Catalytic Arylation

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Tuning the Reactivity of Dirhodium(II) Complexes with Axial N-Heterocyclic Carbene Ligands: The Arylation of Aldehydes**

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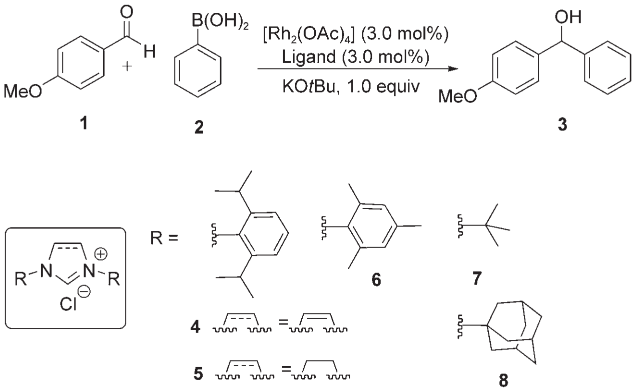
Dirhodium(II) complexes are highly popular in organic synthesis due to their remarkable efficiency in the generation of carbenoids from diazo compounds.[1,2] These complexes contain a Rh−Rh bond, two axial ligands, and four bridging ligands which control the electrophilicity of the catalyst and, in some cases, provide a mechanism for inducing asymmetry. The two axial ligands (normally solvent molecules) form a weaker bond with the metal atoms than do the bridging ligands and are thought to play a less important role in catalysis, as they are easily displaced.[1,2] Despite their unique structural and electronic characteristics and their widespread utilization in the generation of carbenoids from diazo compounds,[1,2] the use of dirhodium(II) complexes as catalysts in other reactions is somewhat infrequent.[3] We, therefore, embarked on a study to establish whether these complexes could provide a source of Rh^{I} for other transformations by simple coordination with the appropriate axial ligand. Among all the possibilities, N-heterocyclic carbene (NHC) ligands seemed to offer good potential, as they are neutral, two-electron-donating (σ-donating) ligands with negligible π backbonding.[4]

To test our hypothesis, we focused on the synthesis of diaryl methanols, which are key structural elements in an array of pharmacologically active compounds.[5,6] On initiating our study with the arylation of aldehyde **1**, we found that combining $[Rh_2(OAc)_4]$ with NHCs prepared in situ by deprotonation of the corresponding imidazolium or imidazolinium salts (Table 1, entries 3–5) gave the secondary alcohol **3** almost quantitatively in less than an hour. Interestingly, all the imidazolium and imidazolinium salts with *N*-aryl substituents afforded the desired product despite having different steric and electronic profiles,[7] whereas salts with bulky *N*-alkyl substituents did not react at all, even after prolonged heating (Table 1, entries 6 and 7). Triphenylphosphine performed better than NHCs with bulky *N*-alkyl substituents, although a yield of only 37 % of the alcohol was obtained (Table 1, entry 8).

Table 1: Ligand evaluation study.



Entry	Complex	Ligand[a]	Solvent[b]	T [°C]	t [h]	Yield [%][c]
1	–	**NHC-4**	DME/H_2O	90	20	trace
2	$[Rh_2(OAc)_4]$	–	DME/H_2O	90	20	n.r.
3	$[Rh_2(OAc)_4]$	**NHC-4**	DME/H_2O	90	0.5	94
4	$[Rh_2(OAc)_4]$	**NHC-5**	DME/H_2O	90	1	99
5	$[Rh_2(OAc)_4]$	**NHC-6**	DME/H_2O	90	1	97
6	$[Rh_2(OAc)_4]$	**NHC-7**	DME/H_2O	90	20	n.r.
7	$[Rh_2(OAc)_4]$	**NHC-8**	DME/H_2O	90	20	trace
8	$[Rh_2(OAc)_4]$	PPh_3	DME/H_2O	90	20	37
9	$[Rh_2(OAc)_4]$	**NHC-4**	DME/H_2O	60	24	n.r.
10	$[Rh_2(pfb)_4]$	**NHC-4**	DME/H_2O	60	24	83
11	$[Rh_2(pfb)_4]$	**NHC-4**	*tert*-amyl alcohol	60	0.5	94
12	$[Rh_2(pfb)_4]$	**NHC-4**	*tert*-amyl alcohol	40	0.5	90
13	$RhCl_3$	**NHC-4**	*tert*-amyl alcohol	40	0.5	n.r.

[a] Compounds **4** (IPrHCl), **5** (SIPrHCl), **6** (IMesHCl), **7** (I*t*BuHCl), and **8** (IAdHCl) are precursors to the ligands **NHC-4**, **NHC-5**, **NHC-6**, **NHC-7**, and **NHC-8**, respectively. [b] DME/H_2O (0.5:0.12 mL). [c] Yields of product obtained after purification by preparative thin-layer chromatography; n.r. = no reaction.

A study of Rh^{II} complexes led to the identification of $[Rh_2(pfb)_4]$ (pfb = perfluorobutyrate) as the most efficient catalyst: in combination with the protic solvent *tert*-amyl alcohol this complex allowed the formation of alcohol **3** in

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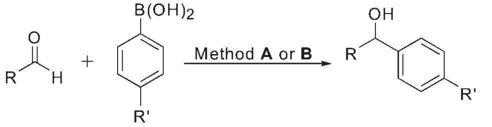
Supporting Information for this article (experimental and computational details, atomic coordinates, and additional information for the optimized species) is available on the WWW under http://www.angewandte.org or from the author.

higher yields at temperatures as low as 40 °C without the use of water (Table 1, entries 9–12).[8]

We tested the optimized catalytic system in the arylation of aryl and alkyl aldehydes (Table 2, entries 1–11). In most cases the reaction proceeded with remarkable efficiency (up to 99 % yield of isolated product) under mild conditions. The methodology proved to have a noteworthy tolerance to functional groups, although it is highly sensitive to electronic effects. In contrast to other catalytic systems,[9] electron-donating groups at the *para* position of the aryl aldehyde clearly activate the aldehyde, whilst strongly electron-withdrawing groups deactivate the aldehyde (Table 2, entries 4 and 7, respectively).

Table 2: Arylation of alkyl and aryl aldehydes.



Entry	R	R′	Product	Method[a]	*T* [°C]	*t* [h]	Yield [%][b]
1	C_6H_5	H	**10**	**A**	60	1	99
2	4-MeC_6H_4	H	**11**	**A**	60	4	91
3	4-ClC_6H_4	H	**12**	**A**	60	0.7	95
4	4-$MeOC_6H_4$	H	**3**	**A**	40	0.5	90
5	4-PhC_6H_4	H	**13**	**A**	60	1	99
6	2-Naphthyl	H	**14**	**A**	80	5	94
7	4-CNC_6H_4	H	**15**	**A**	80	5	80
8	C_6H_5	MeO	**3**	**A**	60	2	95
9	C_6H_5	F	**16**	**A**	60	2	67
10	Cy	H	**17**	**A**	60	3	88
11	*n*-C_7H_{15}	H	**18**	**A**	60	3	77
12	4-$MeOC_6H_4$	H	**3**	**B**	90	1	87
13	(3,4-OCH_2O)C_6H_3	H	**19**	**B**	90	3	96
14	4-CNC_6H_4	H	**15**	**B**	90	6	78
15	C_6H_5	MeO	**3**	**B**	90	1	95
16	C_6H_5	Me	**11**	**B**	90	6	96
17	C_6H_5	F	**16**	**B**	90	6	95
18	*n*-C_7H_{15}	H	**18**	**B**	90	6	99

[a] Method **A**: [$Rh_2(pfb)_4$] (3.0 mol %), **4** (3.0 mol %), KO*t*Bu (1.0 equiv), *tert*-amyl alcohol. Method **B**: **20** (1.0 mol %), KO*t*Bu (10 mol %), *tert*-amyl alcohol. [b] Yields of product obtained after purification by preparative thin-layer chromatography.

In view of these results, we attempted the synthesis of the dirhodium(II) complex bearing NHCs at the axial positions.[10] Thus, we generated **NHC-4** in situ in the presence of [$Rh_2(OAc)_4$] and isolated complex **20**, which has NHC ligands at both axial positions (72 % yield of isolated product). Figure 1 shows the molecular structure of **20**.[11] The Rh–Rh bonding distance and the Rh–C(carbene) distances are within the ranges of values found in related compounds with a carboxylate cage structure.[12] Each Rh^{II} atom displays an almost perfect octahedral coordination geometry, with Rh–O distances of 2.04–2.06 Å and coordination angles of around 90°.

The isolated complex proved to be a catalyst for the arylation of aldehydes (Table 2, entries 12–18), yielding the alcohols in high yields with a considerable reduction of the quantity of catalyst (1.0 mol % for method **B** instead of 3.0 mol % for the in situ method **A**) and base. Particularly noteworthy is the finding that in the synthesis of **11** using complex **20** we were able to isolate the complex with only one NHC ligand **NHC-4** attached to the {$Rh_2(OAc)_4$} moiety (75 % of the initial quantity of complex **20** used). This isolated mono-NHC complex efficiently catalyzed the arylation of *p*-tolualdehyde, affording the alcohol **11** in 95 % yield.

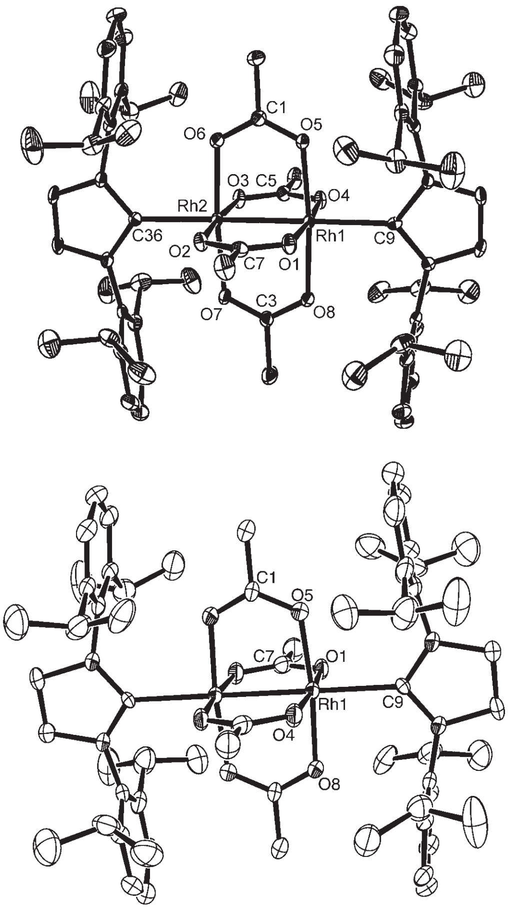


Figure 1. ORTEP[18] diagrams of the dirhodium complexes **20** (top) and **21** (bottom). Ellipsoids are set at 30 % probability. Solvent molecules and hydrogen atoms are omitted. Selected bond lengths [Å] for **20**: Rh1–Rh2 2.4731(3), Rh1–C9 2.228(3), Rh2–C36 2.244(3); for **21**: Rh1–Rh1a 2.4627(12), Rh1–C9 2.244(7). All coordination angles around the Rh centers are near 90°.

Mass-spectrometry analysis of the crude mixture of a similar arylation reaction catalyzed by complex **20** identified the mono-NHC species [(**NHC-4**)$Rh_2(OAc)_4$] and [$Rh_2(OAc)_4$] (complexed with a solvent molecule). The presence of [$Rh_2(OAc)_4$] in the crude reaction mixture suggests that the loss of catalyst (25 %) could be due to decomplexation of **4** from [$Rh_2(OAc)_2$] rather than disproportionation of the Rh^{II} dimer. To test this hypothesis we prepared the complex [(**NHC-5**)$_2$$Rh_2(OAc)_4$] (**21**; 60 % yield of isolated product), with saturated NHC ligands, and determined its molecular structure (Figure 1). The analogous complexes **20** and **21** exhibit different N-C-C-N torsion angles (0.20(2) and 8.35(2)°) and different N–C (1.388(4)/1.391(4) and

1.486(10)/1.469(10) Å) and C–C distances (1.343(4) and 1.495(12) Å).[11]

Under the same reactions conditions as for complex **20**, complex **21** afforded the alcohol **11** in 95% yield. We were able to recover the mono-NHC complex [(**NHC-5**)Rh$_2$(OAc)$_4$] in excellent yield (>97%). These results, along with the observation that no alcohol was formed with the efficient Rh^{III}/NHC catalytic system developed by Fürstner et al. (Table 1, entry 13),[6] clearly indicate that our Rh^{II}–NHC complex maintains its integrity under these reaction conditions and does not disproportionate into Rh^{I} and Rh^{III} species.

We investigated complexes with only one axial NHC ligand, [Rh$_2$(OAc)$_4$(NHC)], as catalysts in the reaction by performing density functional calculations[13] on four optimized structures:[14] complexes with **NHC-4**, **NHC-6**, and **NHC-7**, and the bare metallic fragment [Rh$_2$(OAc)$_4$] for comparison.[15] The stability of the carbene complexes can be evaluated by the energy variation (ΔE) of the complexation reaction,[16] and the values obtained indicate that all complexes are stable relative to the isolated reactants. However, the values of ΔE obtained for **NHC-4** and **NHC-6** (-19 and -26 kcal mol^{-1}, respectively, are quite low by comparison with that obtained for **NHC-7** (-8 kcal mol^{-1}), which may help explain the poor reactivity of **NHC-7** (Table 1, entry 6). The calculated Rh–C distances for **NHC-4** and **NHC-6** are 0.2 Å shorter than for **NHC-7**. This difference reflects the Rh–NHC bond strength, as also shown by the corresponding Wiberg indices (WI)[17] of 0.40 (**NHC-4**), 0.41 (**NHC-6**), and 0.32 (**NHC-7**).

Coordination of the NHC ligand is essentially established by σ donation from the carbene lone pair to the lowest unoccupied molecular orbital (LUMO) of {Rh$_2$(OAc)$_4$}. This is a Rh–Rh antibonding orbital (σ*) derived from the out-of-phase combination of two d_{z^2} orbitals (see the Supporting Information). Thus, the formation of a Rh–NHC bond corresponds to electron transfer from the carbene to the metallic fragment, and to the population of a Rh–Rh antibonding orbital. Accordingly, the Rh–Rh bond length increases from 2.36 Å in isolated [Rh$_2$(OAc)$_4$] complex to 2.44 Å in all the NHC complexes, and reaches 2.47 Å in complex **20** (Figure 1), where both axial positions are occupied by NHC ligands. A more subtle tuning is revealed by the Rh–Rh Wiberg indices of 0.52 (**NHC-4** and **NHC-6**) and 0.58 (**NHC-7**), which indicate that this bond is weaker than in isolated [Rh$_2$(OAc)$_4$] (WI = 0.78), with the effect being more clear-cut for stronger Rh–NHC bonds (**NHC-4** and **NHC-6**).

Electron donation from the NHC ligand affects the charge[19] of the {Rh$_2$(OAc)$_4$} moiety (-0.28 (**NHC-4**), -0.29 (**NHC-6**), and -0.23 (**NHC-7**)), and the weaker bond for **NHC-7** corresponds to an electron-poorer metallic fragment. The same effect is observed for the atomic charge of the Rh centers. These values are 0.74 (terminal Rh) and 0.89 (Rh$_{\mathrm{NHC}}$) for **NHC-4**, while in isolated [Rh$_2$(OAc)$_4$] the Rh charge is 0.92. More importantly, the asymmetry in the Rh charges calculated for **NHC-4** indicates an electron-richer terminal Rh center and shows a trend towards a mixed-oxidation-state complex, as proposed previously,[20] although the difference between the calculated charges does not support a clear Rh^{I}/Rh^{III} separation. The same trend is observed for complexes with **NHC-6** and **NHC-7**.

Coordination of **NHC-4** results in a perfect structural match (Figures 1 and 2). The isopropyl groups fit in between the OAc bridges, and the carbene ring remains in an eclipsed conformation, which is different from the bisecting arrangement observed for the species with *N*-methyl substituents.[9] The stereochemical protection of one Rh center provided by the NHC ligand may help to stabilize the complex. Furthermore, the significant contribution from the terminal Rh center to the LUMO of the complex (Figure 2) affords a coordination position for reactant molecules.

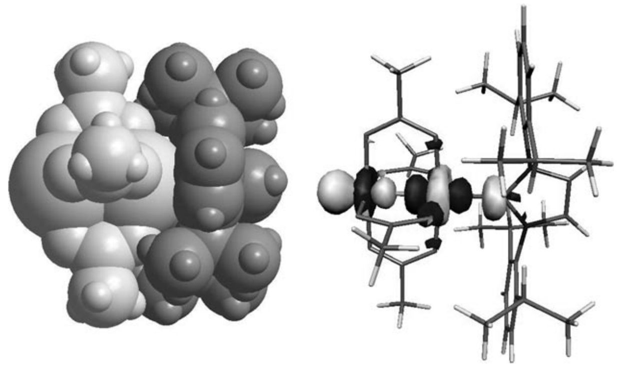


Figure 2. Optimized structure (B3PW91) for [(**NHC-4**)Rh$_2$(OAc)$_4$] (left; NHC is depicted in darker gray), and its LUMO (right).

In summary, we have presented an efficient catalytic system for the arylation of aldehydes based on readily available and highly versatile dirhodium(II) complexes and NHC ligands. The near-perfect structural match between [Rh$_2$(OAc)$_4$] and **NHC-4** found in the X-ray structure of **20** and in the calculated structure of [(**NHC-4**)Rh$_2$(OAc)$_4$], as well as the electronic structure of this species, may explain the catalytic performance of this system. This study highlights a new reaction mode for dirhodium(II) dimers involving the possible transmetalation of the aryl group from boronic acids to dirhodium(II) complexes. Further experimental and computational studies will be conducted in order to extend the scope of these method and to fully elucidate the reaction mechanism.

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[11] Crystallographic data for **20**: $C_{83}H_{108}N_4O_8Rh_2$, $M_r = 1495.55$, orange crystals, $0.18 \times 0.16 \times 0.12$ mm^3, triclinic, space group $P\bar{1}$, $a = 12.6540(2)$, $b = 18.2140(3)$, $c = 19.1580(3)$ Å, $\alpha = 103.5840(10)$, $\beta = 101.3890(10)$, $\gamma = 101.8950(10)°$, $V = 4057.10(11)$ Å^3, $Z = 2$, $T = 150$ K, $\rho_{calcd} = 1.224$ Mg m^{-3}, $\mu = 0.460$ mm^{-1}, $F(000) = 1576$. For **21**: $C_{42}H_{44}N_2O_4Rh$, $M_r = 743.7$, orange crystals, $0.15 \times 0.11 \times 0.10$ mm^3, triclinic, space group $P\bar{1}$, $a = 11.256(2)$, $b = 12.538(3)$, $c = 15.367(5)$ Å, $\alpha = 69.63(2)$, $\beta = 84.172(2)$, $\gamma = 77.614(3)°$, $V = 1984.7(9)$ Å^3, $Z = 2$, $T = 150$ K, $\rho_{calcd} = 1.244$ Mg m^{-3}, $\mu = 0.471$ mm^{-1}, $F(000) = 774$. Data were collected with a Bruker AXS KAPPA APEX II diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). Structures were solved by direct methods (SIR97). Non-hydrogen atoms were refined anisotropically and hydrogen atoms were inserted in calculated positions as riding on the parent carbon atom (WINGX). Of 56487 reflections for complex **20**, 14673 were independent ($R_{int} = 0.0492$); 887 variables were refined to final $R1(I>2\sigma(I)) = 0.0434$, $wR2(I>2\sigma(I)) = 0.0965$, $R1$(all data) $= 0.0815$, $wR2$(all data) $= 0.1065$, GOF $= 1.037$. For complex **21**, of 30833 reflections, 4408 were independent ($R_{int} = 0.0711$); 411 variables were refined to final $R1(I>2\sigma(I)) = 0.0675$, $wR2(I>2\sigma(I)) = 0.1714$, $R1$(all data) $= 0.0945$, $wR2$(all data) $= 0.2028$, GOF $= 1.170$. CCDC-639254 (**20**) and CCDC-644438 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] The calculated structures are depicted in the Supporting Information.

[16] Calculated as the difference between the energy of the two isolated fragments $\{Rh_2(OAc)_4\}$ and NHC and the energy of the final species $[Rh_2(OAc)_4(NHC)]$.

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