Ru-catalyst **1** nitrobenzene was reduced to a mixture of diazobenzene **44** and hydrazobenzene. Aniline **45** however was not detected in the crude mixture. Since nitroso arenes and aryl hydroxylamines or even diazocompounds are potential intermediates in this multistep reduction process we subsequently subjected these compounds to the reaction conditions. Indeed the reduction of **42**–**44** under the standard conditions in the presence of catalyst **1** led to the formation of aniline **45** in excellent yield (Scheme 1).

Furthermore, the reduction of diphenylacetylene and acetophenone were carried out on a 10-mmol scale. Both the organic and inorganic products were separated by filtration and isolated in almost identical yields. The filtrates were evaporated, and the crude products were purified by chromatography. Analysis of the inorganic solids revealed two major aspects: (a) low levels of ruthenium (4.2–26.7 ppm) were detected in ICP-MS[14] and XRD studies decreasing the probability of colloidal ruthenium to be formed and active as the catalyst; and (b) the solids consist of a mixture of zinc, ZnO, and $Zn(OH)_2$ as shown by XRD. These investigations indicate that an almost quantitative regeneration of the $Zn(OH)_2$ could be possible.

Herein we describe a practical and chemoselective reduction of alkynes, ketones, and nitro groups using catalytic amounts of $(Ph_3P)_3RuCl_2$ and stoichiometric amounts of zinc/water as the reductant. In the presence of catalytic amounts of CuI, a selective reduction of alkynes even in the presence of carbonyl groups was achieved; however switching the catalytic additive toward KOH led to a full inversion of the chemoselectivity. Alkynes stay intact, whereas nitro groups and ketones proved to be reactive.

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Supporting Information Available. Full experimental details, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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