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A β-Carbon elimination strategy for convenient *in situ* access to cyclopentadienyl metal complexes†

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The electronic and steric properties of tailored cyclopentadienyl (Cp) ligands are powerful handles to modulate the catalytic properties of their metal complexes. This requires the individual preparation, purification and storage of each ligand/metal combination. Alternative, ideally *in situ*, complexation protocols would be of high utility. We disclose a new approach to access Cp metal complexes. Common metal precursors rapidly react with cyclopentadienyl carbinols *via* β-carbon eliminations to directly give the Cp-metal complexes. An advantage of this is the direct and flexible use of storable pre-ligands. No auxiliary base is required and the Cp complexes can be prepared *in situ* in the reaction vessel for subsequent catalytic transformations.

Introduction

Cyclopentadienyl (Cp)-coordinated transition-metal complexes are ubiquitous and many of them are efficient catalysts for a broad range of versatile, atom-economic transformations.[1] Many of these reactions have highly optimized conditions, but use commercially available complexes with a conserved Cp* or Cp ligand. Only recently, the modulation of the electronic and steric properties of tailored Cp ligands was recognized as a powerful tool to overcome sluggish reactivity,[2] to address regio- and positional issues,[3] and provide entry to enantioselective processes.[4] In rapid reaction discovery and optimization, the ability to combine a library of ligands with a library of metal complexes, performing an *in situ* complexation to give the desired catalyst species is a relevant advantage. While this approach is very common for reactions involving, for instance, phosphine ligands, it is still elusive for Cp ligands. In this case, each ligand/metal combination has to be synthesized individually, purified and stocked prior to any use in catalysis. The typical complexation of common Cp* and Cp complexes involves the metal as a limiting reagent.[5] However, highly elaborate Cp or chiral Cp^x ligands require the use of the CpH derivative as the limiting reactant. In particular for chiral Cp^x ligands, one has to rely on undesirable reaction conditions, for example involving thallium alkoxide in benzene.[4d,6] These shortcomings make the development of complementary complexation strategies a priority. Ideally, such technology proceeds rapidly and in a quantitative manner, without the generation of inhibiting reaction byproducts. It should also be useable with a range of different transition-metals.

β-Carbon elimination has been reported as a complementary method to access organometallic species in catalysis.[7] Normally the forward reaction – the addition across a carbonyl group – is favored and reversing this pathway requires some additional driving force. This could be a combination of using the right transition-metal and the use of substrates leading to the formation of stronger C_{sp}–[M][8] or C_{sp^2}–[M] bonds.[9] The generation of C_{sp^3}–[M] bonds requires energy-rich starting materials, such as *tert*-cyclobutanols[10], releasing strain upon β-C elimination.[11] A particular class of substrate is that of homoallylic alcohols that can give π-bound allyl-metal species by retro-allylation.[12] Along the same lines, a cyclopentadienyl carbinol would give a Cp–[M] species upon C–C bond cleavage. The very strong bond of the cyclopentadienyl anion to the transition-metal would be a very strong driving force. So far, the β-C elimination methodology has been used exclusively as an elementary step in catalytic transformations. Herein we exploit its potential for the preparation of Cp-metal complexes (Scheme 1).

Results and discussion

The required cyclopentadienyl carbinol substrates for the pre-ligands are accessed in a straight forward manner by deprotonation and addition across the desired aldehyde or ketone (Scheme 2, see ESI† for details).[13] In contrast to many lightly substituted cyclopentadienes which frequently undergo Diels–Alder dimerization, all prepared Cp-carbinols are stable and do not dimerize upon storage. Exemplarily for $[Rh(cod)OH]_2$, ligand exchange of the hydroxy ligand by **2** would break up the

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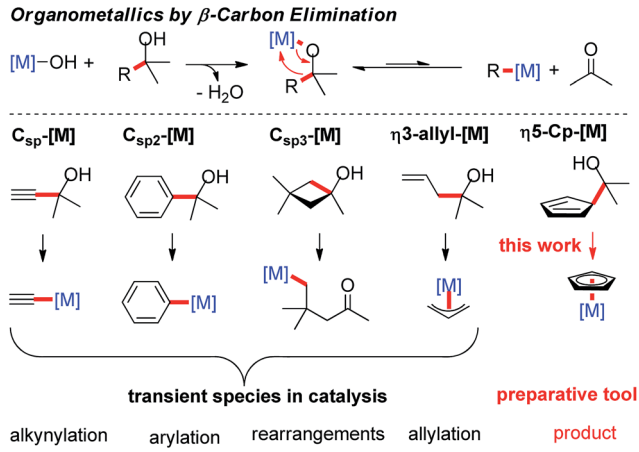
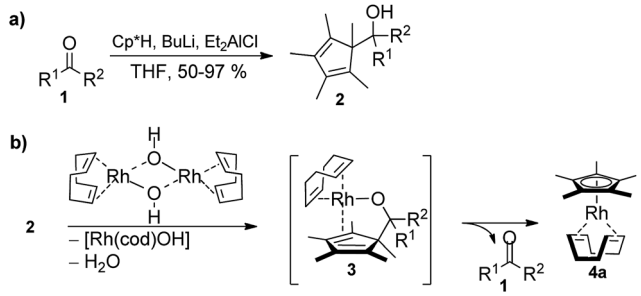


Scheme 1 Generation of organometallics using the β-carbon elimination strategy.



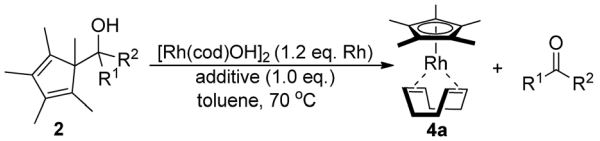
Scheme 2 (a) Synthesis of Cp pre-ligand carbinols **2**. (b) Envisioned β-C elimination to access Cp*Rh(I) complexes.

dimer and release a molecule of water to give intermediate **3**. In turn, **3** is predisposed for the final β-C elimination step to yield the Cp metal complex **4a** and ketone **1**.

A selection of carbinols with sterically and electronically different substituents, R^1 and R^2, were initially evaluated (Table 1). A variety of factors influenced the reaction performance. An aromatic substituent R^1 or R^2 was found to be beneficial for yield and reactivity. A tertiary hydroxyl group is better than a secondary one. Strained ketone derived **2f** and **2g** (entries 6–7) partially underwent the alternative strain-release pathway,[10] opening the four-membered ring instead of leading to the Cp-metal species. Most substrates required the addition of cesium carbonate for shorter reaction times. Without the rhodium complex, carbinols **2** are stable and no conversion to free Cp*H was observed. Notably, some substrates displayed significantly increased reactivity and did not require the addition of any base (entries 8, 10, 13, and 15). The two fastest reactions were **2h** (Ph/CO_2Me) and **2m** (Ph/Me).

Among the tested substrates, the dimethyl-type carbinol moiety was further investigated, despite its lower reactivity, as it releases only volatile acetone as a byproduct (Table 2). It provides a clean complexation giving a range of complexes **4** with different bulks, ranging from Me_3Cp (entry 1) to *t*BuMe_4Cp (entry 5). While substrates with bulky groups react very

Table 1 Evaluation of the influence of the carbinol substituents on β-C elimination[a]



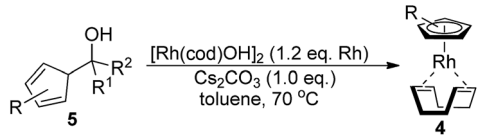
Entry	2	R^1	R^2	Additive	Time	% yield[b]
1	**2a**	H	*n*Pentyl	Cs_2CO_3	3 h	39
2	**2b**	H	Ph	Cs_2CO_3	1 h	95
3	**2c**	H	CO_2Et	Cs_2CO_3	3 h	10
4	**2d**	**Me**	**Me**	**Cs_2CO_3**	**3 h**	**99**
5	**2e**	$CH_2(CH_2)_3CH_2$		Cs_2CO_3	3 h	93
6	**2f**	$CH_2CH_2CH_2$		Cs_2CO_3	1 h	30
7	**2g**	CH_2OCH_2		Cs_2CO_3	3 h	20
8	**2h**	**CO_2Me**	**Ph**	—	**15 min**	**75**
9	**2i**	CO_2Me	Me	Cs_2CO_3	3 h	75
10	**2j**	CO_2Me	*t*Bu	—	1 h	45
11	**2k**	CO_2Me	CF_3	Cs_2CO_3	1 h	<5
12	**2l**	CO_2Et	CO_2Et	Cs_2CO_3	3 h	<5
13	**2m**	**Me**	**Ph**	—	**15 min**	**89**
14	**2n**	Me	Cy	Cs_2CO_3	3 h	80
15	**2o**	CF_3	Ph	—	1 h	95

[a] Conditions: N_2 atmosphere, 0.040 mmol **2**, 0.024 mmol $[Rh(cod)OH]_2$, 0.040 mmol additive, 0.2 M in toluene at 70 °C for the indicated time. [b] Yield determined by NMR with an internal standard.

smoothly, less substituted ones like the trimethyl Cp precursor **5b** react less efficiently due to some fulvene byproduct formation. Indenyl complexes can be prepared with similar efficiency (entries 6–7). Methyl phenylglyoxylate and acetophenone derived pre-ligands **5i** and **5j** are easier to access and better suited in the complexation giving, as before, fast and clean transformations without the requirement of a basic additive (entries 8–9). Importantly, this complexation strategy is equally successful for chiral Cp* ligands equipped with our atropchiral backbone.[4f–i] Importantly, the β-C eliminative complexation is not limited to rhodium. For instance, using $[Ir(cod)OH]_2$ as the metal salt provided access to indenyl Ir(cod) and cyclopentadienyl complexes **6g–6j** in comparable yields (entries 6–9). Exposure of the chiral Cp^x* pre-ligand **5k** to the reaction conditions induced a smooth complexation, providing rhodium complex **4k** in 93% yield (entry 10). This is particularly noteworthy as classical complexation methods[4d,f] for a di-substituted chiral Cp^x ligand failed completely for this chiral penta-substituted analog. Analogously, the chiral iridium complex **6k** could be obtained in 87% yield. Moreover, we could extend the method for the preparation of a chiral Cp^x*Co^{III} complex **7k** (entry 11). For the first time, chiral fully penta-substituted cyclopentadienyl rhodium, iridium and cobalt complexes are now accessible. This sets the stage for future applications in asymmetric catalysis, especially for transformations where previously reported complexes with the disubstituted chiral variants[4a,b] failed to provide adequate reactivity.

Besides the hydroxyl bridged dimer, other $[Rh(cod)X]_2$ complexes (X = OMe, OAc, and Cl) can be used (Table 3, entries

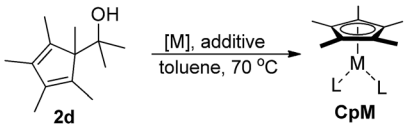
Table 2 Scope for Cp complexation by β-C elimination[a]



Entry	5	R^1	R^2	4	% yield[b]
1	**5b**	Me	Me	**4b**	42
2	**5c**	Me	Me	R=H **4c**	80
3	**5d**	Me	Me	R=*i*Pr **4d**	95
4	**5e**	Me	Me	R=*t*Bu **4e**	90
5	**5f**	Me	Me	R=Ph **4f**	95
6[d]	**5g**	Me	Me	**4g** (M=Rh) **6g** (M=Ir)	90 (**4g**) 88 (**6g**)
7[d]	**5h**	Me	Me	**4h** (M=Rh) **6h** (M=Ir)	95 (**4h**) 86 (**6h**)
8[c,d]	**5i**	Ph	CO_2Me	**4i** (M=Rh) **6i** (M=Ir)	60 (**4i**) 44(**6j**)
9[c,d]	**5j**	Ph	Me	**4j** (M=Rh) **6j** (M=Ir)	95 (**4j**) 63 (**6j**)
10[d]	**5k**	Ph	CO_2Me	**4k** (M=Rh) **6k** (M=Ir)	93 (**4k**)[e] 87 (**6k**)[e]
11[f]	**5k**	Ph	CO_2Me	**7k**	32[e]

[a] Conditions: 0.04 mmol **5**, 0.024 mmol of $[Rh(cod)OH]_2$, 0.040 mmol Cs_2CO_3, 0.2 mL toluene at 70 °C, 15 min–10 h. [b] Determined by NMR with an internal standard. [c] 4 Å molecular sieves instead of Cs_2CO_3 at 23 °C. [d] With $[Ir(cod)OH]_2$ for **6**. [e] Isolated yield. [f] Conditions: 0.06 mmol **5k** and 36 μmol $Co_2(CO)_8$, 0.4 mL CH_2Cl_2 at 40 °C, then I_2 (0.06 mmol).

Table 3 Scope with different transition-metal precursors[a]



Entry	CpM	[M]	Additive	Time	% yield[b]
1	**4a**	$[Rh(cod)OMe]_2$	Cs_2CO_3	3 h	70
2	**4a**	$[Rh(cod)OAc]_2$	Cs_2CO_3	3 h	70
3	**4a**	$[Rh(cod)Cl]_2$	KOH	3 h	90
4	**4l**	$[Rh(nbd)Cl]_2$	KOH	2 h	80
5	**4l**	$[Rh(nbd)OH]_2$	Cs_2CO_3	3 h	99
6	**4m**	$[Rh(CO)_2Cl]_2$	KOH	15 min	49
7	**6a**	$[Ir(cod)OH]_2$	Cs_2CO_3	5 h	92
8[c]	**8**	$[Co_2(CO)_8]$	—	6 h	60
9	**4n**	$[Rh(C_2H_4)_2OAc]_2$	Cs_2CO_3	1 h	10
10[d]	**4n**	$[Rh(C_2H_4)_2Cl]_2$	KOH, 4 Å MS	5 h	70
11[e]	**4o**	$[Rh(C_2H_3TMS)Cl]_2$	KOH, 4 Å MS	1 h	66[f]

[a] Conditions: 0.04 mmol **2d**, 24 μmol [M], 0.04 mmol Cs_2CO_3 or 0.12 mmol KOH, 0.2 mL toluene. [b] Determined by NMR with an internal standard. [c] Conditions: 0.06 mmol **2d** and 36 μmol $Co_2(CO)_8$, 0.4 mL CH_2Cl_2 at 40 °C. [d] With **2m** instead of **2d** at 23 °C. [e] With **2m** instead of **2d**. [f] Isolated yield.

1–3). The chloride containing complexes require the addition of KOH for an *in situ* exchange. Moreover, $[Rh(nbd)X]_2$ (nbd = norbornadiene) and $[Rh(CO)_2Cl]_2$ work similarly (entries 4–6). Without a change in protocol, the corresponding iridium(I) complex **6a** and cobalt(0) complex **8** were prepared (entries 7–8). Solely the rhodium ethylene congener is not well suited for these conditions (entry 9). However, an improved protocol (*vide infra*) solved this issue and provided **4n** and **4o** (entries 10 and 11).

For the Ph/Me substrate **2m**, DFT computations (at the PBE0[14]-dDsC[15]/TZ2P//M06[16]/def2-SVP level in implicit toluene solvent using COSMO-RS,[17] see ESI† for additional details) provided some more details on the reaction profile of the

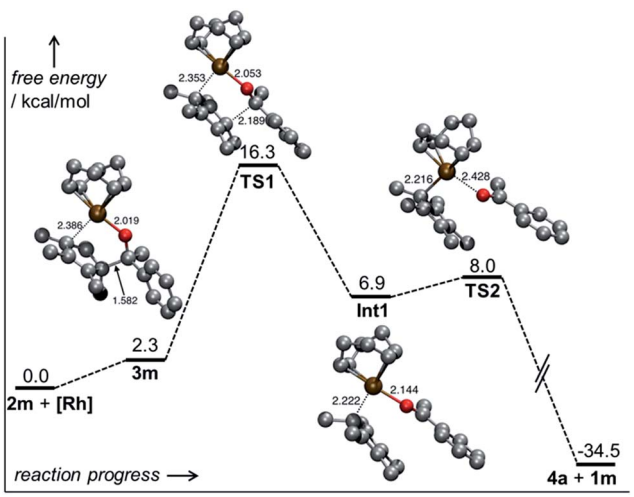


Fig. 1 Reaction profile of the β-C elimination of carbinol **2m**.

complexation reaction (Fig. 1). First, the [Rh(cod)OH] fragment forms complex **3m** with the substrate carbinol. Cleavage of the C–C bond proceeds *via* **TS1** with a barrier of only 16.3 kcal mol^{-1}, which aligns well with the experimentally observed fast reaction. After C–C cleavage, a metastable species (**Int 1**) is formed which quickly dissociates to the products **4a** and **1m** after dissociation of the ketone (**TS2**). The overall process is thermodynamically favourable, being exergonic by 34.5 kcal mol^{-1}.

While the outlined protocol works very well for robust diene containing metal precursors, some more sensitive ones, *e.g.* $[Rh(C_2H_4)_2OAc]_2$ resulted in unsatisfactory yields despite full conversion. DFT computations indicated that the height of the β-C elimination barrier was not the issue. We hypothesized that the reaction rate could be negatively impacted by the increasing amount of formed water. This could compete with the sterically hindered cyclopentadienyl carbinol and be the limiting factor in the ligand exchange of the metal hydroxy complex. Indeed, the addition of 4 Å molecular sieves as traps for the generated water byproduct accelerates the reaction significantly (Table 3, entry 10). Instead of 70 °C, fast and complete complexation occurs at ambient temperature. Under these conditions, the β-carbon elimination was monitored by ^{1}H-NMR spectroscopy (Fig. 2). From all of the tested substrates, the initially selected Cp* dimethyl carbinol **2d** was the slowest one. Methyl phenylglyoxylate derived substrate **2h** initially reacts very fast, but stalls at around 80% yield. Acetophenone derived substrate **2m** reacts smoothly and cleanly, producing the desired complex in 90% yield after 30 minutes and quantitatively after 1 hour at ambient temperature. Moreover, some dependence on the substitution pattern of the aryl group was found. For instance, the *p*-nitro derivative **2p** reacts fastest and the *p*-methoxy congener **2q** is slower than the parent substrate **2m**. DFT results of this substrate set confirmed the observed reactivity trends.

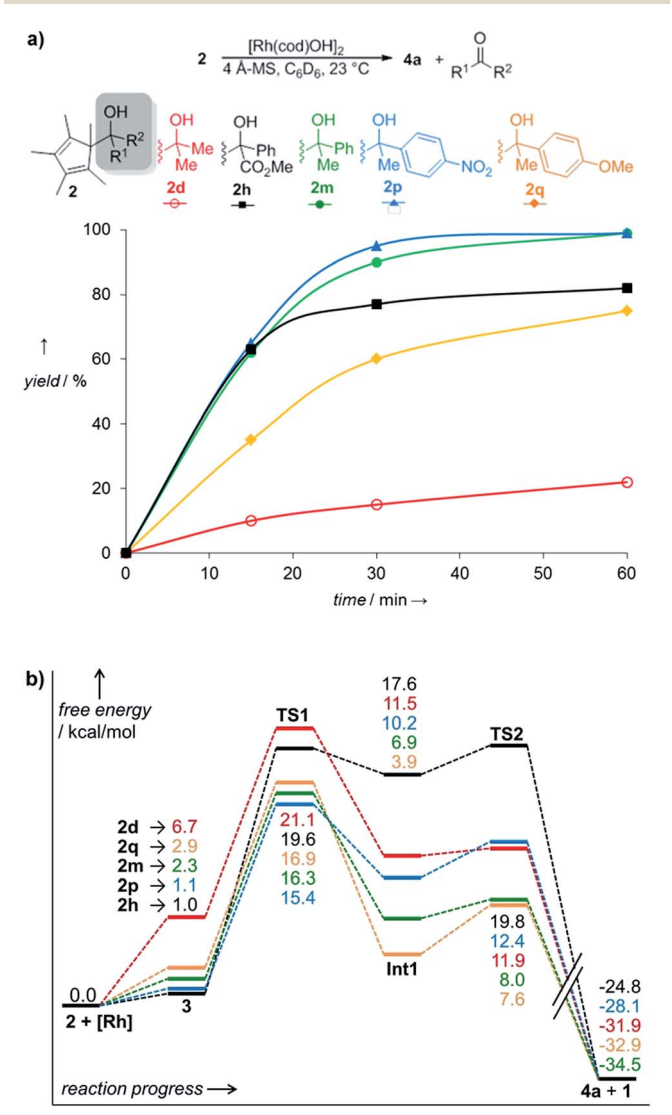
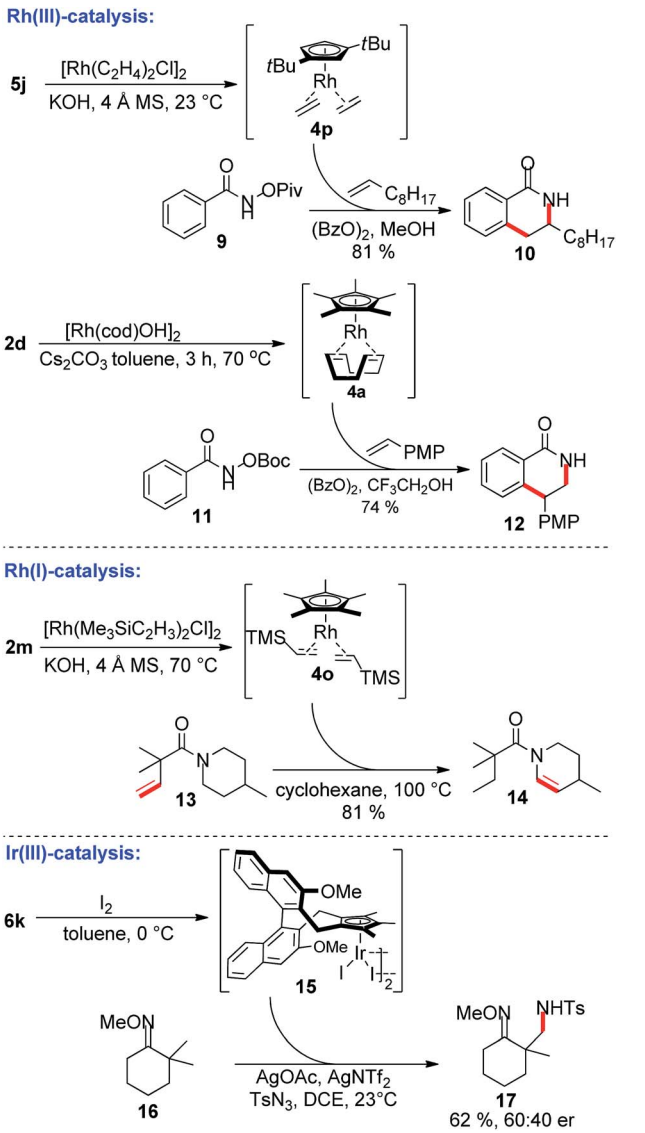


Fig. 2 (a) Complexation rates of different carbinols **2**; yields of **4a** after 60 min: **2d**: 22%; **2h**: 82%; **2m**: 99%; **2p**: 99%; **2q**: 75%. (b) Reaction profiles of carbinols **2** during complexation.



Scheme 3 *In situ* Cp metal complex preparation and direct application in Rh(III), Rh(I) and Ir(III) catalysis. PMP = 4-methoxyphenyl.

Fig. 2b clearly shows that the substitution pattern strongly influences the **TS1** barrier height, with the slower substrate **2d** (21.1 kcal mol^{-1}) having the highest barrier and the fastest substrate, *p*-NO_2 bearing **2p**, having the lowest (15.4 kcal mol^{-1}).

Besides base-free complexation avoiding toxic solvents and bases, the instant preparation and direct subsequent use in catalysis of the formed Cp-metal complex is a salient feature of this protocol (Scheme 3). As an example for Rh(III)-catalysis, the regioselective dihydroisoquinolone formation with terminal 1-decene is shown using the *in situ* formed $Cp^tRh(I)$ complex **4p**. This protocol provides **10** in similar yield and regioselectivity as previously reported by Rovis with an isolated Cp^tRh complex.[3a,b] The simple precatalyst **2d** can be used to access **4a**, which in turn was used for the synthesis of isoquinolone **12** with reversed regioselectivity, again with comparable yield and regioselectivity as previously observed by us.[18] The vinyl-TMS bearing complex **4o** is hardly accessible from the reduction of [Cp*$RhCl_2$] and simplifies applications in Cp*Rh(I) catalysis. For instance, it is a competent catalyst for intramolecular transfer olefinations[19] of piperidinyl amide **13** providing enamide **14**. In addition, chiral $Cp^xIr(I)$ complex **6k** could be smoothly oxidized with iodine to the Ir(III) species **15**. This catalyst provides promising preliminary results for oxime-directed asymmetric C(sp^3)–H functionalizations of substrate **16** yielding the tosylamide product **17**.[20]

Conclusions

In summary, we have reported a new complexation strategy to access late transition-metal Cp complexes. Rapid β-carbon elimination of cyclopentadienyl carbinols in the presence of a common metal precursor provides access to a wide range of Cp metal complexes. The advantages of this process are the direct and flexible use of storable pre-ligands. No auxiliary base is required and the Cp complexes can be prepared *in situ* in the reaction vessel. This protocol should enhance the convenience in applying these complexes in catalysis and allow for more rapid exploitation of the untapped potential of tailored Cp ligands. In particular, we expect this is a door-opener for further application of chiral Cp* metal complexes in catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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