

# Highly Robust and Efficient Blechert-Type Cyclic(alkyl)(amino)carbene Ruthenium Complexes for Olefin Metathesis

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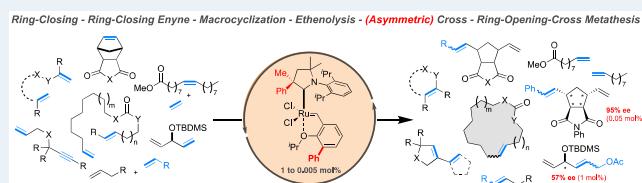
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**ABSTRACT:** New Blechert-type ruthenium complexes containing cyclic(alkyl)(amino)carbene (CAAC) ligands are reported. These catalysts demonstrate remarkable thermal stability in solution and excellent catalytic performances at low catalytic loading (up to 0.005 mol %) in ring-closing metathesis (RCM), macro-RCM, ring-closing enyne metathesis (RCEYM), cross-metathesis (CM), ethenolysis and ring-opening cross metathesis (ROCM). Moreover, up to 95% enantiomeric excess (ee) was obtained in asymmetric ring-opening cross metathesis (AROCM) and 57% ee was obtained in asymmetric cross-metathesis (ACM).

**KEYWORDS:** Olefin metathesis, ruthenium complex, cyclic(alkyl)(amino)carbene, asymmetric catalysis



## INTRODUCTION

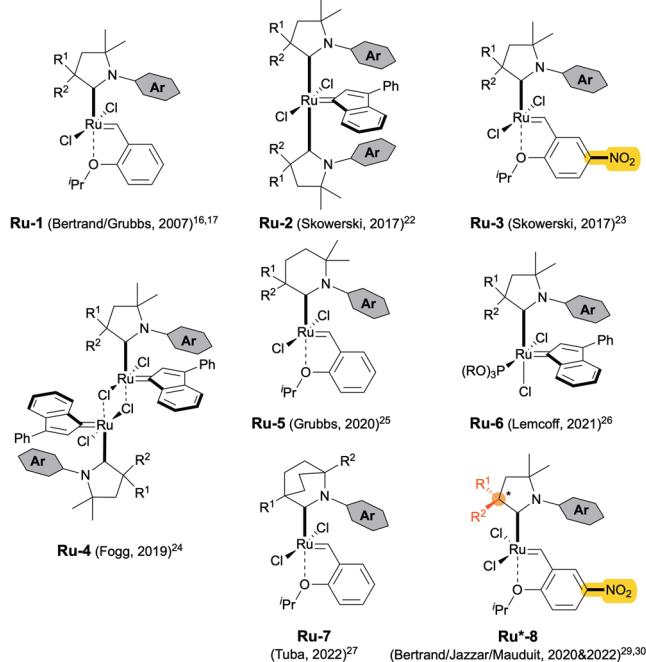
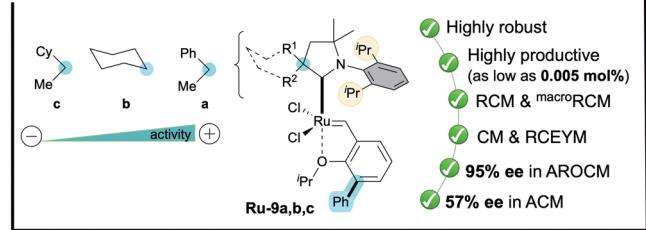
Olefin metathesis represents a highly versatile synthetic tool to build a plethora of valuable building blocks and organic compounds.<sup>1,2</sup> Thanks to the development of bench-stable and well-defined ruthenium-arylidene complexes, this catalytic reaction is intensively used in polymer chemistry<sup>3,4</sup> and fine chemistry,<sup>5</sup> and it has also found applications in the valorization of biomasses<sup>6</sup> and the depolymerization of polyethylene.<sup>7</sup> Despite these remarkable achievements, the quest for more efficient Ru-complexes remains a very active research topic across academia and industry.<sup>1,2</sup> A significant breakthrough was accomplished in 2007 when it was reported that the use of cyclic(alkyl)(amino)carbene (CAAC) ligands<sup>8–15</sup> could provide very active catalysts for the ethenolysis of vegetable oils (0.0001 mol % **Ru-1**; TON up to 390,000).<sup>16,17</sup> This peculiar behavior, surpassing state-of-the art N-heterocyclic carbene (NHC) analogues,<sup>18</sup> was shown to result from the improved stability of the corresponding Ru-methylidene intermediate, imparting resilience toward bimolecular decomposition.<sup>19–21</sup> Obviously, structural modifications of the CAAC ligand framework were thoroughly investigated, which led to several new CAAC Ru-complexes (**Ru-2–Ru-7**, Figure 1A),<sup>22–28</sup> including optically pure congeners **Ru\*-8** recently developed by our groups.<sup>29–31</sup> Based on a benchmark reaction (i.e., RCM of diethyldiallylmalonate **1a** (DEDAM; see Table 1)),<sup>28</sup> a map of structure–activity relationship (SAR) allowed one to highlight two key features: (i) bulky ortho-N-aryl substituents such as 2,6-diisopropylphenyl (DIPP) have a detrimental effect on the

catalyst activity; and (ii) the introduction of NO<sub>2</sub> on the labile styrenyl-ether ligand reduces reaction times.

Thus, CAAC catalysts featuring a 2,6-diethylphenyl (DEP) N-substituent (<sup>DEP</sup>CAAC) and a NO<sub>2</sub> activating group were shown to be very effective across a broad range of olefin metathesis transformations (**Ru-2**, **Ru-3**, and **Ru-4**; TON of 68,000 for RCM of **1a**).<sup>22–24</sup> Notwithstanding these advancements, a few drawbacks in the preparation of these catalysts deserve to be considered. In marked contrast with bulkier 2,6-diisopropylphenyl N-substituted CAAC ligands (<sup>DIPP</sup>CAAC), which are readily accessible in good to excellent yield from first-generation Hoveyda precursors (70%–91%), <sup>DEP</sup>CAAC appears to be more challenging with yields (when reported) ranging from 15% to 45%.<sup>32</sup> This problem extends to nitro-Grela derivatives, which are isolated in poor to moderate yields (14%–50%).<sup>32</sup> In 2002, Blechert and co-workers showed that the introduction of an *ortho*-phenyl group on the chelating benzylidene-ether ligand resulted in steric hindrance that weakened the O–Ru bond and drastically increased the catalyst activity.<sup>33,34</sup> Given the importance of CAAC-Ru complexes for the industrial sector, we focused our attention to the preparation of Blechert-type Ru-complexes **Ru-9** (Figure 1B). Herein, we disclose a new class of CAAC catalysts readily

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**A. State of the art CAAC-ruthenium olefin metathesis complexes****B. Blechert-type DIPP<sup>a</sup>CAAC-Ru catalysts (this work)**

**Figure 1.** (A) Previously developed CAAC-Ru complexes and (B) Blechert-type DIPP<sup>a</sup>CAAC-Ru complexes (this work).

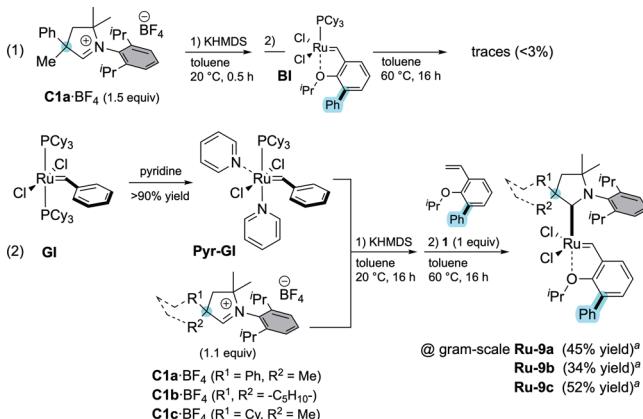
accessible from the commercially available Grubbs first generation complex **GI**<sup>35</sup> in good yields (**Scheme 1**, eq 2). These catalysts demonstrate remarkable catalytic activity (as low as 0.005 mol %) toward a wide range of metathesis transformations. Moreover, up to 95% enantioselectivity could be obtained in asymmetric olefin metathesis with only 0.05 mol % of optically pure **Ru-9**.

## RESULTS AND DISCUSSION

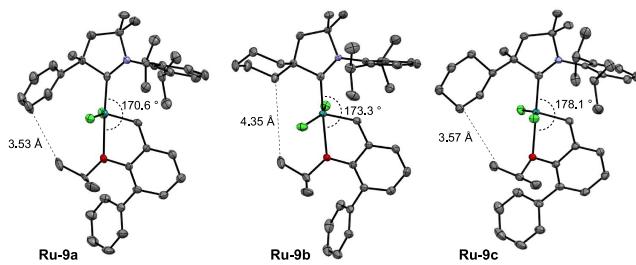
We initiated our study by attempting the preparation of Blechert-type DIPP<sup>a</sup>CAAC **Ru-9** complexes starting from the phosphine-based Blechert precursor **BI** (**Scheme 1**, eq 1).<sup>36</sup> Unfortunately, in this case, only a trace amount of DIPP<sup>a</sup>CAAC **Ru-9a** was observed (<3%) which we attributed to the relative instability of **BI** in solution. In contrast, deprotonation of **C1a**•BF<sub>4</sub> with potassium hexamethyldisilazide (KHMDS) in the presence of **Pyr-GI**<sup>16</sup> afforded the expected DIPP<sup>a</sup>CAAC **Ru-9a** in 45% yield (over two steps) on gram-scale.

It is worth mentioning that **Pyr-GI** is readily accessible from the first-generation **GI** complex in the presence of pyridine (>90% yield, **Scheme 1**, eq 2).<sup>37</sup> Similarly, Blechert-type DIPP<sup>a</sup>CAAC complexes, bearing a spirocyclohexyl (**Ru-9b**) and methyl/cyclohexyl (**Ru-9c**) at the quaternary center were isolated in yields of 34% and 52%, respectively. We confirmed the structure of **Ru-9a**, **Ru-9b**, and **Ru-9c** by X-ray diffraction analysis (**Figure 2**).<sup>38,39</sup> Blechert-type NHC-catalysts often lack

## Scheme 1. Synthesis of Blechert-Type CAAC **Ru-9a–9c**<sup>a</sup>

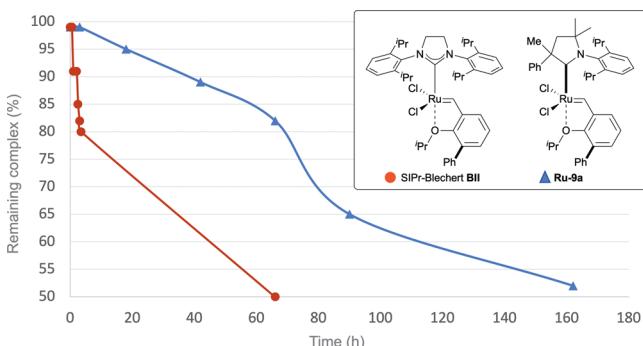


<sup>a</sup> Isolated yield over two steps.



**Figure 2.** Solid-state structure of complexes **Ru-9a**, **Ru-9b**, and **Ru-9c** from single-crystal X-ray diffraction. Displacement ellipsoids are drawn at 30% probability. Hydrogen atoms have been omitted for clarity.

stability in solution.<sup>38</sup> As shown in **Figure 3**, DIPP<sup>a</sup>CAAC **Ru-9a** demonstrated a remarkable stability in the presence of air at 80

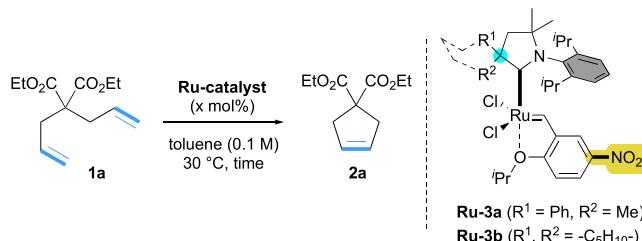


**Figure 3.** Thermal stability of DIPP<sup>a</sup>CAAC **Ru-9a** (blue) and SIPr-Blechert **BII** (red) in toluene-*d*<sub>8</sub> (0.24 M) at 80 °C. Precatalyst decomposition was monitored by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

°C in toluene-*d*<sub>8</sub> (0.24 M), with up to 52% remaining complex after 7 days and a complete decomposition over 28 days (see **Figure 3** and the **Supporting Information (SI)** for details). Of note is that the SIPr-Blechert analogue **BII** (vide infra, **Table 1**, entry 8) showed a lower stability with only 80% remaining complex after 3.5 h and a full decomposition after 3.5 days (see the **SI** for details).

Having confirmed their stability, we next investigated the catalytic performances of Blechert-type DIPP<sup>a</sup>CAAC **Ru-9a**, **Ru-9b**, and **Ru-9c** in the RCM of DEDAM **1a** (**Table 1**). At 0.1

**Table 1.** Catalytic Performances of Blechert-Type DIPP<sup>a</sup>CAAC Ru-9a–Ru-9c in Ring-Closing Metathesis of DEDAM 1a and Comparison with Nitro-Grela Congeners Ru-3a and Ru-3b and SiPr-Blechert BII



entry	catalyst	concentration (mol %)	time (h)	conversion/yield <sup>a</sup> (%)
1	Ru-3a	0.1	1	10 <sup>b</sup>
2	Ru-3b	0.1	1	5 <sup>b</sup>
3	Ru-9b	0.1	2	4 (4)
4	Ru-9b	1	2	99 (96)
5	Ru-9c	0.1	2	7 (7)
6	Ru-9c	1	2	83 (72)
7	Ru-9a	0.1	2	99 (97)
8	BII	0.1	4	75 (73) <sup>e</sup>
9	Ru-9a	0.05	4	99 (96)
10	Ru-9a	0.01	4	50 (48)
11 <sup>c</sup>	Ru-9a	0.01	4	96 (94)
12 <sup>c,d</sup>	Ru-9a	0.005	4	90 (85)
13 <sup>c,d</sup>	Ru-9a	0.0025	4	23 (12)

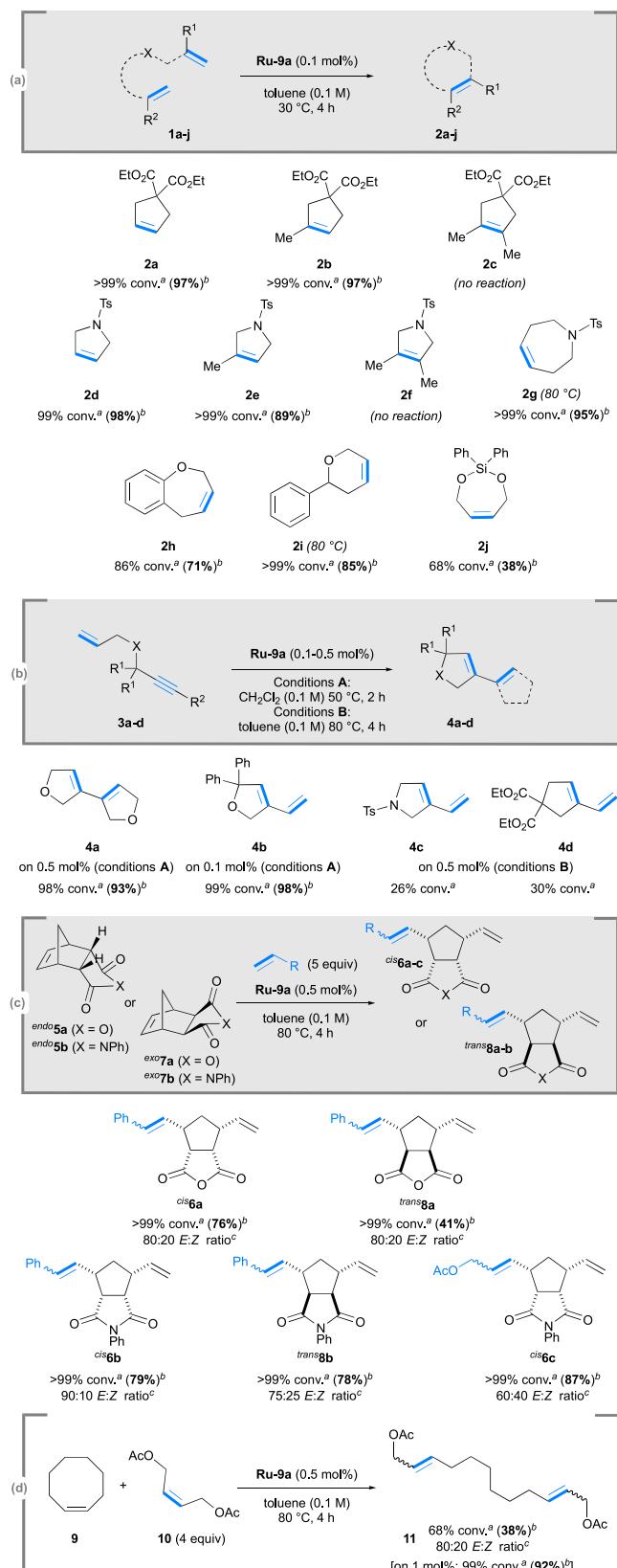
<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (see the SI). <sup>b</sup>Data taken from ref 23.

<sup>c</sup>Toluene (2 M). <sup>d</sup>Reaction performed at 40 °C. <sup>e</sup>70% yield after 2 h.

mol % catalyst loading DIPP<sup>a</sup>CAAC Ru-9b and Ru-9c showed poor reactivity (5%–10% conversion, entries 3 and 5 in Table 1, after 2 h) comparable to that of nitro-Grela DIPP<sup>a</sup>CAAC Ru-3a,b (entries 1 and 2 in Table 1).<sup>40</sup> As expected, higher catalyst concentration led to nearly full conversions (entries 4 and 6 in Table 1). To our surprise, Ru-9a bearing Me/Ph substituents at the quaternary center showed significantly higher reactivity within 2 h at 0.1 mol %, affording the desired cyclopentene 2a in 97% yield, thus surpassing the SiPr-Blechert BII (entry 7 in Table 1 vs entry 8 in Table 1). More interestingly, Ru-9a remains active at lower catalyst concentrations reaching up to 17.000 TON with 0.005 mol % catalyst loading (entries 9–13 in Table 1). Note that, under these conditions, a 20-fold higher solvent concentration (2 M) was required to improve the mass transfer (entry 10 in Table 1 vs entry 11 in Table 1).<sup>41,42</sup>

Having identified Blechert-type DIPP<sup>a</sup>CAAC Ru-9a as the most efficient catalyst, we then investigated its performances in various olefin metathesis transformations at 0.1–0.5 mol %. In ring-closing metathesis (Scheme 2a), full conversions and good to excellent yields (86%–98%) were obtained for the formation of di- or trisubstituted cyclopentenes 2a, 2b, 2d, and 2e. Unfortunately, no reaction was observed with the more challenging tetrasubstituted cyclopentenes 2c and 2f. To our delight, seven-membered rings were also formed in good yields (2g, 2h, 2i; 71%–98%), while the cyclic silane 2j was obtained in moderate yield (38%). We also considered ring-closing enyne metathesis (RCEYM), in which DIPP<sup>a</sup>CAAC Ru-9a showed good activity at 0.1–0.5 mol %, affording 4a and 4b in 93%–98% yield, respectively (Scheme 2b). However, lower conversions (26%–30%) were observed for products 4c and 4d, despite the use of more drastic conditions.

**Scheme 2.** Scope of (a) RCM, (b) RCEYM, and (c, d) ROCM Catalyzed by DIPP<sup>a</sup>CAAC Ru-9a Complex

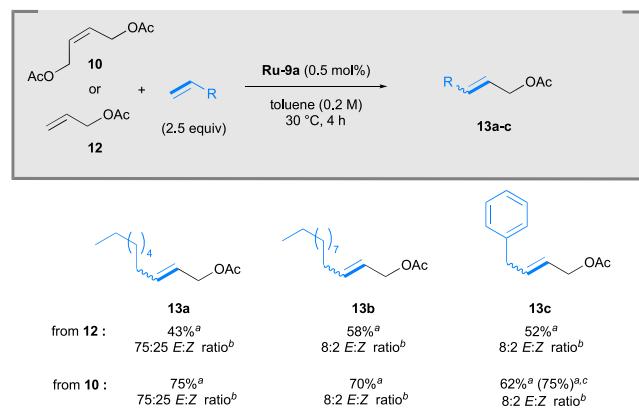


<sup>a</sup>Conversions were determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup>NMR yield. <sup>c</sup>E:Z ratio was monitored by <sup>1</sup>H NMR analysis.

We next considered the ring-opening cross-metathesis (ROCM) of *endo*-norbornenes **5a**, **5b**, and *exo*-norbornenes **7a**, **7b** with styrene, which afforded the corresponding *cis*-cyclopentanes **6a**, **6b**, and *trans*-cyclopentanes **8a**, **8b** in moderate to good yield (41%–79%) and 75:25 to 90:10 *E*:*Z* ratio (**Scheme 2c**). In contrast, ROCM of *endo*-**5b** with allyl acetate gave the expected *cis*-cyclopentane **6c** in 87% yield and a 60:40 *E*:*Z* ratio. Finally, the ROCM between cyclooctene **9** and *cis*-1,4-diacetoxy-2-butene **10** furnished the corresponding linear diene **11** with a modest 38% yield (**Scheme 2d**). Fortunately, the latter can be improved reaching 92% with 1 mol % catalyst loading. Note that all ROCM transformations required thermal activation (80 °C).

Shifting our investigation to cross-metathesis (CM) with various cross-olefin partners (**Scheme 3**), we found that the

### Scheme 3. Scope of CM Catalyzed by $^{DIPPO}_\text{CAAC Ru-9a}$ Complex



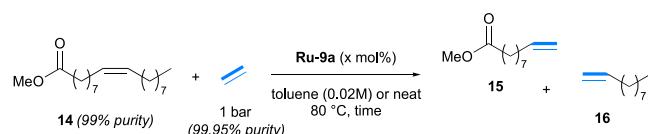
<sup>a</sup>Isolated yield. <sup>b</sup>The *E*:*Z* ratios were monitored by <sup>1</sup>H NMR analysis. <sup>c</sup>1 mol % of catalyst was used.

reaction between allyl acetate **12** and 1-nonene or 1-dodecene led to the expected linear alkenes **13a**, **13b** in isolated yields of 43% and 58% with *E*:*Z* ratios of 75:25 and 80:20, respectively (**Scheme 3**). A similar 52% yield and *E*:*Z* ratio were observed for product **13c**, resulting from the CM with homoallyl benzene. Replacing allyl acetate **12** with *cis*-1,4-diacetoxy-2-butene **10** slightly improved the isolated yields, irrespective of the cross-olefin partners (62%–75%).

We also examined the cross-metathesis between the methyl ester of oleic acid **14** and ethylene (also called ethenolysis). The reaction was performed under 1 bar of ethylene in the presence of 0.1–0.0005 mol % of **Ru-9a** (**Table 2**). We were delighted to obtain a 97% yield for the expected methyl 1-decenoate **15** and 1-decene **16** after 3 h at 80 °C in toluene (entry 1 in **Table 2**). Importantly, despite the use of low pressure of ethylene gas, no trace of self-metathesis products was observed by <sup>1</sup>H NMR (see the **SI** for details), showcasing once again the remarkable selectivity of CAAC-based Ru catalysts for this transformation.<sup>17</sup> In order to increase the TON, we performed the reaction at lower catalyst loading (0.01 mol %) but a poor 7% yield was observed (entry 2 in **Table 2**).

Under neat conditions, the reactivity was improved, affording **15** and **16** in 36% yield (TON 3600, entry 3 in **Table 2**). Noteworthy, a large amount of methyl elaidate—the *E* isomer of the starting material resulting from the reverse cross-metathesis—was also detected (see the **SI** for details).

**Table 2. Low-Pressure Ethenolysis of Methyloleate **14** Catalyzed by  $^{DIPPO}_\text{CAAC Ru-9a}$  Complex**



entry	Ru-9a (mol %)	condition	time (h)	yield (%) <sup>a</sup>	TON
1	0.1	Tol (0.02 M)	3	97	970
2	0.01	Tol (0.02 M)	3	7	700
3	0.01	neat	3	36	3600
4	0.001	neat	6	10	10000
5	0.0005	neat	6	8	16000
6 <sup>b</sup>	0.0005	neat	6	3	6000

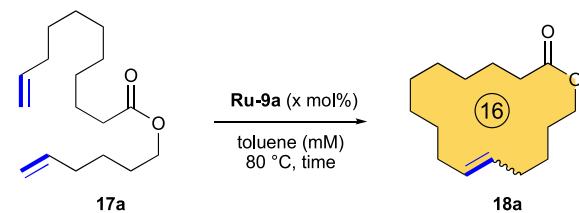
<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (see the **SI**). <sup>b</sup>Reaction performed at 10 bar, 40 °C.

Finally, the best TON (16 000) was achieved at 0.0005 mol % (without any detection of methyl elaidate). The use of higher pressure (10 bar) did not lead to any improvement (compare entries 5 and 6 in **Table 2**).

We then focused our attention toward macrocyclic ring-closing metathesis (macro-RCM), which is used for the synthesis of macrocyclic odorant molecules that are widely employed in perfumery for their strong musk fragrance.<sup>43,44</sup>

We first investigated the catalytic performance of Blechert  $^{DIPPO}_\text{CAAC Ru-9a}$  (0.1 mol %, 5 mM in toluene, **Table 3**, entry

**Table 3. Catalytic Performances of Blechert  $^{DIPPO}_\text{CAAC Ru-9a}$  in Macro-RCM of Hex-5-enyl Undec-10-enoate **17a** Furnishing 16-Membered Exaltolide Precursor **18a****



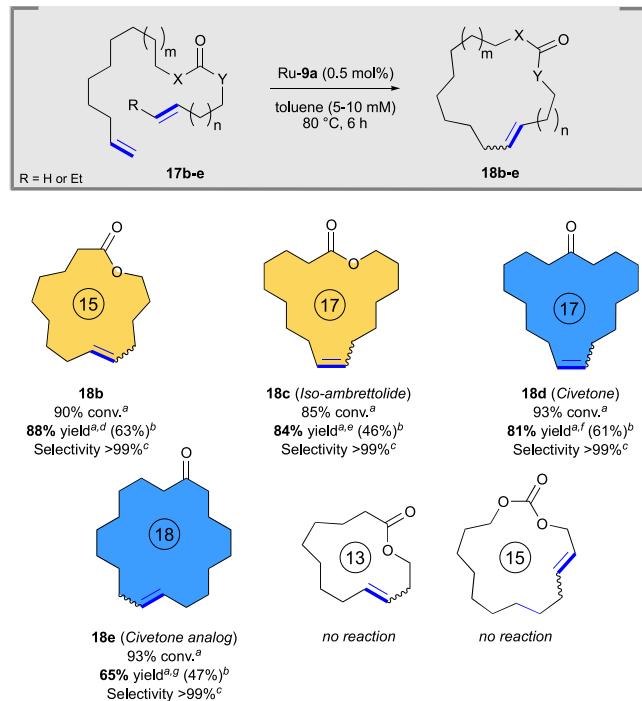
entry	Ru-9a (mol %)	concentration (mM)	time (h)	conversion (yield) <sup>a,b</sup> (%)	purity <sup>c</sup> (%)
1	0.1	5	6	99 (87) <sup>d</sup>	>99
2	0.05	10	6	85 (81)	>99
3	0.01	10	6	55 (55)	>99
4	0.01	25	6	49 (45)	>99
5	0.01	50	6	50 (25)	>99
6	0.01	100	6	49 (25)	>99

<sup>a</sup>Conversions and yields were determined by <sup>1</sup>H NMR spectroscopy, using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>*E*:*Z* ratio: 70:30 (determined by GC analysis). <sup>c</sup>Determined by GC analysis (see the **SI** for details). <sup>d</sup>Isolated yield after SiO<sub>2</sub> purification.

1) in the cyclization of hex-5-enyl undec-10-enoate **17a**. In this case, the resulting 16-membered macrocycle **18a**—a precursor of Exaltolide<sup>45</sup>—was obtained in a *E*:*Z* mixture (70:30 ratio) and 87% isolated yield after silica gel purification. Noteworthy, **18a** showed an excellent purity (>99%) with no byproducts (i.e., ring contraction resulting from isomerization of starting material)<sup>46–49</sup> detected by GC. Interestingly, a 81% yield and >99% purity were obtained at lower dilution (10 mM) and catalyst loading (0.05 mol %; entry 2 in **Table 2**). Attempts to decrease the latter to 0.01 mol % resulted in a significant

decrease in conversion/yield (55%; entry 3 in Table 2), meanwhile increasing the reaction concentration (up to 100 mM) gave lower yields as oligomers were also formed (see entries 5 and 6 in Table 2).<sup>50</sup> To extend the scope of mRCM, we also considered a range of macrocyclic lactones and ketones (Scheme 4). Under optimal conditions (5–10 mM, 0.5 mol %

**Scheme 4. Scope of Macroyclic RCM of Dienic Substrates 17b–17e Z by <sup>DIPP</sup>CAAC Ru-9a Complex Leading to the Corresponding Macro cyclic 18b–21e**



<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Isolated yields after SiO<sub>2</sub> purification.

<sup>c</sup>Determined by GC analysis (see the SI for details). <sup>d</sup>E:Z ratio = 40:60. <sup>e</sup>E:Z ratio = 80:20. <sup>f</sup>E:Z ratio = 70:30. <sup>g</sup>E:Z ratio = 70:30.

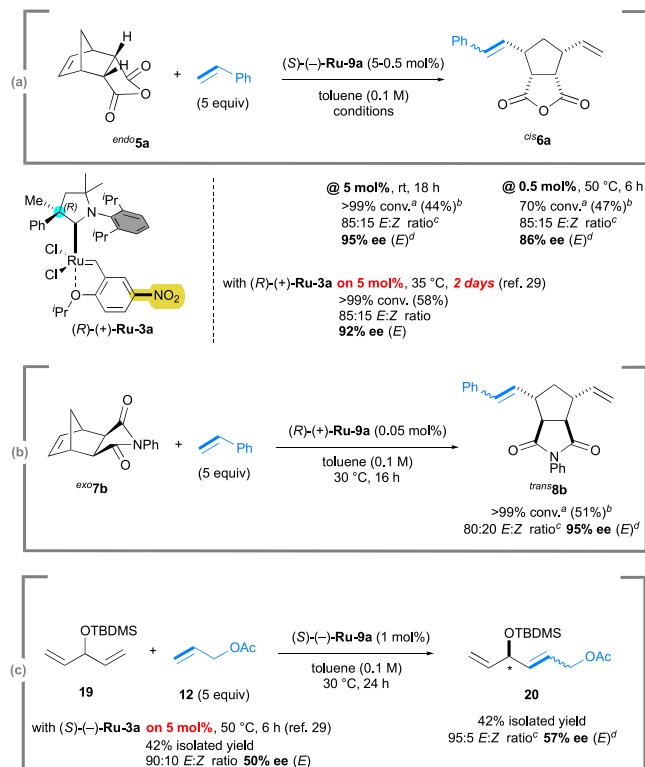
of Ru-9a, 80 °C, 6 h), we were delighted to observe that the 15-membered lactone 18b could be formed in high 88% NMR yield with an excellent >99% purity and a 40:60 E:Z ratio. Unexpectedly, purification of 18b by chromatography separation proved challenging and resulted in a lower yield than anticipated (63%). Similarly, 17-membered lactone 18c (namely, iso-ambrettolide)<sup>51</sup> was also isolated in lower yield (isolated: 46%; NMR: 84%).

Here also, no trace of byproducts was detected (purity of >99%). The 17-membered macrocyclic ketone 18d (namely Civetone)<sup>52–54</sup> was obtained with up to 81% NMR yield (61% isolated yield) while its 18-membered analogue 18e<sup>55</sup> was formed in lower yield (isolated: 47%; NMR: 65%). Note that Blechert <sup>DIPP</sup>CAAC Ru-9a did not afford the 13-membered lactone and 15-membered macrocyclic carbamate under these conditions.

Having recently disclosed the catalytic activity of chiral CAACs (ChiCAACs) in asymmetric olefin metathesis,<sup>29–31,56</sup> we also considered the enantiopure variant of <sup>DIPP</sup>CAAC Ru-9a for the same. Both enantiomers were isolated in good yields and excellent enantiomeric purity (up to >99.5 ee%) by preparative HPLC resolution (see the SI for details). In the AROCM<sup>36,57–61</sup> between *endo*-norbornene 5a and styrene

(Scheme 5a), the expected *cis*-cyclopentane 6a was isolated in 44% yield and an excellent 95% ee using 5 mol % of (*S*)-

**Scheme 5. (a, b) Asymmetric ROCM and CM (c) Catalyzed by Chiral <sup>DIPP</sup>CAAC (*R*)-(+) and (*S*)-(-)Ru-9a Complexes**



<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Isolated yields after SiO<sub>2</sub> purification. <sup>c</sup>Determined by GC-MS analysis. <sup>d</sup>Determined by HPLC or GC analysis on chiral phase (see SI for details).

(*S*)-Ru-9a. In contrast, longer reaction time (48 h) and slightly higher temperature (35 °C) were required to reach similar results with nitro-<sup>DIPP</sup>CAAC (*R*)-(+)Ru-3a.<sup>29</sup> To our delight, the chiral Blechert catalyst remained performant even at lower catalyst loading (0.5 mol %), affording 6a in 86% ee after 6 h at 50 °C. More interestingly, (*R*)-(+)Ru-9a catalyzed the AROCM of *exo*-norbornene 7b with only 0.05 mol % leading to the corresponding *trans*-cyclopentane 8b in 51% yield and high enantioselectivity (95% ee, Scheme 5b).

This impressive reactivity and selectivity were also demonstrated in the challenging asymmetric cross-metathesis (ACM) transformation,<sup>62</sup> for which the best ee reported so far is 54%.<sup>44</sup> (*S*)-(-)-Ru-9a (1 mol %) efficiently catalyzed the CM between the prochiral skipped 1,4-diene 19 and allyl acetate 12, affording 20 in 42% yield and up to 57% ee (Scheme 5, c). Note that these results also surpass those of nitro-<sup>DIPP</sup>CAAC (*S*)-(-)-Ru-3a both in terms of efficiency and selectivity (5 mol %, 50% ee).<sup>29</sup>

## CONCLUSIONS

In summary, we have developed the first Blechert-type ruthenium complexes containing a cyclic(alkyl)(amino)-carbene ligand, <sup>DIPP</sup>CAAC Ru-9a featuring a quaternary center bearing phenyl/methyl substituents proved to be the most robust and efficient catalyst across a wide range of metathesis transformations and, in most cases, under very low catalyst

loadings (ranging from 0.5 mol % to 0.005 mol %). Moderate to good yields were obtained in various RCM, ROCM, CM and ethenolysis reactions.<sup>DIPP</sup>CAAC **Ru-9a** also demonstrated high productivity toward challenging olefin macrocyclization, which delivers valuable odorant molecules with high >99% purity. Used in asymmetric olefin metathesis, chiral (R)-(+)-**Ru-9a** successfully furnished AROCM and ACM products at low catalyst loadings (from 1 mol % to 0.05 mol %) in 95% and 57% ee, respectively. Future work will focus on the use of Blechert-type <sup>DIPP</sup>CAAC **Ru-9a** in continuous flow conditions,<sup>63</sup> as well as in relevant enantioselective metathesis transformations, more specifically toward the highly challenging asymmetric ring-closing enyne metathesis (ARCEYM).<sup>64,65</sup>

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.3c01208>.

NMR spectra of products, GC analyses, and experimental procedures ([PDF](#))

Ru-9a ([CIF](#))

Ru-9b ([CIF](#))

Ru-9c ([CIF](#))

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▼ A.D.V. and J.T. contributed equally to this work. G.B., R.J., and M.M. conceived, designed, and directed the project. A.D.V., J.T., S.C.-R., J.L., and M.R.S. conducted all the experiments. T.R. accomplished of X-ray diffraction analysis. The manuscript was written by G.B., R.J., and M.M. and reviewed by all the authors. The SI was written by A.D.V., J.T., and S.C.-R.

### Notes

The authors declare no competing financial interest.

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