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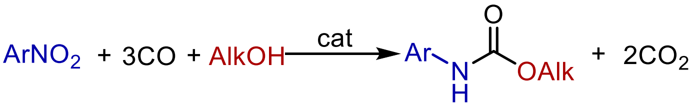
Carbon monoxide as a selective reducing agent in organic chemistry

Alexey A. Tsygankov, Maria Makarova and Denis Chusov

1 Synthesis of Carbamates

The classical route to carbamate synthesis requires the use of dangerous phosgene. One of the alternatives is direct carbonylation of nitro compounds with carbon monoxide in the presence of alcohols (Scheme S1).



(2)

Scheme S1 Reductive carbonylation of nitrobenzenes to carbamates

1.1 Ruthenium Catalysis

In 1984, S. Cenini *et. al.* found that ruthenium carbonyl in the presence of Et_4NCl is an active catalyst for the synthesis of methyl N-phenylcarbamate from nitrobenzene (Table S1, entry 1).[1,2,3,4] Interestingly, in the absence of an alkylammonium salt, the main product of the reaction is aniline. The reported procedure has also been applied to synthesis of carbamates from mono- and disubstituted nitrobenzenes bearing electron-withdrawing groups (such as CO_2Me, CF_3) as well as electron-donating groups (such as CH_3) in good yields (73-88%). Moreover, this catalytic system can be employed in reductive carbonylation of 2,4-dinitrotoluene but only with 45-50% selectivity.

Later the same group studied the influence of different phosphorus and nitrogen ligands on the activity of ruthenium dodecarbonyl in this reaction.[5] It is interesting that monodentate ligands such as PPh_3 do not affect the activity of the catalyst. On the other hand, different bidentate ligands increase the activity of the catalyst. The most active ligand for this system is 2,2'-bipyridine. However, it is still somewhat less active than the catalytic system with an alkylammonium salt (Table S1, entry 2). *t*-BuOH demonstrated best results in the screening of different alcohols (entry 3).[6]

Table S1. Ruthenium-catalyzed systems for reductive carbonylation of nitrobenzenes to carbamates (See scheme S1, Ar = Ph)

Entry	Catalytic system	ROH	CO pressure, bar	T, °C	Reaction time, h	Yield, %	TON up to	Ref. #
1	1 mol% $Ru_3(CO)_{12}$, 7 mol% Et_4NCl	MeOH	82	160-170	5	93	93	1,2
2	1 mol% $Ru_3(CO)_{12}$, 4 mol% 2,2'-bipyridine	MeOH	60	170	15	82	82	5
3	2 mol% $Ru_3(CO)_{12}$, 14 mol% Et_4NCl	^{t}BuOH	28	140	6	97	49	6
4	1 mol% $[RuCl(CO_2)(phpy)]_2$, 11 mol% NaOMe	MeOH	71	150	6	80	80	7

Ru(III) is also capable of catalyzing this transformation.[8–10] Authors investigated the catalytic activity of Ru complexes with different Schiff bases, and $K[Ru(saloph)Cl_2]$ was found to be most active providing TOF greater than 80 h^{-1}.

Ortho-metallated ruthenium (II) complexes of the type $[RuL(CO)_2Cl]_2$ (L = 2-phenylpyridine, benzo(*h*)quinoline, 1-phenylpyrazole, azobenzene) were also tested in reductive carbonylation of nitro compounds.[7] In the absence of any co-catalysts and co-solvents these complexes were totally inactive. In an alcohol medium the presence of acidic co-catalysts, such as $FeCl_3$, $SnCl_4$, $AlCl_3$, NEt_4Cl and TsOH leads to the formation of aniline as a major product. Basic co-catalysts increase the selectivity of carbamate formation. For higher activity mild coordinating solvents are required. Non-coordinating solvents probably cannot cleave a dimer complex while strongly coordinating solvents do not allow formation of a metal-substrate complex. Under the optimal conditions selectivity as high as 80% can be achieved (Table S1, entry 4).

1.2 Palladium Catalysis

At the moment palladium-based systems represent the most explored class of catalysts in reductive carbonylation of nitroaromatics to carbamates. In early reports it was shown that nitrogen bidentate ligands like 1,10-phenanthroline are essential to achieve high conversion and selectivity. G. Mestroni and E. Drent showed that palladium supported on carbon or palladium acetate in combination with a bidentate ligand and 2,4,6-trimethylbenzoic acid (Table S2, entry 1) or $Cu(OTs)_2$ (entry 2) are effective for this transformation.[11–13] Furthermore, complexes such as $[Pd(L)][PF_6]_2$ (L = bidentate ligand) are even more active and the use of them enables this transformation even without co-catalysts (entry 3).[14] Pd-phenanthroline catalytic systems also appear to be tolerant to different functional groups.[15] It was shown that electron-donating substituents in the substrate increase the selectivity of carbamate formation but decrease the activity of the catalytic system, whereas electron-withdrawing groups decrease the selectivity and the azoxybenzene and azobenzene derivatives are formed in significant quantities. Later, P. W. N. M. Leeuwen investigated the effect of different ligands in reductive carbonylation of nitrobenzenes. Within the series of substituted bipyridyl ligands it was shown that ligands with electron-withdrawing groups have decreased activity in comparison with unsubstituted bipyridine. Whereas ligands with higher donating capacity than bipyridine do not increase the overall conversion leaving $[Pd(bpy)_2][OTf]_2$ optimal catalyst for reductive carbonylation within the series of substituted bipyridyl ligands (entry 4).[16] A similar trend of activity was found for the series of phenanthroline ligands. In this case, palladium complex with 4,7-dimethylphenanthroline appeared to be the most active (entry 5).[17]

Table S2. Pd-based catalytic systems for reductive carbonylation of nitrobenzenes to carbamates (See scheme S1, Ar = Ph)

Entry	Catalytic system	ROH	CO pressure, bar	T, °C	Reaction time, h	Yield, %	TON up to	Ref. #
1	0.8 mol% Pd/C (5% wt), 0.8 mol% TMphen, 6.4 mol% 2,4,6-TMBA	EtOH, MeOH	40	180	2	96	120	11,12
2	0.05 mol% $Pd(OAc)_2$, 2 mol% phen, 0.67 mol% $Cu(OTs)_2$	MeOH	60	135	1	98	1960	13
3	0.2 mol% $[Pd(phen)_2][PF_6]_2$, 0.6 mol% phen	MeOH	40	180	1	98	490	14
4	0.3 mol% $[Pd(bpy)_2][OTf]_2$, 1.3 mol% bpy	MeOH	60	135	16	98	327	16
5	0.14 mol% $[Pd(Me_2phen)_2][OTf]_2$, 0.55 mol% Me_2phen	MeOH	60	135	2	84	600	17
6	0.14 mol% $[Pd(phen)_2][OTf]_2$, 0.56 mol% phen, 3.5 mol% 4-chlorobenzoic acid	MeOH	60	135	2	93	664	18
7	0.05 mol% $Pd(OAc)_2$, 0.05 mol% Ag(OAc), 4 mol% phen, 1.5	MeOH	60	135	2	88	1760	19

	mol% p-TsOH, 10 mol% azobenzene							
8	0.027 mol% $[Pd(Phen)_2][BF_4]_2$, 2.7 mol% phen, 5.3 mol% $PhNH_2$, 18 mol% 2-$NH_2C_6H_4COOH$, 2,2-dimethoxypropane	MeOH	60	175	2.5	69	2556	[20]
9	0.35 mol% $[Pd(phen)]Cl_2$, 1.1 mol% phen, 1.9 mol% BAcImPF$_6$	EtOH	60	150	3	92	262	[21]
10	1 mol% $PdCl_2$, 10 mol% phen, $[C_{14}H_{29}(C_6H_{13})_3P]PF_6$ as solvent	MeOH	35	135	24	89	89	[22]
11	0.013 mol% $[Pd(Phen)_2][BF_4]_2$, 1.3 mol% Phen, 2.7 mol% $PhNH_2$, 9.1 mol% H_3PO_4, 2,2-dimethoxypropane	MeOH	100	170	1.5	71	5462	[23,24]
12	0.013 mol% $[Pd(Phen)_2][BF_4]_2$, 1.3 mol% Phen, 0.11 mol% Et_4NF, 2.7 mol% $PhNH_2$, 9.1 mol% H_3PO_4, 2,2-dimethoxypropane	MeOH	60	175	2.5	84	6462	[25]
13	0.007 mol% $[Pd(Phen)_2][BF_4]_2$, 1.5 mol% 4-MeOPhen, 2.6 mol% $PhNH_2$, 9.2 mol% H_3PO_4, 2,2-dimethoxypropane	MeOH	100	170	1.5	61	8714	[26]
14	0.007 mol% $[Pd(Phen)_2][BF_4]_2$, 3.3 mol% 4-(C_6H_5NH)Phen, 2.6 mol% $PhNH_2$, 9.2 mol% H_3PO_4, 2,2-dimethoxypropane	MeOH	60	170	1.5	54.4	7714	[27]
15	Pd-montmorillonite (0.04 mol% of Pd), 0.07 mol% $Ru_3(CO)_{12}$, 10 mol% 2,2’-bipyridine	MeOH	70	180	12	97	2425	[28]
16	$Pd(OAc)_2$-montmorillonite (1 mol% of Pd), 20 mol% $FeCl_3$, 0.67 eq. pyridine	MeOH	60	170	5.5	76	700 (for seven cycles)	[29]
17	2 mol% $[Pd(dppp)]Cl_2$, 3 mol% K_2CO_3	MeOH	20	155-160	24	51	26	[30]
18	0.17 mol% $Pd(OAc)_2$, 1.7 mol% dppp, 4.25 mol% 2,4,6-TMBA	MeOH	60	135	3	78	459	[31]
19	7.6 mol% $PdCl_2$, 0.07 mol% $H_4SiMo_{12}O_{40}$	MeOH	100	160	6	96	13	[32]
20	1 mol% $PdCl_2$, 0.5 mol% $H_5PV_2Mo_{12}O_{40}$	MeOH	40	170	3	94	94	[33]
21	1 mol% $PdCl_2$, 0.5 mol% $H_4PVMo_{11}O_{40}$	MeOH	41	170	3	92	92	[34]
22	1 mol% $PdCl_2$, 5 mol% $FeCl_3$, 10 mol% pyridine	CyOH	100	165	2.5	94	510 (for six cycles)	[35]
23	0.17 mol% $PdCl_2$, 10 mol% Fe, 0.4 mol% I_2, 6.2 mol% pyridine	EtOH	40	180	2	83	488	[36]
24	0.17 mol% $PdCl_2Py_2$, 10 mol% Fe, 0.4 mol% I_2, 6.2 mol% pyridine	EtOH	40	180	2	84	494	[36]
25	0.23 mol% Pd_{black}, 11 mol% Fe, 0.49 mol% I_2, 7.6 mol% pyridine	EtOH	41	170	3	92	400	[37]
26	0.07 mol% $PdCl_2(4\text{-}MePy)_2$, 3.3 mol% Fe, 0.15 mol% I_2, 7.7 mol% 4-MePy	EtOH	40	180	2	53	757	[38,39]

TMphen = 3,4,7,8-tetramethylphenathroline, 2,4,6-TMBA = 2,4,6-trimethylbenzoic acid, Me_2phen = 4,7-dimethylphenanthroline, BAcImPF$_6$ = 1-butyl-3-acetic acid-imidazolium, CyOH =cyclohexanol

Moreover, Brønsted acids are efficient co-catalysts for palladium-phenanthroline system, not only for simple palladium salts. 2-Chlorobenzoic acid proved to be the most efficient co-catalyst amongst various aromatic and aliphatic carboxylic acids (Table S2, entry 6).[18,40] Addition of silver salts and the use of p-toluenesulfonic acid increase the activity of the system even further (entry 7).[19] Anthranilic acid also proved to be efficient cocatalyst in reductive carbonylation of nitrobenzene (entry 8).[20] A. M. Romano *et al*. reported that $[Pd(phen)_2][PF_6]_2$ in combination with free 1,10-phenanthroline and 1,10-phenanthrolinium hexafluorophosphate as acid cocatalyst was efficient catalytic system for synthesis of industrially valuable 2,4-toluenediurethane.[41]

Ionic liquids are also capable of promoting reductive carbonylation of nitroaromatics to urethanes with palladium-phenanthroline system. Deng and coworkers showed that $Pd(phen)_2Cl_2$-BAcImPF$_6$ ionic liquid (BAcIm = 1-butyl-3-acetic acid-imidazolium) is a highly effective catalytic system (Table S2, entry 9).[21] Another example of an application of an ionic liquid in reductive carbonylation was reported by H. Alper *et al.* (entry 10).[22] Although the system required high catalyst loading, it worked well for a great variety of substrates including those with electron-donating and electron-withdrawing groups as well as different types of dinitro compounds.

In 2003 F. Ragaini *et al.* demonstrated that a simple phosphoric acid is a very efficient co-catalyst for Pd-phenanthroline system in reductive carbonylation of nitrobenzene with turnover number up to 5462 (Table S2, entry 11).[23,24] Addition of fluorides in the form of NEt_4F to this system increases the reaction rate and can slightly affect selectivity (entry 12).[25] It was shown by the same group that the catalytic activity of such a system can be even better if nonsymmetric phenanthrolines are employed (entries 13 and 14).[26,27] A catalytic system with 4-anilinophenanthroline is the most active at this moment with turnover frequency over 6000 h^{-1} at 60 bar. Under the same conditions phenanthroline and 4-methoxyphenanthroline give turnover frequency 3600 h^{-1} and 5710 h^{-1}. Interestingly, in the case of reductive carbonylation of dinitrotoluene phenylphosphonic acid is more active than phosphoric acid.[42]

In addition to palladium-phenanthroline system there are other palladium systems that also proved to be efficient in reductive carbonylation of nitrobenzene. In 1991 H. Alper *et al.* reported that palladium supported on montmorillonite in combination with ruthenium carbonyl is an effective catalyst for reductive carbonylation of nitrobenzene and dinitrobenzene derivatives including nitrotoluene, dinitrobenzene, 4,4'-dinitrobiphenyl, and 1,5-dinitronaphthalene in moderate to excellent yields (Table S2, entry 15).[28] Later B. M. Choudary *et. al.* reported similar catalytic system with Pd supported on montmorillonite but $FeCl_3$ was used instead of ruthenium carbonyl (entry 16).[29] Although rather high catalyst loading was employed, this catalytic system could be reused for seven cycles with consistent activity. The reproducible activity and selectivity for several cycles exhibited by this catalytic system without noticeable metal leaching from the support is quite unusual and was observed for the first time in reductive carbonylation of nitrobenzene into methyl *N*-phenylcarbamate.

Bidentate phosphines can also be employed in this reaction instead of bidentate nitrogen ligands, although their activity is lower. H. Alper showed that $[Pd(dppp)_2]Cl_2$ with potassium carbonate as a co-catalyst can catalyze reductive carbonylation of mono- and di-nitroaromatic compounds in moderate to good yields (Table S2, entry 17).[30] Potassium carbonate was shown to be essential for this system, and the palladium complex is totally inactive in its absence. Later P. W. N. M. Leeuwen *et al.* investigated the influence of different P/N and P/P ligands in reductive carbonylation of nitrobenzene.[31] Lower activity of phosphine ligands compared to bidentate nitrogen ligands was explained by oxidation of the phosphorus atom by the nitro substrate. Flexible diphosphine ligands turned out to be more efficient compared to more rigid diphosphines. The highest activity was achieved with dppp as a ligand (entry 18).

Another interesting catalytic system was developed independently by J. K. Yeo and Y. Izumi research groups (Table S2, entry 19-21).[32–34] They proposed the use of palladium chloride in combination with heteropolyacids as basic macroligands. Such catalytic system provides high yields of carbamates, however, rather high catalyst loadings is required. In 1991, A. L. Lapidus *et al.* reported the synthesis of cyclohexyl *N*-phenylcarbamate and cyclohexyl *N*-3-chlorophenylcarbamate from the corresponding nitrobenzenes catalyzed by $PdCl_2$ and $FeCl_3$.[35] Although the catalyst loading was high, the catalytic system can be used for several times without significant loss of the catalytic activity. Efficient catalytic system was developed in the group of J. Skupińska and consisted of palladium source, iron, iodine and pyridine.[36,37,43,44] Palladium may be in the form of $PdCl_2$, $PdCl_2Py_2$ or even Pd_{black} (entries 23-25). Authors also investigated the effect of different pyridines as co-catalysts and found that the activity of the catalytic system increased with the increase of basicity of the pyridine.[38,39] The best result was obtained with 4-methylpyridine (entry 26).

1.3 Rhodium Catalysis

In 1981, it was shown by the group of V. I. Manov-Yuvenskii that $RhCl(CO)(PPh_3)_2$ is active in reductive carbonylation of nitrobenzene (Table S3, entry 1).[45] This system requires high amounts of the catalyst and a Lewis acid and gives a low yield of the carbamate, however short reaction time (20 min) represents its key advantage. Later S. Cenini and coworkers suggested the use of $Rh_6(CO)_{16}$ with 2,2'-bipyridine (entry 2).[5] In the absence of a ligand $Rh_6(CO)_{16}$ was practically inactive in reductive carbonylation. Rhodium supported on Al_2O_3 can catalyze reductive carbonylation as well (entry 3), although somewhat less efficiently than $Rh_6(CO)_{16}$.[46] C. R. Saha and coworkers investigated the catalytic activity of $RhA(CO)_2$ (HA = anthranilic acid) in the presence of different co-catalysts.[47] Interestingly, acidic co-catalysts such as $FeCl_3$, $SnCl_4$ and TsOH led to almost complete conversion of nitrobenzene to diphenylurea and aniline, while basic co-catalysts were selective toward formation of carbamate (entry 4). Different urethanes were obtained from 2- and 4-substituted nitrobenzenes in moderate to good yields (69-85%). Another active complex for reductive carbonylation of nitrobenzenes into carbamates is $[PPN]Rh(CO)_4$ (PPN = bis(triphenylphosphine)iminium). As it was for $Ru_3(CO)_{12}$ (See Table S1, entry 3), *t*-BuOH is more active in carbamate formation if $[PPN]Rh(CO)_4$ is used (entry 5).[6] As in the case of $Rh_6(CO)_{16}$, the activity of $[PPN]Rh(CO)_4$ can be significantly increased if a nitrogen bidentate ligand is used (entry 6).[48] The catalytic activity of $[PPN]Rh(CO)_4$ can be further increased if 2-hydroxypyridine is used instead of bipyridine (entry 7).[49] The most active rhodium catalytic system to date was reported by D. K. Mukherjee. This system consisted of rhodium(I) complex $[Rh(P\text{-}S)(CO)_2]$ (P-S = polymer anchored salicylic acid) (**Rh-1**) and NaOMe as a co-catalyst (entry 8).[50] This system can be successfully reused up to 6 times without significant loss of the product yield.

Table S3. Rh catalytic systems for reductive carbonylation of nitrobenzenes to carbamates (See scheme S1, Ar = Ph)

Entry	Catalytic system	ROH	CO pressure, bar	T, °C	Reaction time, h	Yield, %	TON up to	Ref. #
1	5.1 mol% $RhCl(CO)(PPh_3)_2$, 79 mol% $FeCl_3$	MeOH	60	180	0.33	29	6	[45]
2	0.5 mol% $Rh_6(CO)_{16}$, 1.5 mol% 2,2’-bipy	MeOH	60	170	1.5	71	142	[5]
3	0.5 mol% Rh/Al_2O_3, 4 mol% 2,2’-bipy	MeOH	100	200	3	42	84	[46]
4	1 mol% $RhA(CO)_2$, 40 mol% NaOMe	MeOH	80	140	5.5	85	85	[47]
5	2 mol% $[PPN]Rh(CO)_4$, 14 mol% Et_4NCl	tBuOH	28	160	12	96	48	[6]
6	0.33 mol% $[PPN]Rh(CO)_4$, 1 mol% bipyridine	MeOH	60	200	1.5	88	267	[48]
7	0.17 mol% $[PPN]Rh(CO)_4$, 2 mol% 2-OH-Py,	MeOH	60	200	1.5	47	282	[49]

	15 mol% $PhNH_2$							
8	**Rh-1** (0.025 mol% of Rh), 25 mol% NaOMe	MeOH	80	100	16	74	17520 for 6 cycles	[50]

1.4 Other catalytic systems

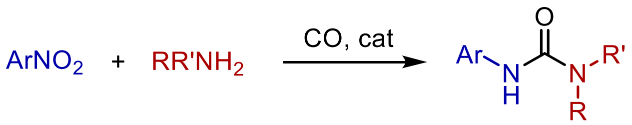
In 1982, Y. Watanabe reported platinum-catalyzed carbonylation of nitrobenzene into urethane in the presence of tin (IV) chloride and Et_3N (Table S4, entry 1).[51] Later the same authors fully investigated this system by varying different Lewis acids, bases and platinum catalysts.[52] The best system was still based on $PtCl_2(PPh_3)_2$, $SnCl_4$ and Et_3N, although iron (III) chloride, aluminum chloride and titanium chloride had activities comparable to tin(IV) chloride. The authors were also able to expand the substrate scope to different substituted nitrobenzenes[52] and even 2,4-dinitrotoluene.[53] However, the activity was still low if compared to palladium systems.

Development of catalytic systems which do not include noble metals such as rhodium, palladium and ruthenium can be economically useful. In 2009, selenium-catalyzed carbonylation of 1-nitronaphthalene was reported by X. Zhang *et al.* (Table S4, entry 2).[54] Among several tested alcohols only tertiary alcohols did not give desired product. Another example of non-noble metal catalytic system was reported by L. Chen and coworkers (entry 3).[55] They employed cobalt complex with saloph-type ligands in redox carbonylation of aniline and nitrobenzene. In this case, carbon monoxide is used mostly as a carbonyl source and not as a reducing agent. Still, it was evidenced by the authors that some amount of aniline was additionally formed by reduction of nitrobenzene by carbon monoxide. Quite recently Z. Bangtun and coworkers showed that a silica-supported chitosan-iron complex SiO_2-CS-$FeCl_3$ is active in reductive carbonylation of nitrobenzene in presence of $NiCl_2$ as cocatalyst (entry 4).[56]

Table S4. Other catalytic systems for reductive carbonylation of nitrobenzenes to carbamates (See Scheme S1)

Entry	Catalytic system	ROH	CO pressure, bar	T, °C	Reaction time, h	Yield, %	TON up to	Ref. #
1	0.5 mol % $Pt(PPh_3)_2Cl_2$, 5 mol% $SnCl_4$, 18 mol% Et_3N	EtOH	60	180	4	83	166	[51]
2	5 mol% Se, 2 eq. Et_3N, 4.8 mol% PPh_3, 1.6 mol% TsOH	ROH	20	160	6-10	46-89	18	[54]
3	1 mol% $Co[(OH)_2saloph]$, 1 mol% TsOH, 2 eq. aniline	MeOH	50	170	2	81	81	[55]
2	SiO_2-CS-$FeCl_3$ (0.4 mol% of Fe), 1.6 mol% $NiCl_2$, 4.8 mol% PPh_3, 16 mol% p-TsOH	EtOH	40	180	4	59	148	[56]

2 Synthesis of Ureas



Scheme S2 Reductive carbonylation of nitrobenzenes to urea

In 1975, R. F. Heck reported synthesis of *N*,*N*-diarylurea from nitro compounds and amines under relatively mild conditions (Table S5, entry 1),[57] on using $Pd(OAc)_2$-Ph_3P catalytic system with *n*-Bu_3N and Et_3NCl as additive. This system worked well for the preparation of symmetric ureas but gave mixtures when the synthesis of unsymmetrical ureas was attempted. Only *p*-substituted nirobenzene and aniline derivatives were tested. Under harsh conditions the activity of this system increases and no longer requires a tertiary amine as a co-catalyst (entry 2).[58] The increase in aniline/nitrobenzene ratio improved the stability of the catalytic system allowing to use this system for at least 4 cycles without any loss of activity.[59]

Table S5. Pd catalytic systems for reductive carbonylation of nitrobenzenes to ureas (See scheme S2)

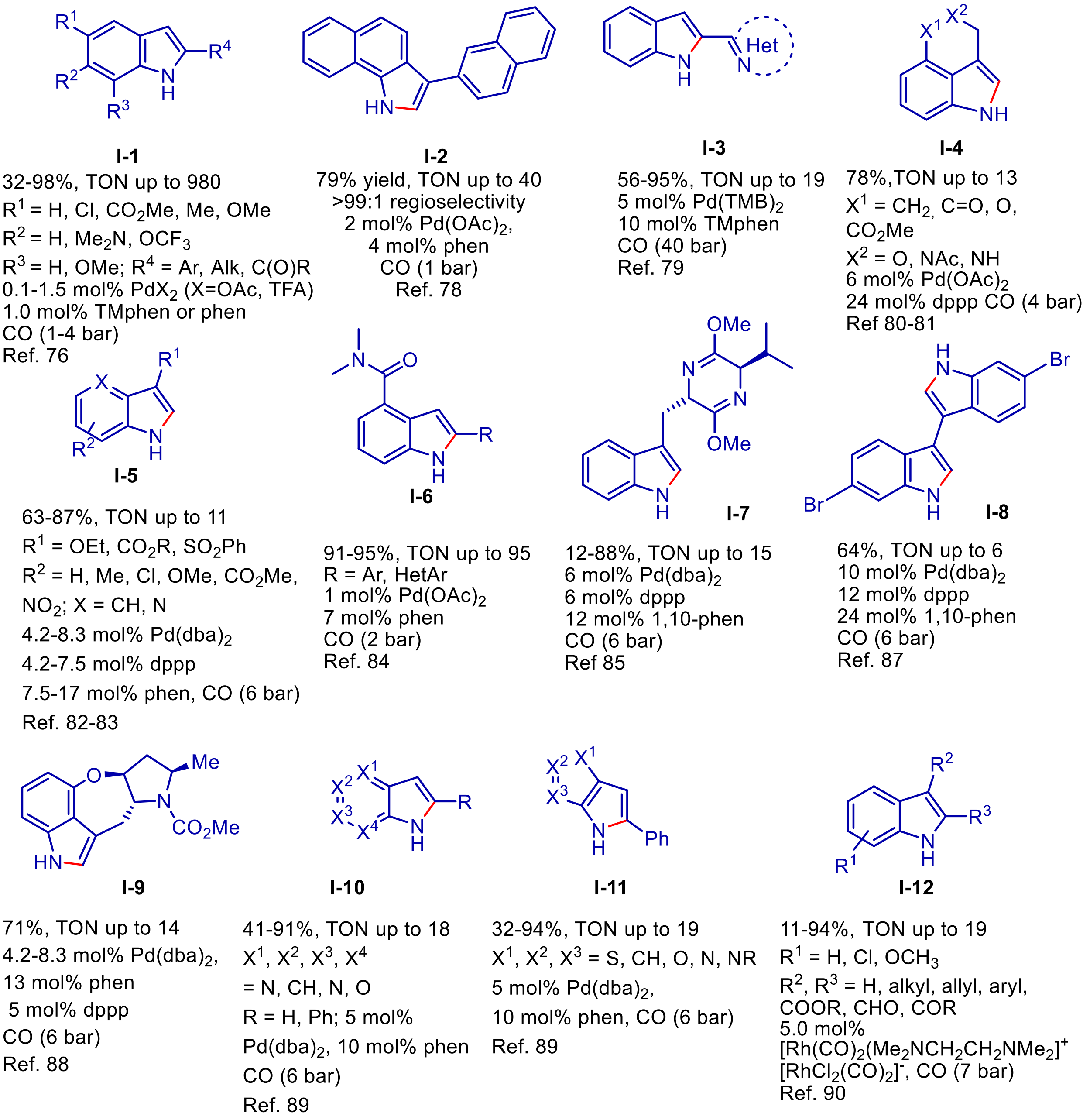
Entry	Catalytic system	Amine to nitro compound ratio	CO pressure, bar	T, °C	Reaction time, h	Yield, %	TON up to	Ref. #
1	2 mol% $Pd(OAc)_2$, 4 mol% Ph_3P, 15 mol% Et_4NCl, 54 mol% Bu_3N	1:1.1	1	90	2.6	64	32	57
2	1.3 mol% $Pd(OAc)_2$, 7.6 mol% PPh_3, 24 mol% Et_4NCl	2:1	40	120	2	98	300 (for 4 cycles)	58
3	1.4 mol% $Pd(OTs)_2dppf$	0:1	45	100	5	91	65	60
4	5 mol% Se, 1 eq. Et_3N	1:1	30	150-160	1.5	50-80	16	61
5	5 mol% Se or SeO_2, 2 eq. Et_3N	1:1	30	160	4	26-93	19	62–65
6	2 mol% $Pt(PPh_3)_2Cl_2$, 10 mol% $SnCl_4$, 18 mol% Et_3N, 54 mol% Bu_3N	1.1:1	60	140	4	20-67	34	66
7	4 mol% $Ru_3(CO)_{12}$	0:1	60	170	5	36-88	22	67,68
8	**Ru-1** (0.09 mol% of Ru), 2.1 eq. $FeCl_3$, 6 eq. MeOH	2:1	60	120	5	4-97	970	69
9	**Rh-2** (0.04 mol%), 10 mol% MeOH	1:1	60	80	4	70	1750	70

This effect was explained by proposing another pathway for urea formation with different stoichiometry of substrates.[71,72] The originally proposed mechanism, which is believed to proceed through a nitrene intermediate, is favored by bidentate phosphine ligands.[73,74] Recently, A. Vavasori *et al.* investigated the activity of palladium complexes with different bidentate phosphines.[60] The most active complex was $Pd(OTs)_2dppf$, which catalyzed the synthesis of diphenylurea without any co-catalysts (Table S5, entry 3). In 1999, S. Lu *et al.* reported the synthesis of unsymmetrical ureas from nitrobenzene and aliphatic secondary amines in moderate to good yields catalyzed by selenium (entry 4).[61] Primary amines gave mixtures of symmetrical and unsymmetrical ureas. This system was further expanded to substituted nitrobenzenes and aminopyrimidines or aminopyridines (entry 5).[62–64] Instead of selenium its oxide can be used as well. The system worked well without noticeable influence of steric or electronic effects and gave ureas in moderate to good yields. Nitropyridines also undergo this transformation under these conditions.[65] Amides can also be employed instead of anilines to give corresponding *N*-arylamides.[75] In 1985, Y. Watanabe reported that the system previously employed for the synthesis of carbamates (See Table S4, entry 1) is also efficient for the preparation of symmetrical ureas (entry 6), albeit with rather low yields if compared to palladium systems.[66] B. Rindone and coworkers showed that $Ru_3(CO)_{12}$ can also catalyze the formation of ureas,[67,68] in the presence of alkenes as solvents (entry 7). Only *para*-substituted nitrobenzenes were tested and the yield of diphenylurea formation was high (88%), while the yields in case of *p*-nitrotoluene and 4-chloronitrobenzene were twice as low. 4-Nitrobenzoate did not furnish any urea product at all. In this work, interesting product of allylic addition of nitrobenzene to alkene was observed. Although there were only traces of this product authors were able to modify catalytic system for the synthesis of it which will be discussed in the next section.

Recently, S. Islam investigated the activity of complex $[Ru(PS\text{-}imd)(CO)_2Cl_2]$ (PS-imd = polystyrene anchored imidazole) (**Ru-1**) in the synthesis of unsymmetrical ureas.[69] Different para-substituted nitrobenzenes and aromatic as well as aliphatic amines were successfully transformed to the corresponding ureas (Table S5, entry 8). It should be noted that authors calculated turnover number from total amount of substrates (nitrobenzene derivative + amine), whereas we calculated from amount of nitrobenzene. A very active catalytic system was suggested by C. R. Saha *et al.*[70] RhA(CO)(Ph_2PCH_2-polystryrene) (HA = 2-aminobenzoic acid) (**Rh-2**) showed very high activity in diphenylurea formation (entry 9).[70]

3. Synthesis of indoles

Various applications of Pd-mediated synthesis of indoles from nitroaromatics were discovered. Using new catalytic systems, mild conditions and relatively low catalyst loadings (0.1 mol% palladium trifluoroacetate) were achieved (Scheme S3, **I-1**).[76] This system was employed for the synthesis of precursor of KDR kinase inhibitor.[76] Afterwards, the $Pd(OAc)_2/PPh_3$ catalytic system has been used in the synthesis of 2,4-dimethylindole (66% yield), 4-(hydroxymethyl)-2-methylindole (85% yield), and 4-(methoxymethyl)-2-methylindole (76% yield), which are alkaloids isolated from two species of European Basidomycetes (*Tricholoma virgatum* and *Tricholoma sciodes*).[77]



I-1
32-98%, TON up to 980
R^1 = H, Cl, CO_2Me, Me, OMe
R^2 = H, Me_2N, OCF_3
R^3 = H, OMe; R^4 = Ar, Alk, C(O)R
0.1-1.5 mol% PdX_2 (X=OAc, TFA)
1.0 mol% TMphen or phen
CO (1-4 bar)
Ref. 76

I-2
79% yield, TON up to 40
>99:1 regioselectivity
2 mol% $Pd(OAc)_2$,
4 mol% phen
CO (1 bar)
Ref. 78

I-3
56-95%, TON up to 19
5 mol% $Pd(TMB)_2$
10 mol% TMphen
CO (40 bar)
Ref. 79

I-4
78%,TON up to 13
X^1 = CH_2, C=O, O, CO_2Me
X^2 = O, NAc, NH
6 mol% $Pd(OAc)_2$
24 mol% dppp CO (4 bar)
Ref 80-81

I-5
63-87%, TON up to 11
R^1 = OEt, CO_2R, SO_2Ph
R^2 = H, Me, Cl, OMe, CO_2Me, NO_2; X = CH, N
4.2-8.3 mol% $Pd(dba)_2$
4.2-7.5 mol% dppp
7.5-17 mol% phen, CO (6 bar)
Ref. 82-83

I-6
91-95%, TON up to 95
R = Ar, HetAr
1 mol% $Pd(OAc)_2$
7 mol% phen
CO (2 bar)
Ref. 84

I-7
12-88%, TON up to 15
6 mol% $Pd(dba)_2$
6 mol% dppp
12 mol% 1,10-phen
CO (6 bar)
Ref 85

I-8
64%, TON up to 6
10 mol% $Pd(dba)_2$
12 mol% dppp
24 mol% 1,10-phen
CO (6 bar)
Ref. 87

I-9
71%, TON up to 14
4.2-8.3 mol% $Pd(dba)_2$,
13 mol% phen
5 mol% dppp
CO (6 bar)
Ref. 88

I-10
41-91%, TON up to 18
X^1, X^2, X^3, X^4 = N, CH, N, O
R = H, Ph; 5 mol% $Pd(dba)_2$, 10 mol% phen
CO (6 bar)
Ref. 89

I-11
32-94%, TON up to 19
X^1, X^2, X^3 = S, CH, O, N, NR
5 mol% $Pd(dba)_2$,
10 mol% phen, CO (6 bar)
Ref. 89

I-12
11-94%, TON up to 19
R^1 = H, Cl, OCH_3
R^2, R^3 = H, alkyl, allyl, aryl, COOR, CHO, COR
5.0 mol% $[Rh(CO)_2(Me_2NCH_2CH_2NMe_2]^+$ $[RhCl_2(CO)_2]^-$, CO (7 bar)
Ref. 90

Scheme S3 Pd-phenanthroline catalyzed synthesis of indoles

T. H. H. Hsieh and V. M. Dong[78] managed to expand the substrate scope and to conduct a Pd-catalyzed reaction under even milder conditions. In their work, 2 mol% of palladium acetate and 4 mol.% of phen ligand were used, and yields of indoles reached 98% under only 1 bar of CO and heating at 110 °C for 3-6 hours. Furthermore, high regioselectivity was demonstrated (Scheme S3, **I-2**). This cyclization reaction was applied to the synthesis of indole-containing polydentate ligands with yields up to 95% (Scheme S3, **I-3**).[79] Moreover, this palladium-catalyzed reaction has been applied to the synthesis of fused indoles (Scheme S3, **I-4**),[80,81] 3-indolecarboxylic acid derivatives (Scheme S3, **I-5**),[82,83] 2-arylindole-4-carboxylic amide derivatives (Scheme S3, **I-6**),[84] and even tryptophan derivatives (Scheme S3, **I-7**)[85]. Moreover, in the works of N. H. Ansari *et al*.[86] biindoles including naturally occurring[87] polybrominated 3,3'-bi-1*H*-indoles were synthesized using the Pd-catalyzed process (Scheme S3, **I-8**). The methodology was even used in total synthesis of a tetracyclic indole alkaloid ht-13-B[88] (Scheme S3, **I-9**).[88] Moreover, Pd-mediated indole synthesis was implemented into the preparation of bicyclic pyrrolo-fused heteroaromatic molecules (Scheme S3, **I-10** and **I-11**).[89] New catalytic systems including ionic diamine rhodium complex (Scheme S3, **I-12**) were also explored.[90]

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