Scalable Synthesis of Esp and Rhodium(II) Carboxylates from Acetylacetone and RhCl$_3$·xH$_2$O

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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 and a fertile playground to create and test new chemistries. Despite the dominance of natural product and pharmaceutical targets in these studies, our group and others have used ligands to inspire synthetic innovations. 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. Traditional pivalate complexes have evolved into congested carboxylates to tackle the most challenging transformations. In particular, the pursuit of aliphatic C–H amination resulted in the development in 2004 of Rh$_2$esp$_2$ (1; esp = $\alpha$,$\alpha$,$\alpha'$,$\alpha'$-tetramethyl-1,3-benzenedipropionic acid) by Du Bois and co-workers (Scheme 1A). This catalyst displays a double chelate structure with two bis-carboxylate ligands, which stabilize the labile mixed-valence intermediates involved in the catalysis.

Rh$_2$esp$_2$ (1) has currently been extensively deployed in natural product total synthesis and is increasingly finding new applications in carbene-, nitrene-, and oxo-transfer reactions 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.

Despite its importance, the chemical synthesis of the ligand esp (2) and its rhodium complex 1 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). The latter is elaborated to esp (2) through a thermal hydration process. 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...
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. 19,20 This finding invited exploration of basic anions that would inhibit ligand depletion as well as stabilize the rhodium(II) intermediates likely involved. 20 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 counterion (entry 9–11). Li2CO3 offers the best balance between 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 32,33 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; pKa = 13) using mild inorganic bases instead of the nitrile anion 4 derived from isobutyronitrile (3; pKa ~ 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 acylation of acetylacetone (13) with methyl iodide (14) was performed using K2CO3 as base and acetonitrile as solvent. 32 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 acylation, 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, K2CO3, and butanone were required to mitigate the volatility of methyl iodide in this reaction. 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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 strategy3d toward congested carboxylates in process-scale.

With large quantities of esp ligand in hand, we scaled up the synthesis to produce gram quantities of Rh2esp2 (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.

Scheme 2. Scalable Synthesis of Rh2esp2 (1)

| entry | base    | solvent | yield (%) |
|-------|---------|---------|-----------|
| 1     | LiOH    | MeOH    | 0         |
| 2     | NaOH    | MeOH    | 95        |
| 3     | Na2CO3  | MeOH    | 58        |
| 4     | NaOH    | PhCF3   | 61        |
| 5     | NaOH    | HFP     | 78        |
| 6     | NaOH    | DCM     | 77        |
| 7     | NaOH    | DMF     | 69        |
| 8     | NaOH    | DMSO    | 67        |
| 9     | NaOH    | t-amylOH| 62        |

“1 equiv = 1 mol/mol pure 8.

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 Rh2esp2 (1) and Rh2TPA4 (17) has been benchmarked against current commercial catalysts in challenging carbene and nitrene transfer reactions (Scheme 3). Even the bulky triphenylacetic acid yields the congested Rh2TPA4 catalyst (17) 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 Rh2esp2 (1; Scheme 2B).

Scheme 3. Direct Preparation of Rh(II) Monocarboxylates from RhCl3·xH2O and Catalyst Benchmarking Studies

| catalyst | yield (%) |
|----------|-----------|
| 15 t-Bu | [Rh2(Piv)3] 71 |
| 16 n-Oct | [Rh2(Ocit)3] 67 |
| 17 CPh3  | [Rh2(TPA)4] 66b |

“1 equiv = 1 mol/mol pure 8. b = equiv of Li2CO3 was used. Ar, 4-tert-butylphenyl; Nph, naphthalimide; alt., alternative commercial catalyst.
The performance of the Rh.esp₂ (1) and Rh.TPA (17) directly prepared from RhCl₃·xH₂O (8) were found to be identical to the corresponding commercial complexes in representative cyclopropanation, aziridination, or C–H amination reactions.

In summary, the synthesis of Rh.esp₂ (1) has inspired the development of a mild and direct synthesis protocol from RhCl₃·xH₂O 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.

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