Kinetics of Rh(II)-Catalyzed α-Diazo-β-ketoester Decomposition and Application to the [3+6+3+6] Synthesis of Macrocycles on a Large Scale and at Low Catalyst Loadings

Daniele Poggiali,[†] Alexandre Homberg,[†] Timothée Lathion,[‡] Claude Piguet,[‡] and Jérôme Lacour*,[†]

[†]Department of Organic Chemistry and [‡]Department of Inorganic and Analytical Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

S Supporting Information

ABSTRACT: In the context of [3+6+3+6] macrocyclization reactions, precise kinetics of α-diazo-β-ketoester decomposition were measured by *in situ* infrared (IR) monitoring. Dirhodium complexes of Ikegami−Hashimoto type—and perchlorinated phthalimido derivatives in particular—performed better than classical achiral complexes. Clear correlations were found between speciation among dirhodium species and catalytic activity. With these results, novel cyclohexyl-derived catalysts were developed, affording good yields of macrocycles (up to 78%), at low catalyst loadings (from 0.01 mol % to 0.001 mol %) and on a large scale (from 1 g to 20 g).


From decomposition kinetics to large scale synthesis

KEYWORDS: acceptor-acceptor diazo reagents, dirhodium complexes, in situ IR monitoring, kinetics, low catalyst loading, multigram synthesis, speciation, ylides
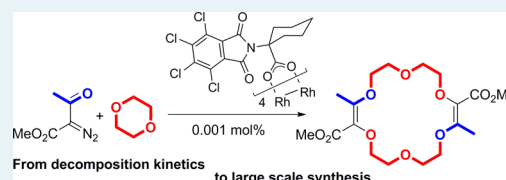
Type **1** α-diazo-β-ketoesters (Figure 1) constitute an important class of diazo reagents that combine substantial chemical stability with yet effective decomposition reactivity under thermal,[1] photochemical,[2] or metal-catalyzed conditions.[3] In the latter case, these acceptor-acceptor diazo derivatives generate electrophilic metal carbene intermediates that react and form a variety of products via, principally, C−H insertions, cyclopropanations and ylide formation reactions (and subsequent rearrangements).[4] With dirhodium complexes of type **2**, it is established that the diazo decomposition reactivity is influenced by the nature of the diazo reagent and by the ligands (L) that surround the metal atoms.[5] While precise kinetic information can be found for acceptor or donor−acceptor diazo derivatives,[6] such data were missing for reagents of type **1**. Herein, in the context of formal [3+6+3+6] macrocyclizations that combine carbenes and cyclic ethers,[7] the rate of decomposition of acceptor−acceptor diazo **1** is studied by *in situ* infrared (IR) monitoring. It is shown, for instance, that Ikegami−Hashimoto's catalyst **2e** reacts 14 times faster than Rh₂(OAc)₄ (**2a**). This reactivity is furthermore modulated by the presence of 1,4-dioxane (**3**). Characterization of the coordination of complexes **2b**−**2e** by Lewis base **3** was provided using ultraviolet−visible (UV-vis) titration experiments. Importantly, a correlation is evidenced between the rate of diazo decomposition and the speciation of the dirhodium species in the presence of **3**. Finally, cyclohexyl-derived Rh₂L₄ complexes **2f** and **2g** are reported (Figure 1, bottom) and compared to classical **2d** and **2e**. These active species can be used in catalyst loadings as low as 0.001 mol % for the formation of macrocycles of type **4** and in reactions using up to 20 g of **1**. Extension of this chemistry to other cyclic ether substrates is also demonstrated.
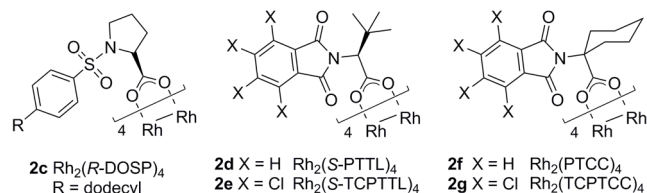

1. Previously (ref. 6)
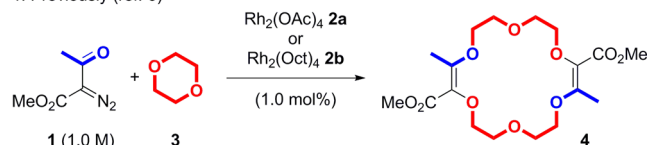
2. This work

in situ IR monitoring
Kinetics of diazo decomposition
Rationale catalyst selection
Influence of cyclic ether concentration
Rh₂L₄ & 1,4-dioxane : Speciation
New catalysts & loadings down to 0.001 mol%
Multigram synthesis (up to 20 g of 4 in one batch)

Dirhodium catalysts

2c Rh₂(R-DOSP)₄
R = dodecyl

2d X = H Rh₂(S-PTTL)₄
2e X = Cl Rh₂(S-TCPTTL)₄

2f X = H Rh₂(PTCC)₄
2g X = Cl Rh₂(TCPTCC)₄

Figure 1. (Top) Rh(II)-catalyzed macrocyclization of α-diazo-β-ketoesters and 1,4-dioxane. (Bottom) Dirhodium complexes.

Previously, it was shown that diazo β-ketoesters of type **1** react at high concentration (~1.0 M) in 1,4-dioxane (**3**) to yield, in the presence of Rh(II) complexes, unsaturated polyether macrocycles of type **4**.[7] Compound **4** acts as a versatile building block for the generation of chiral macrocycles, nanosensors, or ratiometric luminescent switches.[8] In the previously reported studies, product **4** was synthesized on a 1-g scale at most.[7a] Rh₂(OAc)₄ (**2a**) or Rh₂(Oct)₄ (**2b**) were used in rather large quantities, typically 1.0 mol %. Knowing that certain diazo decomposition reactions can be achieved with catalyst loadings as low as 0.00005 mol %,[9] we searched for conditions that would permit the synthesis of compound **4** with a minimal amount of dirhodium catalysts, and on a larger scale.

First, to select the most active catalyst (family), kinetic studies on the decomposition of diazo **1** in the presence of classical Rh(II) complexes were performed (**2a**–**2e**; see Figure 1). To achieve such a task, it was necessary to develop homogeneous conditions to avoid the precipitation of **4** that occurs when 1,4-dioxane is used as solvent (and reactant). Several other solvents were investigated and a rapid screening led to the selection of CH_2Cl_2 or $CHCl_3$ (**1**, 0.6 M). With these solvents and 6.0 equiv of 1,4-dioxane **3**, macrocycle **4** was obtained in 67%–68% yield.[10,11] Kinetic measurements were then started. Dirhodium complexes **2a**–**2e** were engaged at a loading of 1.0 mol %. The evolution of diazo **1** concentration was followed by *in situ* IR monitoring using the characteristic N=N=C stretching band at 2146 cm^{-1}. Reaction profiles are displayed in Figure 2. The pseudo-first-order kinetic rate constants k_1 for the decomposition were obtained after linearization (see Figure S2 and Table S2 in the Supporting Information).
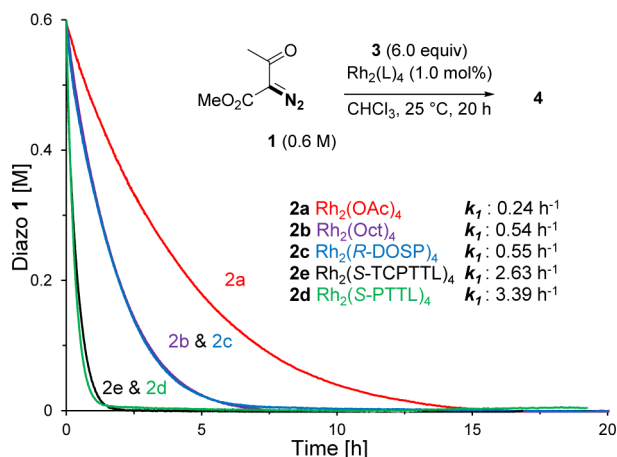
Figure 2. *In situ* infrared (IR) monitoring (2146 cm^{-1}) of diazo **1** concentration in the presence of Rh(II) complexes **2a**–**2e**.

Rh₂(OAc)₄ (**2a**) was the least effective catalyst (k_1 = 0.24 h^{-1}), decomposing diazo **1** twice as slow as Rh₂(Oct)₄ **2b** (0.54 h^{-1}). Surprisingly, knowing the usual efficiency of Rh₂(*R*-DOSP)₄,[9b] a relatively slow diazo decomposition was observed for **2c** (0.55 h^{-1}), the reaction profile being essentially superimposable to that of **2b** (Figure 2). Then, Rh₂(*S*-PTTL)₄ (**2d**) and Rh₂(*S*-TCPTTL)₄ (**2e**) were tested and the two complexes performed particularly well, with k_1 values of 3.39 and 2.63 h^{-1}, respectively. This order of reactivity was confirmed in a series of experiments using catalysts **2b**–**2e** at a loading of 0.1 mol %; **2d** and **2e** performed better than **2b** and **2c** (see Figures S3 and S4 and Table S3 in the Supporting

Information). On average, independent of the loading, dirhodium catalysts **2d** and **2e** react at least six times faster than the other metallic species.[12]

To possibly understand this difference among complexes **2b**–**2e**, a study of their interaction with 1,4-dioxane (**3**) was undertaken. In fact, it is well-established that dirhodium complexes Rh₂L₄ are Lewis acids. They possess two vacant sites along the Rh–Rh axis that coordinate sequentially one or two Lewis bases, such as 1,4-dioxane (**3**).[6d,13] Three distinct species are then possible: complexes Rh₂L₄, Rh₂L₄·**3**, and Rh₂L₄·**3**₂. While Rh₂L₄ and Rh₂L₄·**3** possess vacant site(s) and are catalytically active, Rh₂L₄·**3**₂ is inert (Table 1, top). These

Table 1. Equilibria among Rh₂L₄, Rh₂L₄·3, and Rh₂L₄·3₂ Species[a]

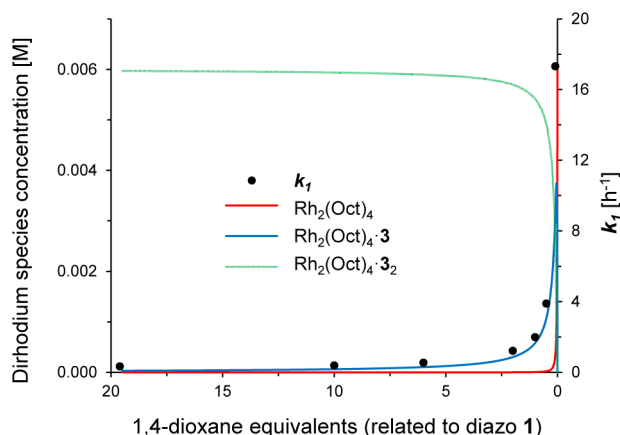| | | | | Composition (%) | | |
entry	**2**	K_1	K_2	Rh₂L₄	Rh₂L₄·**3**	Rh₂L₄·**3**₂
1	**2b**	183	16	<0.003	1.7	98.3
2	**2c**	1309	12	<0.001	2.3	97.7
3	**2d**	3540	44	<0.001	0.6	99.4
4	**2e**	6839	64	<0.001	0.4	99.6

[a]K_1 and K_2 values computed for a reference standard state of c^θ = 1 M.[17] Speciation with 6.0 equiv of 1,4-dioxane (**3**) in $CHCl_3$.

species are furthermore in equilibrium with each other. A determination of constants K_1 and K_2 under the reaction conditions was deemed essential for better comprehension. For this purpose, spectrophotometric titrations were performed following the changes in the absorption of the complexes. Mathematical treatments were performed with the help of factor analysis,[14] followed by nonlinear least-squares refinements.[15] The procedure and results are reported in Figures S5–S33 in the Supporting Information and gathered in Table 1. Note that the K_1 values are more than twice as large as K_2. It indicates that the successive coordination of two 1,4-dioxane does not obey statistics and the first binding event decreases the affinity of the metallic center in the Rh₂L₄·**3** complex for the fixation of a second dioxane ligand. Such anticooperative behavior could be tentatively assigned to the Lewis basic nature of **3** that tames the reactivity of complex Rh₂L₄·**3**. However, solvation effects may be as important as intramolecular electronic coupling effects, and the reduction of the dipole moment in the centro-symmetrical complex Rh₂L₄·**3**₂ may significantly contribute to the anticooperative process.[16] Also important is the observation that the equilibrium constants K_1 and K_2 increase from **2b** to **2e**, with the binding of 1,4-dioxane (**3**) being therefore stronger with the *tert*-leucine-derived complexes than the acetate or octanoate species.

A method to perceive the results of this analysis is to consider the speciation of the three different species in solution, for instance, in $CHCl_3$ in the presence of 6.0 equiv of **3** (Table 1, right columns). First and importantly, the percentage of "free" Rh₂L₄ complexes is extremely small (<0.003%). Among the two species that remain essentially, Rh₂L₄·**3** and Rh₂L₄·**3**₂, the equilibria are strongly shifted toward the latter (inactive) species; the percentage varies from 97.7% (**2c**) to 99.6% (**2e**). This data indicated, *a priori*, that only a small percentage of

catalytically able Rh$_2$L$_4$·**3** species (0.4%−2.3%) was responsible for the diazo decomposition.[18]

Care was taken to demonstrate the following assumptions: (i) by monitoring the rate of diazo **1** decomposition in variable amounts of 1,4-dioxane (**3**), and (ii) by correlating the results to the speciation of the different species in solution. In fact, using complexes Rh$_2$(Oct)$_4$ (**2b**) or Rh$_2$(*S*-PTTL)$_4$ (**2d**) as catalysts (1.0 mol %), reactions were performed with 19.6, 10, 6, 2, 1, 0.5, and 0.1 equiv of **3**, respectively (see Figures S34 and S37 in the Supporting Information for the reaction profiles). Kinetic rate constants k_1 were calculated for each experiment (see Figures S35 and S38 and Tables S8 and S9 in the Supporting Information). Figure 3 summarizes the results in

Figure 3. Pseudo-first-order rate constants k_1 (●) for the decomposition of **1** in the presence of variable amounts of **3**. [Legend describing the speciation of species: red curve, Rh$_2$(Oct)$_4$; blue curve, Rh$_2$(Oct)$_4$·**3**; and green curve, Rh$_2$(Oct)$_4$·**3**$_2$.]

the case of Rh$_2$(Oct)$_4$ (k_1, black dots). Not surprisingly, we observed an increase in pseudo-first-order k_1 values upon reducing the number of 1,4-dioxane equivalents per mole of catalyst, moderate at first and then sharp. In Figure 3, care was also taken to overlay the concentration curves of species Rh$_2$L$_4$, Rh$_2$L$_4$·**3**, and Rh$_2$L$_4$·**3**$_2$ using previously determined K_1 and K_2 values for the calculation. A direct correlation can then be drawn between the amount of Rh$_2$L$_4$·**3** in solution and the experimental rates of diazo **1** decomposition (see Figure 3, as well as Figures S36 and S39 in the Supporting Information). Evidently, at low concentration of **3**, the higher percentage of complexes Rh$_2$L$_4$·**3** favors the dinitrogen extrusion. Unfortunately, this acceleration in the diazo decomposition is coupled to a sharp decrease in yields of macrocycle **4** as 1,4-dioxane (**3**) is also needed as a nucleophile in subsequent reactions. As such, a compromise must be found between catalytic activity and global reaction efficacy, with 6.0 equiv of 1,4-dioxane being often an optimum for good reactivity and yields.

Then, considering the superior catalytic activity of complexes carrying phthalimido-based ligands, cyclohexyl-derived Rh$_2$(PTCC)$_4$ (**2f**) and Rh$_2$(TCPTCC)$_4$ (**2g**) (Figure 1) were synthesized, characterized, and compared with classical Rh$_2$(*S*-PTTL)$_4$ (**2d**) and Rh$_2$(*S*-TCPTTL)$_4$ (**2e**).[19] This development was pursued with one main goal—that of reducing catalyst loadings to 0.01 or 0.001 mol %.[20,21] As it could be expected, with such low amounts of complexes, it was necessary to run reactions at 60 °C and stir them for several days to achieve full conversions. The results with 0.001 mol % of catalysts are compiled in Table 2.
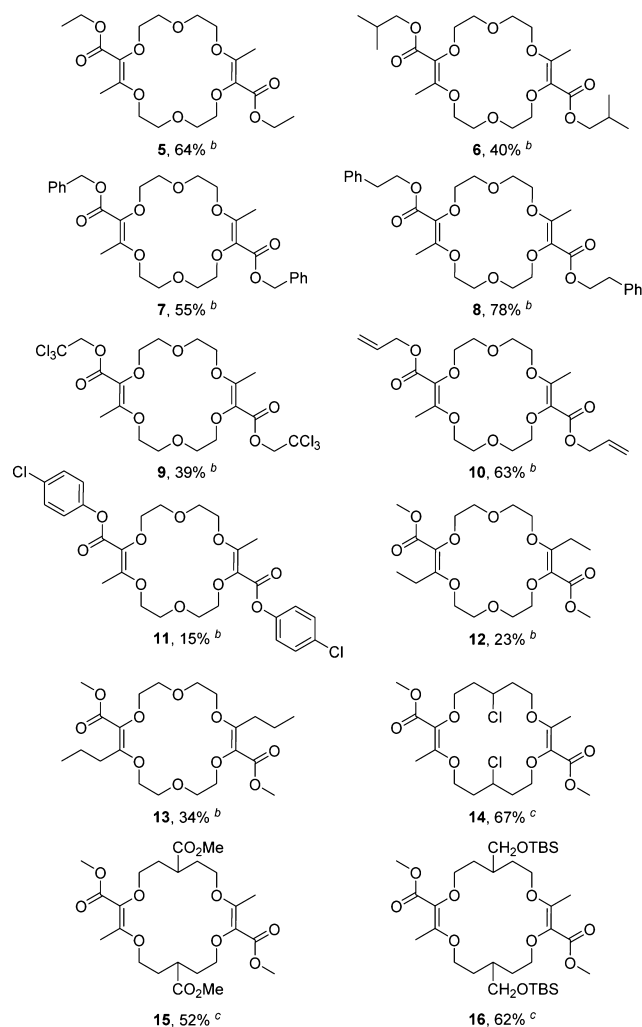
Table 2. Macrocycle Synthesis at a Catalyst Loading of 0.001 mol %

entry	catalyst	scale (g)	time (d)	yield (%)
1[a]	2d	0.2	4	70
2[a]	2e	0.2	3	63
3[a]	2f	0.2	8	62
4[a]	2g	0.2	4	60
5[a]	2e	1.0	3	65
6[a]	2g	1.0	4	65
7[b]	2e	0.2	7	68
8[b]	2g	0.2	5	67
9[b]	2d	20	9	53[c]
10[b]	2e	20	6	55[c]
11[b]	2f	20	19	65
12[b]	2g	20	5	72

[a]60 °C, 0.6 M in diazo, 6.0 equiv of **3** in CHCl$_3$. [b]60 °C, 0.6 M in diazo, 1,4-dioxane **3** as solvent. [c]Yield after recrystallization.

Satisfactorily, for reactions performed with 200 mg of diazo **1** in closed vials (entries 1−4), **2f** and **2g** afforded good yields of **4** (62% and 60%) similar to that of **2d** and **2e**—with a slight preference for Rh$_2$(*S*-PTTL)$_4$ (**2d**), in this case (70%). Yet, complexes carrying perchlorinated phthalimido ligands led to faster reactions than their "classical" counterparts. This trend will be found to be general and **2e** and **2g** were thus selected for 1-g scale experiments in CHCl$_3$ conditions (entries 5 and 6 in Table 2). Similar yields (65%) and reaction times (3−4 d) were observed. For comparison and practical reasons (easier isolation by precipitation), reactions were also performed in 1,4-dioxane. On a 200 mg scale, as it could be expected from the kinetic studies, reactions were slower (5−7 d, entries 7 and 8 in Table 2) but similar yields were obtained. Reactions on a 20-g scale with the four catalysts confirmed these results (entries 9−12 in Table 2). With Rh$_2$(*S*-PTTL)$_4$ (**2d**) and Rh$_2$(*S*-TCPTTL)$_4$ (**2e**), 9 and 6 days were necessary for full conversion. To our surprise, on this larger scale, the precipitation of macrocycle **4** was tainted by the presence of a polymeric material coming from the decomposition of 1,4-dioxane (**3**) (see Figure S43 in the Supporting Information). It was thus necessary to recrystallize the product and, hence, lower yields of 53% and 55% in isolated **4** were obtained with **2d** and **2e**, respectively (entries 9 and 10 in Table 2). With cyclohexyl-derived Rh$_2$(PTCC)$_4$ (**2f**) and Rh$_2$(TCPTCC)$_4$ (**2g**), reaction times of 19 and only 5 days were achieved with yields of 65% and 72%, respectively (entries 11 and 12 in Table 2). Satisfactorily, with these two catalysts, side products could not be found in ^{1}H NMR spectroscopic or GC-FID analyses of isolated **4**; catalyst **2g** then becomes the clear choice for performing the reaction on a larger scale.

With new catalyst **2g** in hand, the reaction was generalized using a variety of α-diazo β-ketoesters and a few substituted tetrahydropyrans. A catalyst loading of 0.01 mol % was selected to reduce reaction times to 15−20 h. The diazo reagents were used at 7 mmol (≥1 g scale). Products **5−16** are detailed in Chart 1. Moderate to good yields were obtained (39%−78%), with the exceptions of macrocycle **11**, which has sensitive

Chart 1. Substrate Scope[a]

5, 64% [b] **6**, 40% [b]

7, 55% [b] **8**, 78% [b]

9, 39% [b] **10**, 63% [b]

11, 15% [b] **12**, 23% [b]

13, 34% [b] **14**, 67% [c]

15, 52% [c] **16**, 62% [c]

[a]Reaction conditions: **2g**, 0.01 mol %. [b]60 °C, 15 h, 0.6 M in diazo, 1,4-dioxane **3** as solvent. [c]40 °C, 20 h, 0.6 M in diazo, 6.0 equiv of cyclic ethers in CHCl₃.

chlorophenol ester groups (15%), and derivatives **12** and **13**, which have longer alkyl appendages (ethyl, 23%; propyl, 34%).

The structures of **17** and **18** are shown in Figure 4. Interestingly, in the reaction of diazo **17** leading to bis-
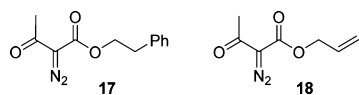
Figure 4. Structures of **17** and **18**.

homobenzylic **8**, the macrocycle was obtained in good yield (78%), with no trace of the product of intramolecular C−H insertion of the derived metal-carbene.[22] In the case of bis-allylic **10** made from **18**, a competition between macro-cyclization and intramolecular cyclopropanation reactions occurred, which product **10** being favored over the corresponding cyclopropane in a 4:1 ratio.[7a,23] The macro-cyclization study was extended to THP derivatives using 6.0 equiv of the cyclic ethers in CHCl₃ solutions. The temperature was reduced to 40 °C with only a moderate increase of reaction time (20 h vs 15 h). Products **14**−**16** were obtained in 52%−

67% yields.[24] As previously reported, mixtures of stereoisomers were obtained in these cases, with the ratio between *racemic* and *meso* products being 1:1 in the crude mixtures.[25]

In conclusion, thanks to precise kinetic (*in situ* IR) and thermodynamic (UV-vis titration) studies, we could evidence that perchlorinated dirhodium Ikegami−Hashimoto complexes present a superior catalytic activity in [3+6+3+6] macro-cyclization reactions. Novel cyclohexyl-derived catalysts were furthermore developed that afford, in one batch, macrocycles at low catalyst loadings (from 0.01 mol % to 0.001 mol %) and on practical scales (from 1 g to 20 g).

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01283.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: jerome.lacour@unige.ch.

Notes
The authors declare no competing financial interest.

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(10) The number of equivalents of 1,4-dioxane (**3**) is determined, relative to the amount of diazo **1** engaged in the reaction (1 equiv).

(11) Using lower amounts of **3** (4.0 and 2.0 equiv), the yields in **4** were no longer satisfactory (54% and 20%, respectively).

(12) These results confirm the high decomposition activity of substrates of type **1** by complexes **2d** and **2e** reported by Hashimoto and co-workers in their study of intramolecular C−H insertion reactions. See ref 9a.

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(18) The fastest catalysts present also the highest K_1 and K_2 values. Therefore, a higher Lewis acidity is crucial for the diazo decomposition activity.

(19) For a preliminary report of the use of complex **2f** in diazo decomposition studies, see: Chuprakov, S.; Worrell, B. T.; Selander, N.; Sit, R. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 195−202.

(20) For comparison purposes, catalysts **2f** and **2g** were tested at a loading of 0.1 mol% in the decomposition of diazo **1** with k_1 values of 0.08 h^{-1} and 0.41 h^{-1}, respectively (see Figures S41 and S42 and Table S10 in the Supporting Information); **2g** presents a higher kinetic constant than **2d** and **2e** (k_1 = 0.32 and 0.33 h^{-1}, respectively; see Table S3 in the Supporting Information).

(21) While **2g** is sufficiently soluble for kinetic experiments in the presence of 6 equiv of 1,4-dioxane (**3**), it is not soluble enough in pure CHCl$_3$ or in the presence of fewer equivalents of the Lewis base to allow titration experiments. The K_1 and K_2 values could not be determined.

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(24) Previously, using 1.0 mol% of Rh$_2$(Oct)$_4$ (**2b**), compounds **14** and **15** were obtained in yields of 55% and 42%, respectively. See ref 7b.

(25) After chromatographic purification (Al$_2$O$_3$), the macrocycles are isolated together in a *dr* ratio of 1.0:0.8 for **13** and **14**, and 1.0:0.6 for **12**, with the nature of the predominant stereoisomers being unknown.