Synthetic Methods

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[CpRu]-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis through S_N1-Like Chemistry with Retention of Configuration**

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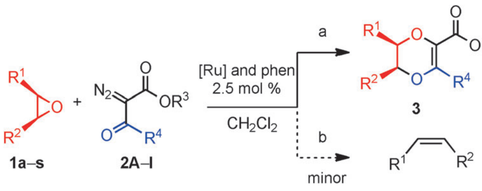
Dedicated to Professor Paul Müller on the occasion of his 75th birthday

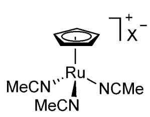
Abstract: *Rather than lead to the usual deoxygenation pathway, metal carbenes derived from α-diazo-β-ketoesters undergo three-atom insertions into epoxides using a combination of 1,10-phenanthroline and [CpRu(CH_3CN)$_3$][BAr_F] as the catalyst. Original 1,4-dioxene motifs are obtained as single regio- and stereoisomers. A perfect syn stereochemistry (retention, e.r. up to 97:3) is observed for the ring opening, which behaves as an S_N1-like transformation.*

Epoxides (**1**; or oxiranes; Scheme 1) are indispensable synthetic building blocks, which are readily accessible in well-defined stereochemical forms through efficient stereo- and enantioselective functional-group transformations, or otherwise available from commercial sources.[1] Owing to the strain of the three-membered ring, epoxides react with a wide array of nucleophiles and acids, thus leading to ring-opening reactions, often with excellent levels of regioselectivity and/or stereoselectivity.[1] Yet, as a rule, epoxides react differently with (metal) carbenes. Effective deoxygenation processes occur, thus transforming oxiranes into alkenes.[2] For instance, treatment of epoxides with acceptor/acceptor diazo reagents in the presence of a catalytic amount of [$Rh_2(OAc)_4$] leads to a quantitative capture of the oxygen atom and a stereospecific formation of the corresponding olefins.[3,4] Herein, in a new development, we report that metal carbenes derived from the α-diazo-β-ketoester reagents **2** undergo three-atom insertions into a large variety of epoxides (Scheme 1). The transformation specifically uses a combination of 1,10-phenanthroline (phen) and the complex [CpRu(CH_3CN)$_3$][BAr_F] as the catalyst (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).[5] Original 1,4-dioxene motifs of the type **3** are obtained as single regio- and stereoisomers. A perfect *syn* stereochemistry (retention; e.r. up to 97:3) is observed for the ring opening, which otherwise behaves as an S_N1-like transformation.



Scheme 1. Preferred *syn*-stereoselective 1,4-dioxene formation.

Recently, using combinations of [CpRu(CH_3CN)$_3$][PF_6] ([**4**][PF_6])[6] and diimine ligands as catalysts,[7] the reagents **2** provided selective 1,3-C−H insertions into THF[8] and O−H insertion and condensation reactions with alcohols, nitriles, ketones and aldehydes.[9] These results led us to examine the reactivity of other Lewis basic moieties with the catalytic combination, and epoxides in particular. In practice, the first experiments were performed by treatment of a CH_2Cl_2 solution of the cyclooctene oxide **1a** (1.0 equiv), the complex [**4**][PF_6] (2.5 mol %), and phen (2.5 mol %) with the methyl diazoacetoacetate **2A** ($R^3 = R^4 =$ Me, 0.5 M; Scheme 1). At 60 °C, gas evolution was observed and complete consumption of **2A** was achieved in 4 hours. Analysis of the reaction mixture indicated the formation of one major product (**3aA**, 60 %)[10] together with some unreacted epoxide. Cyclooctene was only a minor component of the crude reaction mixture. Based on detailed ^{1}H and ^{13}C NMR spectroscopy, and IR analyses, only the original bicyclic structure with a 1,4-dioxene core and a *cis* junction between the two rings ($^3J = 9.5$ Hz) was



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consistent with the data. The motif was confirmed by X-ray diffraction studies (Figure 1).[11,12]

First, total conversion of **1a** was obtained using an excess of the **2A** (2 equiv). This 1:2 ratio between epoxide and diazo reagent was maintained for the rest of the study. A search for the best catalytic combination was performed. The results are summarized in Table 1 for ruthenium complexes. The phenanthroline is clearly important, because in its absence the reaction leads to larger amounts of the undesired cyclooctene **5a** (entries 2 and 3; up to 30% of **5a**). Most probably, phen acts as a donor chelate ligand which stays on the metal throughout the reaction and the catalytic cycle. Changing the nature of the counterion additionally improved the conversions (entries 4–6). The reactions were faster with lipophilic anions like TRISPHAT [tris(tetrachlorobenzenediolato) phosphate],[13] BAr$_F$, and SbF$_6$, when compared to that with PF$_6$. Not surprisingly, conversions were lower with an anion which is able to coordinate to the metal center (TRISPHAT-N).[14] The complex [Cp*Ru(CH$_3$CN)$_3$][7b] (Cp* = pentamethylcyclopentadienyl) and its mono-CF$_3$ analogue did not improve the transformation (entries 8–10). Other metal sources were briefly tested. While copper salts did not induce the formation of the dioxene product, only a small amount (10%) of **3aA** was observed in the reaction catalyzed by [Rh$_2$(OAc)$_4$]. The 1:1 combination of phen and the salt [**4**][BAr$_F$] (entry 6) was thus selected and used in further experiments.

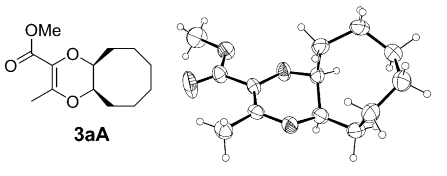
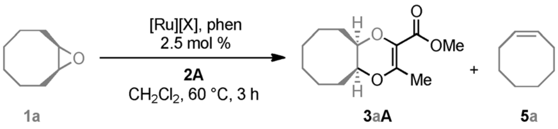


Figure 1. ORTEP view of the crystal structure of the *cis*-configurated **3aA**. Thermal ellipsoids are drawn at 50% probability.

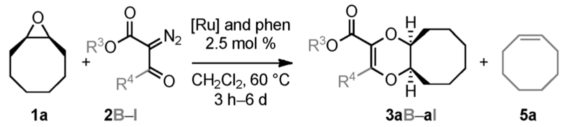
Table 1: Ruthenium complex selection.[a]

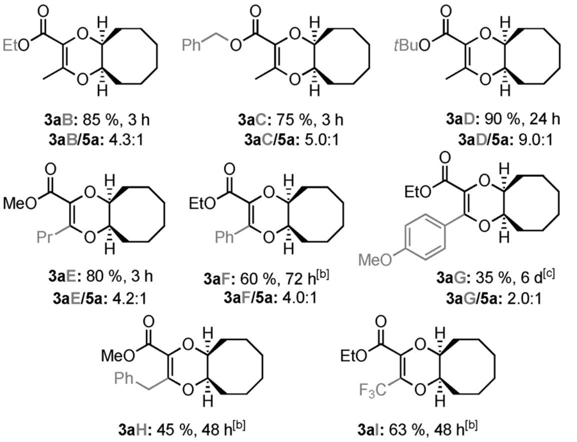


Entry	[Ru]	Anion	Conv.[b]	3/5[c]
1	[CpRu(CH$_3$CN)$_3$]	PF$_6$	86	4.5:1
2[d]	[CpRu(naphthalene)]	PF$_6$	69[d]	2.5:1
3[d]	[CpRu(CH$_3$CN)$_3$]	PF$_6$	85[d]	2.5:1
4	[CpRu(CH$_3$CN)$_3$]	SbF$_6$	94	4.4:1
5	[CpRu(CH$_3$CN)$_3$]	TRISPHAT	95	3.7:1
6	[CpRu(CH$_3$CN)$_3$]	BAr$_F$	100	4.4:1
7	[CpRu(CH$_3$CN)$_3$]	TRISPHAT-N	45	2:1
8	[Cp*Ru(CH$_3$CN)$_3$]	PF$_6$	63	2:1
9	[Cp*Ru(CH$_3$CN)$_3$]	SbF$_6$	42	2.4:1
10	[(C$_{10}$H$_{12}$F$_3$)Ru(CH$_3$CN)$_3$]	PF$_6$	44	2.4:1

[a] Reaction conditions: diazo compound **2A** (0.64 mmol), [Ru] and phen (2.5 mol % each), and **1a** (0.32 mmol) in CH$_2$Cl$_2$ (0.6 mL) for 3 h at 60°C. [b] Conversions of **1a** monitored by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal reference. [c] Ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Without phen ligand.

Table 2: Diazo reagent scope.[a]





3aB: 85 %, 3 h
3aB/5a: 4.3:1

3aC: 75 %, 3 h
3aC/5a: 5.0:1

3aD: 90 %, 24 h
3aD/5a: 9.0:1

3aE: 80 %, 3 h
3aE/5a: 4.2:1

3aF: 60 %, 72 h[b]
3aF/5a: 4.0:1

3aG: 35 %, 6 d[c]
3aG/5a: 2.0:1

3aH: 45 %, 48 h[b]
3aH/5a: 2.0:1

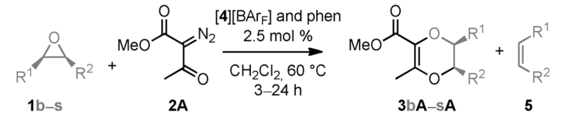
3aI: 63 %, 48 h[b]
3aI/5a: 5.7/1

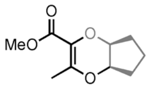
[a] Reaction conditions: diazo compound **2B–I** (0.64 mmol), **1a** (0.32 mmol), [**4**][BAr$_F$], and phen (2.5 mol % each) in CH$_2$Cl$_2$ (0.6 mL) at 60°C. Reaction times and ratios between dioxene and corresponding alkenes are indicated. Yield of isolated compound **3** is an average of at least two reactions. [b] Conv. = 80%. [c] Conv. = 81%.

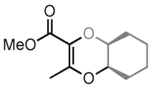
Diazo reagents with different alkyl ester substituents, **2B–I**, were then tested and reactions with **1a** were allowed to run until full conversion (Table 2). Good yields of the isolated products **3** were afforded with bulkier alkyl esters, sometimes after prolonged reaction times (**3aB–aD**). With the reagents **2B–D**, dioxene formation was clearly favored over the alkene formation. In all cases, *cis* isomers were obtained as determined by NMR spectroscopy. The preference for the *syn*-stereoselective epoxide opening was confirmed with reagents **2E–I**, which bear substituents other than methyl in the α-position of the keto group. In the presence of a propyl chain (**2E**, R^4 = Pr), a similar reactivity was observed (**3aE**). With aryl and benzyl residues, reactions were slower and lower yields were obtained (**3aF–H**). In the case of the CF$_3$-substituted diazo **2I**, a longer reaction time was also necessary (80% conversion after 48 h) to afford **3aI** as a single stereoisomer (63% yield upon isolation). Such a trifluoromethylated heterocycle is related to known agrochemicals, the preparation of which requires six steps.[15]

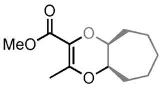
The reaction was then tested with a variety of *cis*-configurated epoxides (**1b–l**), using **2A** as the diazo reagent (Table 3). Satisfactorily, the 1,4-dioxene products **3bA–lA** were obtained in all cases as single *cis* isomers irrespective of the cyclic or acyclic nature of the oxiranes.[16,17] Even the sterically crowded epoxide **1e** reacted well under the standard conditions. By using the nonsymmetrical disubstituted oxiranes **1i–l**, reactions proceeded equally well. Importantly, in addition to being *syn* stereoselective, ring openings were fully regioselective as single dioxene products **3iA–lA** were again obtained.[18] Clearly, the substitution reactions occur at the more activated carbon centers bearing aryl or vinyl substitu-

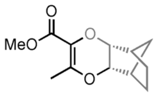
Table 3: Substrate scope.[a]

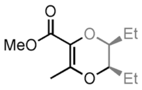


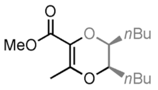

3bA: 50 %
3bA/5b: 3.3:1

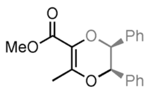

3cA: 66 %
3cA/5c: 3.3:1

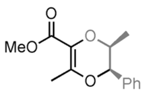

3dA: 68 %
3dA/5d: 5:1

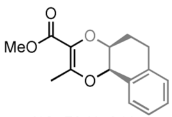

3eA: 70 %
3eA/5e: 1:0

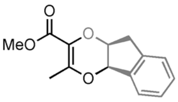

3fA: 58 %
3fA/5f: >10:1

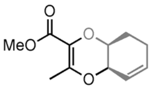

3gA: 94 %
3gA/5g: >10:1

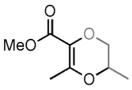

3hA: 37 %
3hA/5h: 1:2.5

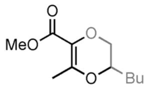

3iA: 60 %, 24 h
3iA/5i: 1.5:1

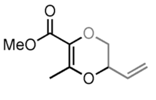

3jA: 70 %, 24 h
3jA/5j: 1.4:1

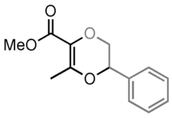

3kA: 21 %, 24 h
3kA/5k: 1/3.3

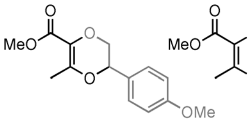

3lA: 50 %, 24 h
3lA/5l: 1.3/1

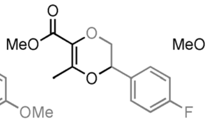

3mA: 65 %
3mA/5m: >10:1

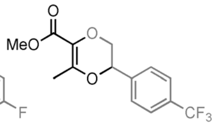

3nA: 55 %, 24 h
3nA/5n: 1.5:1


3oA: 55 %, 24 h
3oA/5o: 1.4:1


3pA: 40 %, 24 h
3pA/5p: 4.0:1


3qA: 41 %, 3 h
3qA/5q: 1.6:1


3rA: 38 %, 24 h
3rA/5r: 4.1:1


3sA: 37 %, 24 h
3sA/5s: 1:1

[a] Reaction conditions: diazo compound **2 A** (0.64 mmol), **1 b–s** (0.32 mmol), [**4**][BAr$_F$], and phen (2.5 mol % each) in CH$_2$Cl$_2$ (0.6 mL) at 60 °C. Ratios between dioxene and the corresponding alkenes are indicated. Yield of the isolated compound **3** is an average of at least two reactions. Reaction time 3 h, unless otherwise stated.

Table 4: Chirality transfer.[a]

Entry	X[b]	Substrate	e.r.[c]	Product	e.r.[c]
1	H	(+)-(*R*)-**1 p**	99.5:0.5	(−)-(*R*)-**3 pA**	97:3
2	H	(−)-(*S*)-**1 p**	99.5:0.5	(+)-(*S*)-**3 pA**	97:3
3	OMe	(+)-(*R*)-**1 q**	99.0:1.0	(−)-**3 qA**	77:23
4	F	(+)-(*R*)-**1 r**	98.5:1.5	(−)-**3 rA**	94:6

[a] Reaction conditions: see Table 3, entries 15–17. [b] The *para* substituent on substrates **1 p**, **1 q**, and **1 r**. [c] Determined by CSP-HPLC. Average of at least two reactions.

ents. Encouraged by these results, reactions were attempted with the monosubstituted substrates **1m–s**. To our satisfaction, full control over the regioselectivity was again obtained, with the ring opening occurring only at the more substituted carbon atom. These important observations will be discussed in the mechanistic discussion (see below). Interestingly, with vinyl epoxides **1l–o**, only the 1,4-dioxenes **3lA** and **3oA** were isolated. These results contrast with literature precedents for which products of [1,2]-insertion or [2,3]-sigmatropic rearrangements were observed, however such compounds are absent from the current transformation.[2d,j,k] Also, with epoxides carrying aryl substituents, slower reactions and lower yields were globally observed. Possibly, **4** reacts with the aromatic rings, thus leading to a decrease in the effective concentration of the catalyst.[19,20]

To shed light on the process, the styrene oxides **1p–r** were then used in highly enantioenriched forms (Table 4). Both (*R*)- and (*S*)-**1p** were tested and the product **3pA** was obtained with a 97:3 e.r. in favor of the levo- and dextrorotatory enantiomers respectively. With (*R*)-**1q** and (*R*)-**1r**, strong and slight decreases in the enantiospecificity of the reaction were noticed (**3qA**: e.r. 77:23 and **3rA**: e.r. 94:6). The origin of this variation is discussed in the mechanism section.

Care was taken to determine the absolute configuration of the ring-opened products. It was established by vibrational circular dichroism (VCD).[21,22] IR absorption and VCD spectra were measured for solutions (CD$_2$Cl$_2$) of both (−)- and (+)-**3pA** and compared to the most stable conformer of (*S*)-**3pA** (Figure 2), thus accounting for about 95 % according to its Boltzmann weight. Overall, a good agreement between the experimental and theoretical spectra was observed, thus allowing the assignment of *S* and *R* configurations for the dioxenes (+)- and (−)-**3pA**, respectively. This finding was confirmed by an X-ray crystallographic study of (+)-**3pA**.[23] These results clearly indicate that the formation of **3pA** occurs with retention of configuration.

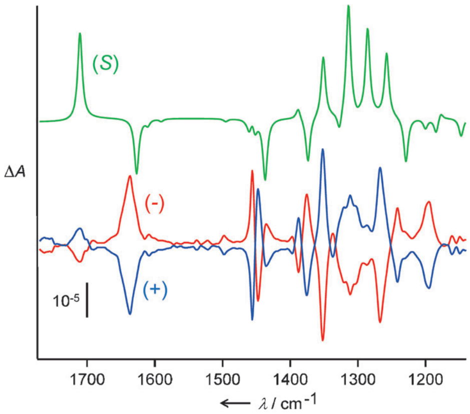
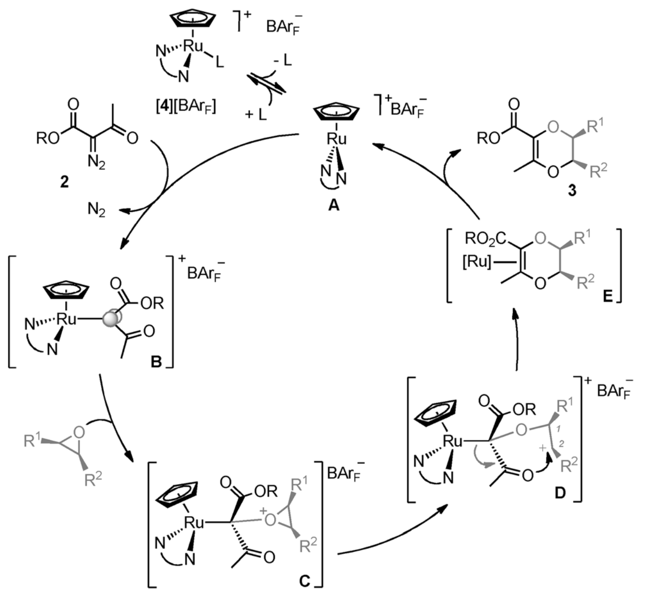


Figure 2. Experimental VCD spectra (CD$_2$Cl$_2$, 298 K) of (−)-**3 pA** (red) and (+)-**3 pA** (blue). Calculated spectrum of (*S*)-**3 pA** (green).

A mechanistic rationale, consistent with all the experimental information collected, is proposed in Scheme 2. The catalyst precursor [**4**][BAr$_F$] reacts with phen to generate a [Cp(phen)(CH$_3$CN)Ru][BAr$_F$] species which, upon dissociation of the monodentate ligand, forms the catalytically active 16-e$^-$ complex **A**. The diazo reagents **2** then react with this electron-deficient species to afford the metal carbene intermediate **B**. At this stage, a nucleophilic attack of the epoxide



Scheme 2. Mechanistic rationale. $\overset{\frown}{NN}$ represents the ligand phen. $R^2 > R^1$ in terms of electron-donating ability.

occurs and the metal oxonium ylide intermediate **C** is formed. Promoted by strain and by the electrophilic activation, a C–O bond cleavage occurs in the direction of the carbon atom which better stabilizes the developing positive charge. This step (**C**→**D**) involving an S_N1-like pathway explains the observed regioselectivity.[24] The carbocationic intermediate **D** is then trapped by the keto group to form the cyclic 1,4-dioxene skeleton. To retain the original configuration of the reacting carbon center, this step (**D**→**E**) must be fast, otherwise a racemization/epimerization occurs by a scrambling of the stereotopic faces through an internal rotation around the C1–C2 bond. It is fortunately happening only with **1q** for which the intermediate **D** is strongly stabilized by the *para*-methoxy group. The products **3** are then released and the catalytic cycle continues.[25]

In conclusion, a new reactivity is reported for metal carbene reactions with epoxides owing to the combination of 1,10-phenanthroline and [CpRu(CH_3CN)$_3$][BAr$_F$] as the catalyst. Novel 1,4-dioxene motifs of the type **3** are obtained as single regio- and stereoisomers. A *syn* stereochemistry (retention, e.r. up to 97:3) is observed for the ring opening, which behaves as an S_N1-like transformation. Further applications of this approach are looked for.

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Keywords: carbenes · diazo compounds · ruthenium · stereoselectivity · ylides

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[10] In product **3xY**, the first and second letters **x** and **Y** relate to the reactive epoxide **1x** and diazo **2Y** respectively.

[11] Product **3aA** was found to be moderately soluble in a 3:1 mixture of hexanes and CH_2Cl_2 at 25 °C. X-ray quality crystals were afforded and a structural analysis was performed (see Table S1 in the Supporting Information for details).

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[16] Corresponding alkenes were usually observed in most cases as minor products with percentages around 5–15%.

[17] The *cis* configuration was ascertained by X-ray analysis. The ORTEP diagram of **3hA** is detailed in the Figure S1.

[18] Regio- and stereoselectivity were ascertained by X-ray analysis. The ORTEP diagram of **3jA** is detailed in the Figure S2.

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[20] Alternatively, as a result of the the presence of the benzo groups, ansa-ligated $\mathrm{Ru^{II}}$ η^6-arene complexes made by ligand exchange between the aryl and cyclopentadienyl moieties could also be formed: a) Y. Miyaki, T. Onishi, H. Kurosawa, *Inorg. Chim. Acta* **2000**, *300–302*, 369–377; b) P. Pinto, A. W. Goetz, G. Marconi, B. A. Hess, A. Marinetti, F. W. Heinemann, U. Zenneck, *Organometallics* **2006**, *25*, 2607–2616; c) B. Therrien, *Coord. Chem. Rev.* **2009**, *253*, 493–519.

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[22] Calculations of several conformers were done at the DFT B3LYP level of theory using a 6-311++g(d,p) basis set. Frequencies were scaled by 0.98. VCD spectra were constructed from calculated rotational strengths assuming Loretzian band shape with a half-width at half maximum of 5 $\mathrm{cm^{-1}}$. All calculations were performed using Gaussian 09, Revision C.01.

[23] The product (+)-**3pA** was purified up to a 99.5:0.5 e.r. by semipreparative CSP-HPLC and crystallized in a dichloromethane/pentane mixture. Using a single crystal, the Flack parameter was affined to 0.0(2) value indicative of a *S* configuration as well. The ORTEP diagram of (+)-**3pA** is detailed in the Figure S3.

[24] With disubstituted unsymmetrical epoxides, the C–O bond cleavage occurs to preferentially form benzylic carbenium ions. With monosubstituted epoxides, secondary rather than primary carbocations are formed.

[25] Preliminary computational studies starting from the intermediate **B** (R^1 = H, R^2 = Ph) confirm the proposed mechanism. The rate-limiting step of the reaction is the coordination of the epoxide (+9.8 $\mathrm{kcal\,mol^{-1}}$) en route to the oxonium ylide intermediate **C**. From this species, the formation of intermediate **D** requires only 1.7 $\mathrm{kcal\,mol^{-1}}$. The final C–O bond formation is a barrier less process (+0.4 $\mathrm{kcal\,mol^{-1}}$), which explains why the retention of configuration is so kinetically favored. Further calculations are in progress.

Communications

Synthetic Methods

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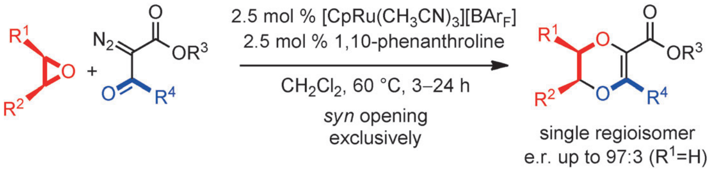
[CpRu]-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis through S_N1-Like Chemistry with Retention of Configuration



Oxygen sticks around: Rather than lead to the usual deoxygenation pathway, metal carbenes derived from α-diazo-β-ketoesters undergo three-atom insertions into epoxides using a combination of 1,10-phenanthroline and $[CpRu(CH_3CN)_3][BAr_F]$. 1,4-Dioxene motifs are obtained as single regio- and stereoisomers with perfect *syn* stereochemistry. BAr_F = tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate, Cp = cyclopentadienyl.