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Reductive amination catalyzed by iridium complexes using carbon monoxide as a reducing agent†

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Development of novel, sustainable catalytic methodologies to provide access to amines represents a goal of fundamental importance. Herein we describe a systematic study for the construction of a variety of amines catalyzed by a well-defined homogeneous iridium complex using carbon monoxide as a reducing agent. The methodology was shown to be compatible with functional groups prone to reduction by hydrogen or complex hydrides.

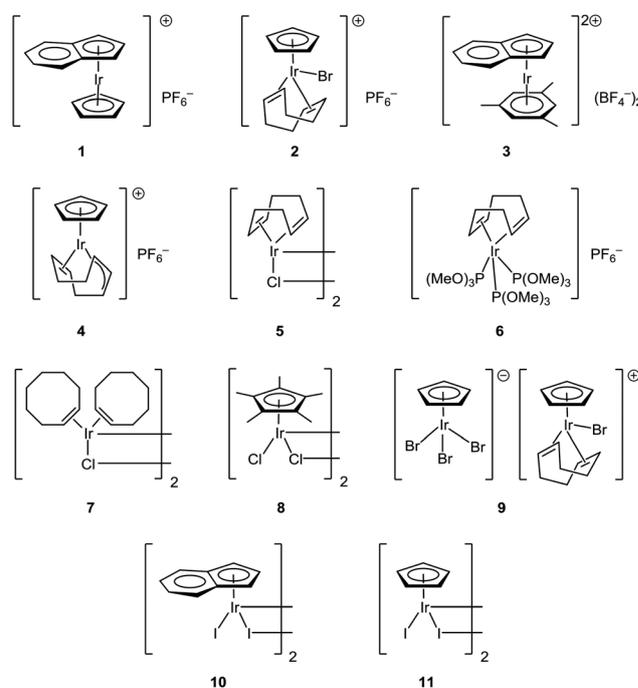
Among the transformations which are conventionally classified as reductions, reductive amination is notable for particularly high preparative significance, being one of the most convenient and versatile methods of C–N bond formation.^{1,2} Notably, a representative screening of publications in the field of medicinal chemistry demonstrated that reductive amination is used more frequently than the eight most popular reductive processes combined,³ which is not surprising in light of the numerous advantages of this type of transformation, such as accessibility of starting materials, modular nature and the possibility of rapid build-up of molecular complexity.

Our group has recently discovered a catalytic reductive methodology⁴ which takes advantage of the deoxygenative potential of carbon monoxide and does not require an external hydrogen source unlike the conventional approaches to *e.g.* reductive amination.

So far only rhodium and ruthenium complexes were found to be capable of catalyzing CO-assisted^{5,6} reductive reactions.⁷ In this work, we tried to expand our knowledge about this type of processes and tried both iridium(i) and iridium(III) complexes with weakly and strongly bonded ligands with η-1, η-2,

η-3, η-5 and η-6 coordination types (Scheme 1) as potential catalysts. As a result, herein we report the first example of iridium-catalyzed CO-assisted reductive amination.

Complexes [CpIrI₂]₂, [Cp*IrCl₂]₂, [CpIr(cod)Br]PF₆, [CpIr(cod)Br][CpIrBr₃], [(η⁵-indenyl)IrI₂]₂, [(η⁵-indenyl)IrCp]PF₆, [(η⁵-indenyl)Ir(η⁶-C₆H₃Me₃)](BF₄)₂ were synthesized by known



Scheme 1 Iridium complexes tested as pre-catalysts for the reductive amination reaction.

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procedures.^{8–11} Cyclooctadienyl complex $[\text{CpIr}(\eta^3, \eta^2\text{-C}_8\text{H}_{11})]\text{PF}_6$ was prepared by the reaction of $\text{CpIr}(\text{cod})$ with silver trifluoroacetate (Scheme 2; anions are omitted in the schemes for clarity). Probably, this reaction proceeds *via* intermediate formation of dication $[\text{CpIr}(\text{cod})]^{2+}$ which undergoes spontaneous deprotonation to give $[\text{CpIr}(\eta^3, \eta^2\text{-C}_8\text{H}_{11})]^+$. Earlier, Maitlis and coworkers synthesized the pentamethyl analog $[\text{Cp}^*\text{Ir}(\eta^3, \eta^2\text{-C}_8\text{H}_{11})]\text{PF}_6$ by interaction of $[\text{Cp}^*\text{Ir}(\text{Me}_2\text{CO})_3]^{2+}$ with cyclooctadiene.¹²

Phosphite complexes $[(\text{cod})\text{Ir}\{\text{P}(\text{OR})_3\}_3]\text{PF}_6$ ($\text{R} = \text{Me}, \text{Et}$) were unexpectedly formed in the reaction of $[\text{CpIr}(\text{cod})\text{Br}]\text{PF}_6$ with phosphites (Scheme 3). Notably, phosphites play a dual role in this reaction: they serve both as ligands and reducing agents. Indeed, there are signals for five-valence phosphorus species (2.5–30 ppm) along with those for coordinated and free phosphite (89 and 140 ppm, respectively) in the ^{31}P NMR spectrum of the reaction mixture. Usually, binding of cyclopentadienyl ligand to transition metals is considerably stronger than that of cyclooctadiene. Probably, reduction of $\text{Ir}(\text{III})$ to $\text{Ir}(\text{I})$ facilitates substitution of Cp in this case. In contrast, a similar reaction of $[\text{CpIr}(\text{cod})\text{Br}]\text{PF}_6$ with 2,2'-bipyridyl, which does not possess reducing ability, leads to substitution of cyclooctadiene with the formation of $[\text{CpIr}(2,2'\text{-bipy})\text{Br}]\text{PF}_6$ (Scheme 3).

The structure of $[(\text{cod})\text{Ir}\{\text{P}(\text{OMe})_3\}_3]\text{PF}_6$ was determined by X-ray diffraction (Fig. 1). The Ir–P bonds (2.248–2.317, av. 2.278 Å) in cation $[(\text{cod})\text{Ir}\{\text{P}(\text{OMe})_3\}_3]^+$ are considerably shorter than those in the previously reported phosphide complex $[(\text{cod})\text{Ir}(\text{PMe}_3)_3]^+$ (2.327–2.379, av. 2.348 Å).¹³ The strong Ir–P bonds correlate well with low catalytic activity of $[(\text{cod})\text{Ir}\{\text{P}(\text{OMe})_3\}_3]\text{PF}_6$ in reductive amination reactions (see below). In accordance with the trans-effect, the Ir–cod bonds in the phosphite complex (2.182–2.312, av. 2.248 Å) are longer than the corresponding bonds in the phosphide analog (2.178–2.237, av. 2.207 Å).

After all the catalysts had been synthesized, we decided to compare them using *p*-methylbenzaldehyde and *p*-anisidine as model substrates (Table 1). It was found that dimeric iridium(III) complexes with bridging halide ligands are considerably more catalytically active than cationic monomeric species (Table 1,

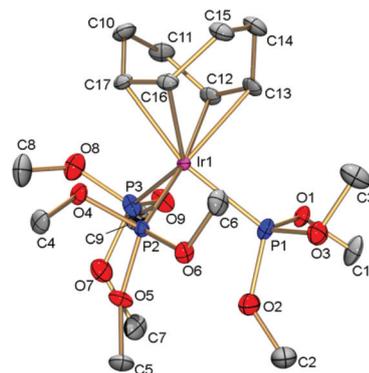
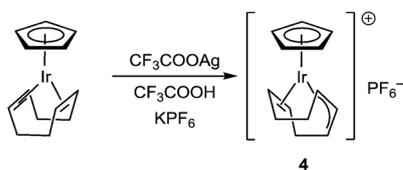


Fig. 1 Cation $[(\text{cod})\text{Ir}\{\text{P}(\text{OMe})_3\}_3]^+$ with atoms shown as thermal ellipsoids at 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Ir1–C12 2.289(3), Ir1–C13 2.312(3), Ir1–C16 2.209(3), Ir1–C17 2.182(3), Ir1–P1 2.2691(8), Ir1–P2 2.2480(7), Ir1–P3 2.3177(8), C12–C13 1.395(5), C16–C17 1.433(4).

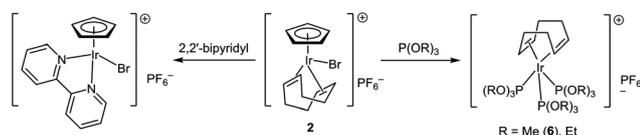
Table 1 Catalyst screening in the model reductive amination reaction^a

Entry	Catalyst	Catalyst loading [mol%]	Yield [%]
1	1	1.0	5
2	2	1.0	8
3	3	1.0	8
4	4	1.0	12
5	5	0.5	14
6	6	1.0	25
7	7	0.5	29
8	8	0.5	28
9	9	1.0	21
10	10	0.5	39
11	11	0.5	57
12	IrCl_3	1.0	33
13	$\text{IrCl}_3 + 3\text{NaI}$	1.0	47

^a 1 : 1 ratio of the amine and the aldehyde was employed. 0.2 mmol scale.



Scheme 2 Synthesis of $[\text{CpIr}(\eta^3, \eta^2\text{-C}_8\text{H}_{11})]^+$.

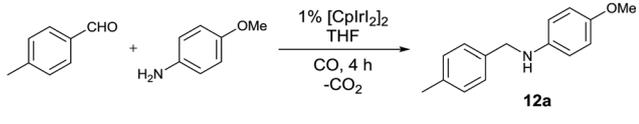


Scheme 3 Reactivity of $[\text{CpIr}(\text{cod})\text{Br}]^+$.

entries 8–11 vs. 1–4). Iridium(I) complexes give moderate yields (entries 5–7). Superior performance was observed for complexes of iridium(III) with Cp and halogens (Table 1, entries 8–10). Cyclopentadienyl iridium(III) diiodide was found to provide the best results among the tested metal complexes (entry 11) and was therefore used for the further optimization studies. The effect of iodine counterion seems to be general for the iridium complexes. When sodium iodide was added to iridium trichloride the yield increases from 33 to 47% (Table 1, entries 11 and 12).

Solvent screening revealed ethereal solvents and alcohols as the optimum media for the reaction (see ESI†). To avoid any possibility of hydrogen transfer reaction we chose tetrahydrofuran as a solvent instead of isopropanol. The temperature studies showed no significant trend at temperatures higher



Table 2 Temperature and pressure influence for the model reductive amination reaction^a


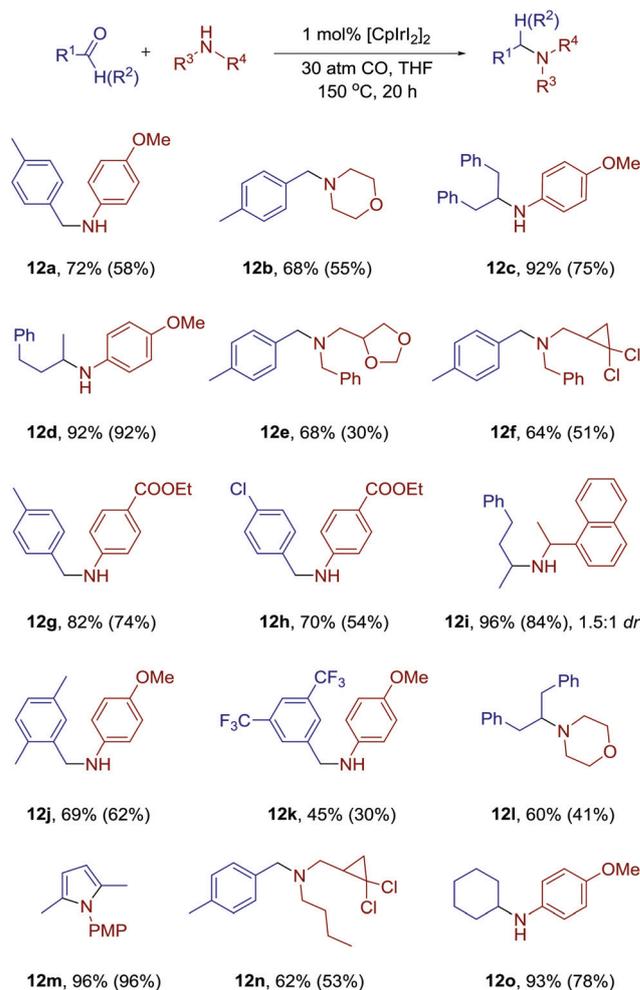
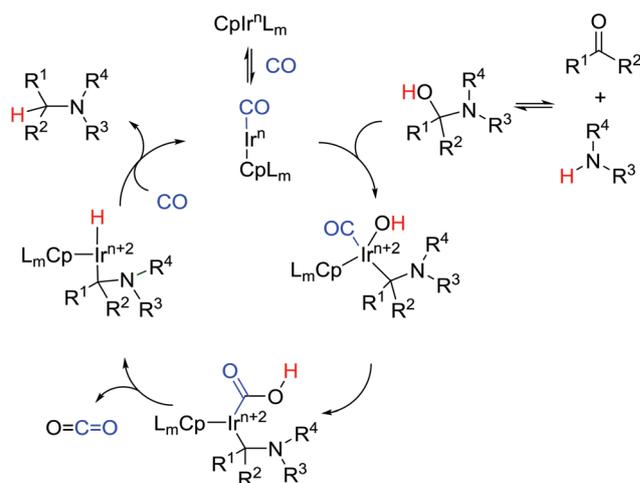
Entry	Solvent ^b	T [°C]	P [bar]	Catalyst loading [mol%]	Yield ^c [%]
1	THF	140	50	1.0	49
2	THF	150	50	1.0	54
3	THF	160	50	1.0	57
4	THF	150	60	0.5	39
5	THF	150	50	0.5	37
6	THF	150	30	0.5	34
7	THF	150	20	0.5	11
8	THF	150	10	0.5	9
9	THF	150	5	0.5	2
10 ^b	THF	130	50	1.0	67
11 ^b	THF	140	50	1.0	67
12 ^b	THF	150	50	1.0	72

^a 1.5 : 1 ratio of the amine and the aldehyde was employed. 0.1 mmol scale. ^b 2 : 1 ratio of the amine and the aldehyde was employed. 22 h. ^c Yields were determined by GC.

than 140 °C (Table 2, entries 1–3). The pressure had almost no influence on the reaction outcome above 30 bar, which can be explained by the supercritical nature of carbon monoxide (Table 2, entries 4–7). When the pressure was decreased from 30 to 20 bar the reaction rate was significantly lower (Table 2, entry 6 vs. 7). Nonetheless, the reaction still proceeded to some extent even at the pressure of as low as 5 bar (Table 2, entry 9). The yield becomes significantly higher at amine to aldehyde ratio of 2 : 1 (Table 2, entries 10–12). Comparison iridium catalysis with our previous data clearly shows that for the most nucleophilic amines rhodium still represents the best choice. For ruthenium catalyzed reactions with nucleophilic aliphatic amines, *N*-formamide was detected as a side product; no such byproduct was found in case of iridium catalysis.

With the optimized conditions in hand, we turned to investigation of the scope of the developed methodology (Scheme 4). We found that chlorinated cyclopropanes could react with amines without any erosion of either cyclopropane rings or halogen substitution (**12f**, **12n**). The stability of the dioxalane moiety was also successfully validated (**12e**). *N*-Benzyl moiety, which is usually fragile under various reductive conditions, remained fully intact in our system. Both aromatic and aliphatic amines are suitable for the reaction, and both primary and secondary amines can be used.

Surprisingly, ketones are even more suitable for this reaction. Only when hexane-2,5-dione was used as a starting material exclusive formation of *N*-PMP-2,5-dimethylpyrrole **12m** was detected. When naphthylethylamine was used together with benzylacetone the product of 1.5 : 1 dr was obtained (**12i**). Based on our previous studies we suggest a plausible mechanism of the process (Scheme 5). The reaction between an amine and a carbonyl compound leads to the formation of a hemiam-

**Scheme 4** Substrate scope of reductive amination catalyzed by CpIrL₂ in the presence of carbon monoxide. Yields were determined by NMR with an internal standard. Isolated yields are given in parentheses.**Scheme 5** Plausible mechanism.

inal. The oxidative addition of iridium complex to C–O bond of the heminal leads to a new complex. After an attack of hydroxyl group on the coordinated CO and elimination of CO₂, the iridium hydride complex should be formed. Reductive elimination then leads to the formation of the product and regeneration of the catalytic species.

Conclusions

In summary, we have found a new type of catalyst which can provide atom-economical reductive amination of aldehydes and ketones. The methodology takes advantage of the unique deoxygenative potential of carbon monoxide and does not require an external hydrogen source, which enables full compatibility with a range of functional groups prone to reduction (e.g. *N*-benzyl, dioxalane, halo-, cyclopropanes).

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Notes and references

- (a) E. W. Baxter and A. B. Reitz, in *Organic Reactions*, ed. L. E. Overman and A. Overman, Wiley-VCH, Weinheim, 2002, vol. 59; (b) A. F. Abdel-Magid and S. J. Mehrman, *Org. Process Res. Dev.*, 2006, **10**, 971; (c) R. P. Tripathi, S. S. Verma, J. Pandey and V. K. Tiwari, *Curr. Org. Chem.*, 2008, **12**, 1093; (d) P. Margaretha, in *Science of Synthesis Knowledge Updates 2010/4*, Thieme, Stuttgart, 2011, p. 405.
- For selected recent papers on reductive amination see: (a) H. Alinezhad, H. Yavari and F. Salehian, *Curr. Org. Chem.*, 2015, **19**, 1021; (b) S. Pisiewicz, T. Stemmler, A.-E. Surkus, K. Junge and M. Beller, *ChemCatChem*, 2015, **7**, 62; (c) M. Zhu, *Catal. Lett.*, 2014, **144**, 1568; (d) X. Yan, E. Sokol, X. Li, G. Li, S. Xu and R. Graham Cooks, *Angew. Chem., Int. Ed.*, 2014, **53**, 5931; (e) E. E. Drinkel, R. R. Campedelli, A. M. Manfredi, H. D. Fiedler and F. Nome, *J. Org. Chem.*, 2014, **79**, 2574; (f) D. Talwar, N. Poyatos Salguero, C. M. Robertson and J. Xiao, *Chem. – Eur. J.*, 2014, **20**, 245; (g) S. Werkmeister, K. Junge and M. Beller, *Green Chem.*, 2012, **14**, 2371; (h) N. K. Pahadi, M. Paley, R. Jana, S. R. Waetzig and J. A. Tunge, *J. Am. Chem. Soc.*, 2009, **131**(46), 16626; (i) J. P. Patel, A.-H. Li, H. Dong, V. L. Korlipara and M. J. Mulvihill, *Tetrahedron Lett.*, 2009, **50**(44), 5975.
- S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.
- (a) D. Chusov and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 5199; (b) P. N. Kolesnikov, D. L. Usanov, E. A. Barablina, V. I. Maleev and D. Chusov, *Org. Lett.*, 2014, **16**, 5068; (c) P. N. Kolesnikov, N. Z. Yagafarov, D. L. Usanov, V. I. Maleev and D. Chusov, *Org. Lett.*, 2015, **17**, 173; (d) N. Z. Yagafarov, P. N. Kolesnikov, D. L. Usanov, V. V. Novikov, Y. V. Nelyubina and D. Chusov, *Chem. Commun.*, 2016, **52**, 1397; (e) O. I. Afanasyev, A. A. Tsygankov, D. L. Usanov and D. Chusov, *Org. Lett.*, 2016, **18**(22), 5968.
- For the recent examples of using carbon monoxide for nitro group reductive transformation see: H.-Q. Li, X. Liu, Q. Zhang, S.-S. Li, Y.-M. Liu, H.-Y. He and Y. Cao, *Chem. Commun.*, 2015, **51**, 11217.
- For the state-of-the-art examples of reductive application CO in the water-gas shift reaction in organic chemistry see: (a) S. E. Denmark, M. Y. S. Ibrahim and A. Ambrosi, *ACS Catal.*, 2017, **7**(1), 613; (b) A. Ambrosi and S. E. Denmark, *Angew. Chem., Int. Ed.*, 2016, **55**, 12164; (c) J. W. Park and Y. K. Chung, *ACS Catal.*, 2015, **5**, 4846; (d) S. E. Denmark and Z. D. Matesich, *J. Org. Chem.*, 2014, **79**, 5970; (e) S. E. Denmark and S. T. Nguyen, *Org. Lett.*, 2009, **11**, 781; (f) L. He, L. C. Wang, H. Sun, J. Ni, Y. Cao, H. Y. He and K. N. Fan, *Angew. Chem., Int. Ed.*, 2009, **48**, 9538; (g) J. Huang, L. Yu, L. He, Y. M. Liu, Y. Cao and K. N. Fan, *Green Chem.*, 2011, **13**, 2672; (h) J. Dong, M. Zhu, G. Zhang, Y. Liu, Y. Cao, S. Liu and Y. Wang, *Chin. J. Catal.*, 2016, **37**, 1669; (i) J. Ni, L. He, Y. M. Liu, Y. Cao, H. Y. He and K. N. Fan, *Chem. Commun.*, 2011, **47**, 812; (j) L. He, F.-J. Yu, X.-B. Lou, Y. Cao, H.-Y. He and K. N. Fan, *Chem. Commun.*, 2010, **46**, 1553.
- For the recent examples of metal carbonyl as the source of carbon monoxide see: (a) N. Jana, F. Zhou and T. G. Driver, *J. Am. Chem. Soc.*, 2015, **137**(21), 6738; (b) F. Zhou, D. S. Wang and T. G. Driver, *Adv. Synth. Catal.*, 2015, **357**(16–17), 3463.
- A. R. Kudinov, D. A. Loginov, Z. A. Starikova and P. V. Petrovskii, *J. Organomet. Chem.*, 2002, **649**, 136.
- C. White, A. Yates and P. M. Maitlis, *Inorg. Synth.*, 1992, **29**, 228.
- D. A. Loginov, A. M. Miloserdov, Z. A. Starikova, P. V. Petrovskii and A. R. Kudinov, *Mendeleev Commun.*, 2012, **22**, 192.
- A. A. Chamkin, A. M. Finogenova, Yu. V. Nelyubina, J. Laskova, A. R. Kudinov and D. A. Loginov, *Mendeleev Commun.*, 2016, **26**, 491.
- C. White, S. J. Thompson and P. M. Maitlis, *Dalton Trans.*, 1978, **10**, 1305.
- J. F. Frazier and J. S. Merola, *Polyhedron*, 1992, **11**, 2917.

