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Communication

Scalable Synthesis of Esp and Rhodium(II) Carboxylates from Acetylacetone and $RhCl_3 \cdot xH_2O$

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Cite This: *Org. Process Res. Dev.* 2020, 24, 1207–1212

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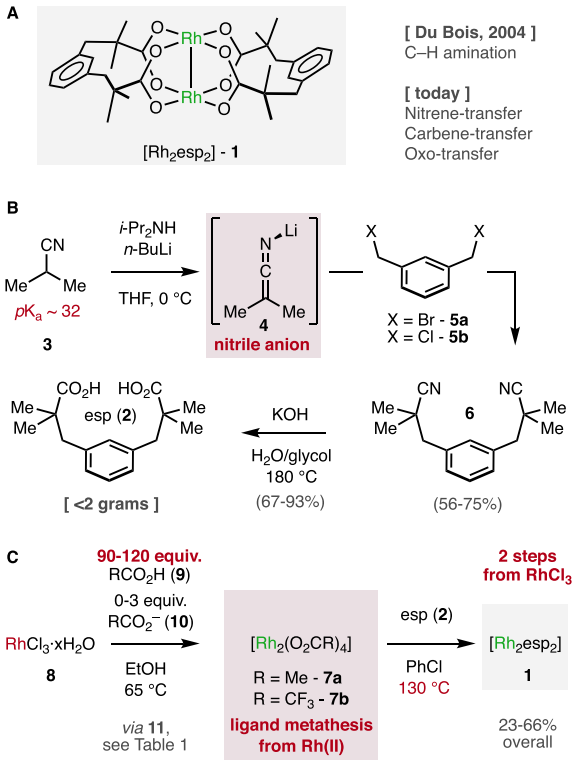
ABSTRACT: Rhodium(II) carboxylates are privileged catalysts for the most challenging carbene-, nitrene-, and oxo-transfer reactions. In this work, we address the strategic challenges of current organic and inorganic synthesis methods to access these rhodium(II) complexes through an oxidative rearrangement strategy and a reductive ligation reaction. These studies illustrate the multiple benefits of oxidative rearrangement in the process-scale synthesis of congested carboxylates over nitrile anion alkylation reactions, and the impressive effect of inorganic additives in the reductive ligation of rhodium(III) salts.

KEYWORDS: *rhodium catalysis, oxidative rearrangement, 1,3-diketone, sigmatropic shift, rhodium(II)*

Total synthesis has been a major resource to facilitate the supply of scarce substances[1] and a fertile playground to create and test new chemistries.[2] Despite the dominance of natural product and pharmaceutical targets in these studies, our group[3] and others[4] have used ligands to inspire synthetic innovations.[5] The synthesis of metal catalysts offers uncharted opportunities for basic research in both organic and inorganic chemistry and can facilitate the introduction of state-of-the-art catalysts in industrial production. In this sense, metal carboxylates have historically played a key role in the development of homogeneous catalysis, particularly in the field of C−H functionalization.[6] Traditional pivalate complexes[7] have evolved into congested carboxylates to tackle the most challenging transformations.[6c,2d,8] In particular, the pursuit of aliphatic C−H amination[9,10] resulted in the development in 2004 of Rh_2esp_2 (**1**; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) by Du Bois and coworkers (Scheme 1A).[11] This catalyst displays a double chelate structure with two bis-carboxylate ligands **2**, which stabilize the labile mixed-valence intermediates involved in the catalysis.[12] Rh_2esp_2 (**1**) has currently been extensively deployed in natural product total synthesis[8] and is increasingly finding new applications in carbene-,[13] nitrene-,[14] and oxo-transfer reactions[15] due to its unique properties. Moreover, the ligand esp (**2**) is now widespread in unrelated types of catalysis with palladium, rhenium, ruthenium, copper, cobalt, or bismuth.[16]

Despite its importance, the chemical synthesis of the ligand esp (**2**)[11,16a,17] and its rhodium complex **1**[11] have not evolved along their applications. The synthetic strategy toward the congested bis-carboxylate ligand **2** is based on the alkylation of isobutyronitrile (**3**) via the nitrile anion **4** with *m*-xylene dihalides **5** to forge the all-carbon quaternary center in the dinitrile intermediate **6** (see Scheme 1B).[11,16a,17,18] The latter is elaborated to esp (**2**) through a thermal hydration process.[11,16a,17] The nitrile anion strategy seems to be responsible for the high cost of this ligand as it requires inert conditions, anhydrous solvents, and large amounts of *n*-BuLi to generate LDA on-scale. On the inorganic synthesis side

Scheme 1. Organic and Inorganic Challenges in the Synthesis of Rh_2esp_2 (1)



Received: April 6, 2020
Published: April 14, 2020

https://dx.doi.org/10.1021/acs.oprd.0c00164
Org. Process Res. Dev. 2020, 24, 1207−1212

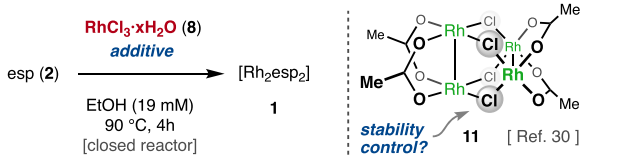
(Scheme 1C), Rh_2esp_2 (**1**) is prepared by high-temperature ligand metathesis from rhodium(II) acetate or trifluoroacetate (**7a** and **b**) like many other rhodium(II) carboxylates.[11,12d,17b] $Rh_2(OAc)_4$ (**7a**) and Rh_2TFA_4 (**7b**) are separately obtained by reduction of the accessible rhodium(III) chloride hydrate (**8**) in the presence of excess carboxylic acid **9a** and **b** and a minor amount of its conjugate base **10a** and **b**.[19] Rhodium trichloride (**8**) is the main source of coordination compounds of this metal due to its facile preparation from recycled metallic rhodium and therefore is a more desirable source of advanced rhodium(II) catalysts.[20]

Our recent studies in redox-active carbene transfer[21] and oxidative rearrangement reactions[3d] sparked our interest to revise the current organic[5,11,16a,17] and inorganic[11] synthesis methods toward Rh_2esp_2 (**1**). Namely, our goal was to avoid nitrile anion alkylation in the synthesis of the ligand **2** (Scheme 1B) and bypass the preparation of intermediate rhodium(II) carboxylates (i.e., **7a** and **b**) in the preparation of the metal complex **1** (Scheme 1C).[11,12,17]

We questioned whether Rh_2esp_2 (**1**) could be prepared directly from $RhCl_3{\cdot}xH_2O$ (**8**) and esp (**2**), similarly to the simpler rhodium(II) carboxylates **7a** and **b**.[11,12,17,22−27] In the classic synthesis by Wilkinson of $Rh_2(OAc)_4$ (**7a**; Scheme 1C),[19] rhodium(III) chloride **8** is reduced by ethanol in the presence of 90−120 equiv of the acetic acid ligand and small amounts of sodium acetate.[19d] In fact, acidic conditions are commonly used to reduce rhodium(III) using alcohols (E^0{Rh(III)−Rh(II)} = 0.7 V vs SHE),[28,29] and this principle has not been questioned since the early work by Wilkinson.[19] This is due to the over-reduction to rhodium(0) (nano)-particles that occurs in basic media with excess sodium acetate.[30,31] Although the detailed mechanism for the synthesis of $Rh_2(OAc)_4$ (**7a**) remains unknown, a recent study revealed the key intermediacy of the tetranuclear chloride-bridged intermediate **11** (Table 1) that evolves into $Rh_2(OAc)_4$ (**7a**) upon addition of base.[30]

In our case, the direct reaction of esp (**2**) and $RhCl_3{\cdot}xH_2O$ (**8**) under the conventional acidic conditions presented above[19] results in extensive formation of rhodium black, even in the presence of 10-fold excess of the esp ligand (**2**; Table 1; entry 1). This result points to the particularly rapid aggregation of the rhodium intermediates facilitated by the chelating ability of esp (**2**). We reasoned that the control of the relative reduction rate of rhodium(III) chloride **8** and the polynuclear rhodium(II) intermediates involved (see **11**) was key to limit over-reduction. In principle, the reduction potential of rhodium(III) and the stability of multinuclear intermediates depend on their anionic ligands, which would allow cost-effective inorganic additives to control this process without large excess of elaborate carboxylates.[19] It was observed that in acidic thermal conditions the ligand **2** undergoes esterification by ethanol, which may be the reason for the large excess of ligand employed in current methods.[19] This finding invited exploration of basic anions that would inhibit ligand depletion as well as stabilize the rhodium(II) intermediates likely involved.[30] In agreement with previous studies, small quantities of base were unsuccessful (entries 2, 3).[19] However, the addition of more than 2 equiv results in a drastic improvement (entry 4), which may indicate that a carboxylate dianion is involved, in stark contrast with previous syntheses.[19] Other organic and inorganic bases perform variably (entries 5−9) with large influence of the countercation (entry 9−11). Li_2CO_3 offers the best balance between

Table 1. Optimization of the Direct Synthesis of Rh_2esp_2 (1) from $RhCl_3{\cdot}xH_2O$ (8)



entry	**2** (equiv)[a]	additive	equiv[a]	**1** (%)[b]
1	10.0	none		0
2	1.4	NaOH	0.8	0
3	3.5	NaOH	2.0	0
4	1.4	NaOH	3.7	61
5	1.4	KOH	3.7	60
6	1.4	KO^{t}Bu	3.7	56
7	1.4	2,4,6-collidine	3.7	78
8	1.4	Et_3N	3.7	66
9	1.4	LiF	3.7	0
10	1.4	KF	3.7	56
11	1.4	TBAF	3.7	85
12	1.4	Li_2CO_3	3.7	78
13	1.4	Na_2CO_3	3.7	64
14	1.4	K_2CO_3	3.7	61
15	1.4	Li_2CO_3[c]	3.7	86

[a]1 equiv = 1 mol/mol pure **8**. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [c]In the presence of LiCl (40 equiv).

efficiency, cost, and process mass intensity (entry 12), and it facilitates the isolation of the pure **1**. Carbonate anions may also stabilize the multinuclear intermediates as carboxylate surrogate ligand,[22,30] and the lithium salt was significantly more efficient (entries 13, 14). It was found that the presence of LiCl is beneficial to enhance yield and robustness of the process (entry 15), particularly in large scale reactions. This additive enhances the solubility of rhodium(III) chloride probably forming a more stable tetrachlororhodate reservoir of rhodium(III).

We recognized that esp (**2**) could be synthesized via the oxidative rearrangement of 1,3-diketones in basic media that our group has recently developed,[3d,32] provided that the acyclic tetraketone intermediate **12** (Scheme 2A) would be a suitable substrate for a double rearrangement reaction. Should this be the case, the tetraketone **12** could be prepared from bulk acetylacetone (**13**; pK_a = 13) using mild inorganic bases instead of the nitrile anion **4** derived from isobutyronitrile (**3**; $pK_a \sim 32$) used in previous syntheses (Scheme 1B).[11,16a,17,18] To maximize the potential of our strategy, a single-step procedure to obtain tetraketone **12** was developed (Scheme 2, step 1). Initial alkylation of acetylacetone (**13**) with methyl iodide (**14**) was performed using K_2CO_3 as base and acetone as solvent.[33] On-scale, we found that an autoclave reactor and butanone were required to mitigate the volatility of methyl iodide in this reaction. For the second alkylation, the cost-effective *m*-xylene dichloride (**5b**) was used in a mixture of butanone and glyme. This way, after the initial methylation was deemed complete, glyme, K_2CO_3, and *m*-xylene dichloride (**5b**) were added to obtain the crude **12** in one pot. The tetraketone **12** was crystallized from technical ethanol, yielding 169 g of **12** per batch. Surprisingly, the oxidative rearrangement of 1,3-diketones in basic media using LiOH and H_2O_2 that we recently developed[3d] proved completely ineffective in

https://dx.doi.org/10.1021/acs.oprd.0c00164
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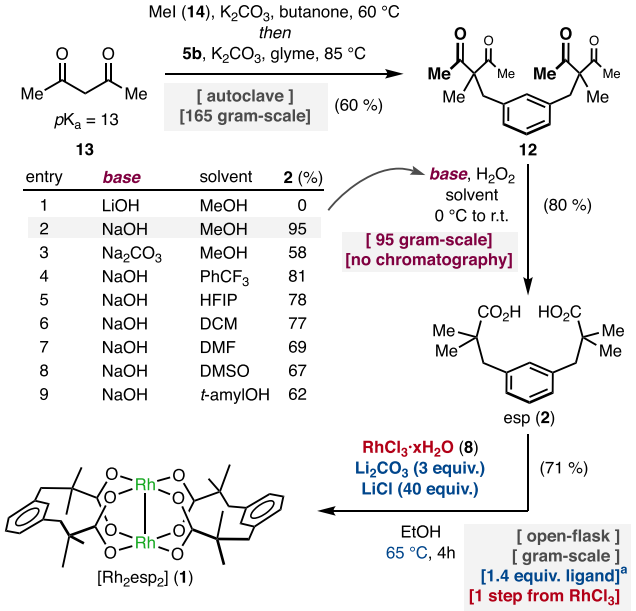
Scheme 2. Scalable Synthesis of Rh_2esp_2 (1)



entry	base	solvent	2 (%)
1	LiOH	MeOH	0
2	NaOH	MeOH	95
3	Na_2CO_3	MeOH	58
4	NaOH	$PhCF_3$	81
5	NaOH	HFIP	78
6	NaOH	DCM	77
7	NaOH	DMF	69
8	NaOH	DMSO	67
9	NaOH	*t*-amylOH	62

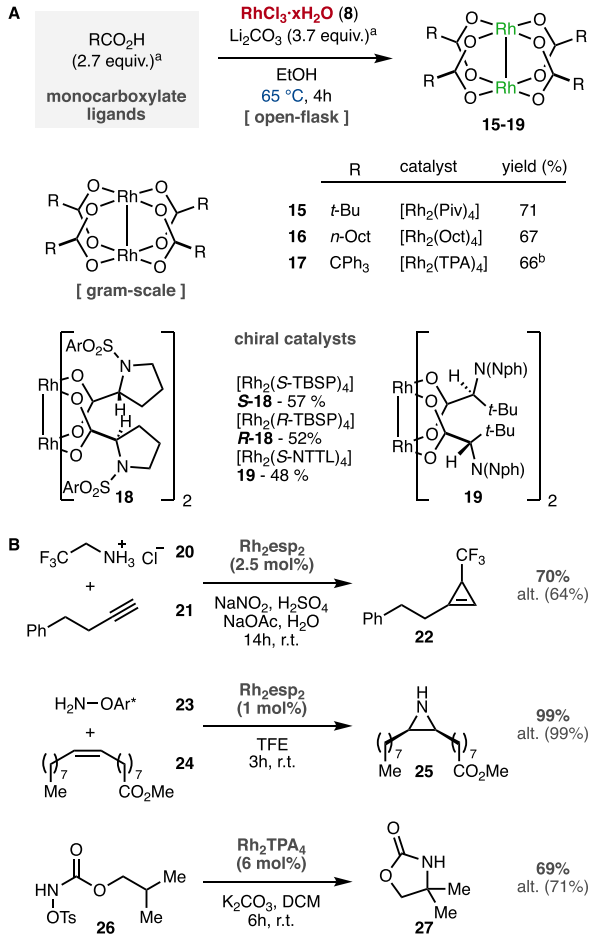
[a]1 equiv = 1 mol/mol pure **8**.

the tetraketone substrate **12** (entry 1). A detailed analysis of this reaction revealed quantitative retro-Claisen deacylation of the tetraketone **12**, in clear contrast with our previous studies using diketones.[3d] We reasoned that the high Lewis acidity of the lithium cation may be involved in this side reaction. To our delight, it was found that replacing the base by NaOH suppressed this process, obtaining the doubly rearranged esp ligand (**2**) in excellent yield (entry 2). Interestingly, the similar carbonate base was significantly less efficient than hydroxide (entry 3). The reaction also occurred in a variety of solvents (entries 4−9), but none proved superior to methanol.[34] Using these conditions, the tetraketone **12** was smoothly rearranged into esp (**2**) below 25 °C in large scale (Scheme 2, step 2). The product **2** could be recrystallized directly from the reaction crude to yield 95.5 g of esp ligand (**2**) in a single run. This contrasts with the limitations in scale, cost, mass intensity and safety that is inherent to nitrile anion alkylation reactions, and demonstrates for the first time the advantages of the oxidative rearrangement strategy[3d] toward congested carboxylates in process-scale.

With large quantities of esp ligand in hand, we scaled up the synthesis to produce gram quantities of Rh_2esp_2 (**1**) in a simple reflux system using technical ethanol under air (Scheme 2, step 3).[35] Oxygen and moisture were found inconsequential for the efficiency of this reaction. However, a controlled ramp to steadily reach the reflux temperature (see Supporting Information) was important to obtain reproducible results. To put these results in perspective, it is important to highlight that only 1.4 equiv of the esp ligand is used, as opposed to the 90−120 equiv that was previously required with simpler carboxylic acids.[19] Moreover, the catalyst is obtained for the first time in a single step from rhodium(III) chloride, thus minimizing the overall environmental impact and operational costs.

Given the particular chelate structure of the ligand esp (**2**), we interrogated whether it was possible to obtain with the same method other privileged monocarboxylate rhodium(II) catalysts, which are relevant in a wide range of carbene and nitrene insertion reactions.[23−27] To our delight, using only marginal excess of the simple pivalic[23] or octanoic[24] acids under similar conditions, the corresponding complexes **15** and **16** were also produced (Scheme 3). Even the bulky

Scheme 3. Direct Preparation of Rh(II) Monocarboxylates from $RhCl_3{\cdot}xH_2O$ and Catalyst Benchmarking Studies



	R	catalyst	yield (%)
15	*t*-Bu	$[Rh_2(Piv)_4]$	71
16	*n*-Oct	$[Rh_2(Oct)_4]$	67
17	CPh_3	$[Rh_2(TPA)_4]$	66[b]

[a]1 equiv = 1 mol/mol pure **8**. [b]3 equiv of Li_2CO_3 was used. Ar, 4-*tert*-butylphenyl; Nph, naphthalimide; alt., alternative commercial catalyst.

triphenylacetic acid yields the congested Rh_2TPA_4 catalyst (**17**)[25] at significantly lower temperature than through current ligand metathesis. Interestingly, these monocarboxylate catalysts **15**−**18** could be prepared in multigram amounts in the absence of LiCl, unlike the chelate Rh_2esp_2 (**1**; Scheme 2B). The chiral monocarboxylate catalysts derived from *tert*-leucine and proline are widely employed in asymmetric catalysis.[26,27] As representative examples, both enantiomers of $Rh_2(TBSP)_4$ (**18**)[27] and the catalyst $Rh_2(NTTL)_4$ (**19**)[26] have been directly synthesized in moderate yields. Unfortunately, low efficiencies are observed using this protocol with the most extremely hindered cyclopropanecarboxylate ligands,[35] probably due to unfavorable binding kinetics.

The purity of the isolated complexes synthesized using this method have been routinely assessed to be >98% pure using ^1H NMR analysis (see Supporting Information). The catalytic activity of the obtained Rh_2esp_2 (**1**) and Rh_2TPA_4 (**17**) has been benchmarked against current commercial catalysts in challenging carbene and nitrene transfer reactions (Scheme

https://dx.doi.org/10.1021/acs.oprd.0c00164
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3B). The performance of the Rh_2esp_2 (**1**) and Rh_2TPA_4 (**17**) directly prepared from $RhCl_3{\cdot}xH_2O$ (**8**) were found to be identical to the corresponding commercial complexes in representative cyclopropenation,[13e] aziridination,[14a] or C−H amination reactions.[25a]

In summary, the synthesis of Rh_2esp_2 (**1**) has inspired the development of a mild and direct synthesis protocol from $RhCl_3{\cdot}xH_2O$ using key inorganic additives to suppress over-reduction to rhodium(0). This method allows important rhodium(II) catalysts to be obtained in a single operation and decreases two orders of magnitude the excess of carboxylate ligand required. Also, the alternative synthetic strategy toward the ligand esp (**2**) that has been presented herein demonstrates for the first time the fundamental step of oxidative rearrangement of 1,3-diketones in the process-scale production of all-carbon quaternary carboxylates. Overall, this work displays the potential of catalyst synthesis to inspire synthetic developments in both organic and inorganic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00164.

Synthetic procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Knut and Alice Wallenberg Foundation (KAW2016.0153) and the European Research Council (714737) is gratefully acknowledged. We are indebted to the personnel of AstraZeneca Gothenburg and the Department of Organic Chemistry and the EXSELENT Center on Porous Materials at Stockholm University for unrestricted support.

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