

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

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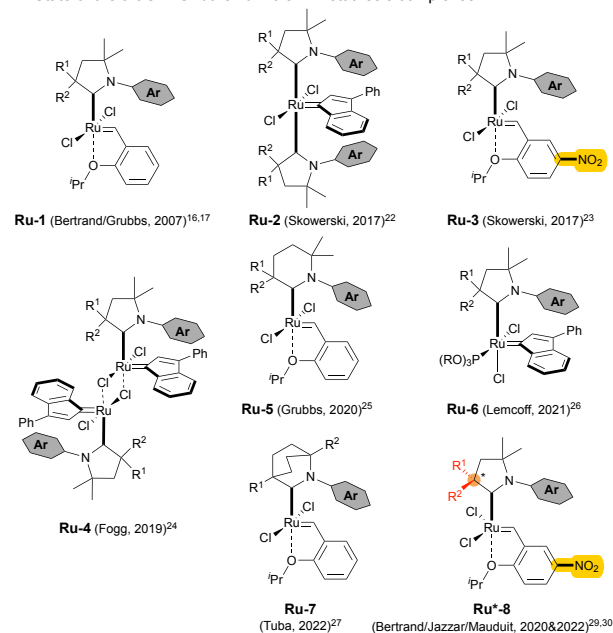
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**ABSTRACT:** The first Blechert-type ruthenium complexes containing cyclic(alkyl)(amino)carbene (CAAC) ligands are reported. These catalysts demonstrate remarkable thermal stability in solution and excellent catalytic performances at low catalytic 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% *ee* was obtained in asymmetric ring-opening cross metathesis (AROCM) and 57% *ee* asymmetric cross-metathesis (ACM)

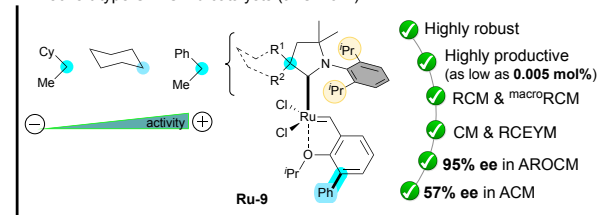
## INTRODUCTION

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 has also found applications in the valorisation of biomasses<sup>6</sup> and the depolymerisation 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 behaviour, 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 was thoroughly investigated which led to a number of new CAAC Ru-complexes (**Ru-2-7**; Figure 1, A),<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 diallyldiethylmalonate **1a**; DEDAM, see table 1) a map of structural-activity relationship (SAR) allowed 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; ii) introduction of NO<sub>2</sub> on the labile styrenylether ligand improves reaction times.

## A. State of the art CAAC-ruthenium olefin metathesis complexes



## B. Blechert-type CAAC-Ru catalysts (this work)

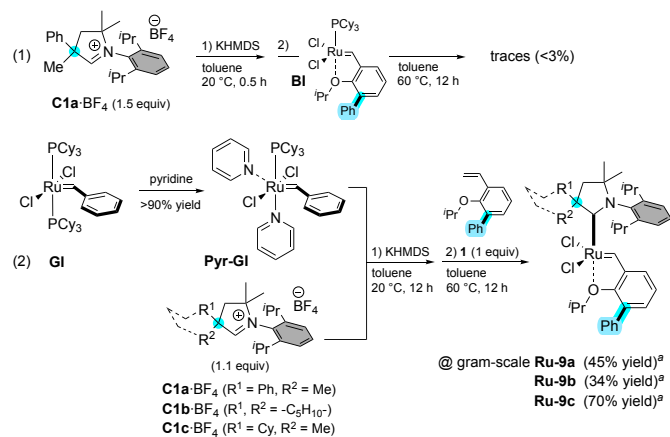


**Figure 1** (A) Previously developed CAAC-Ru complexes. (B) Blechert-type CAAC-Ru complexes (this work).

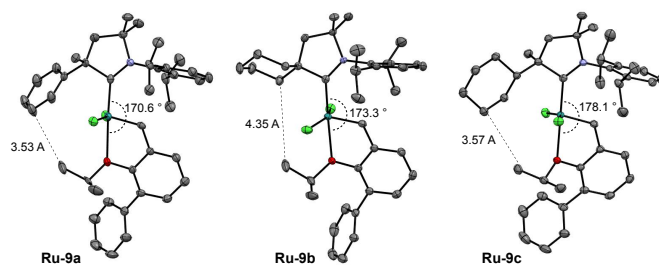
Thus, CAAC-catalysts featuring a 2,6-diethylphenyl (DEP) *N*-substituent (<sup>DEP</sup>CAAC) and a NO<sub>2</sub> activating group were shown to be very effective across a broad range of olefin metathesis transformations (**Ru-2,3,4**; TON of 68.000 for RCM of **1a**).<sup>22-24</sup> Notwithstanding 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 1<sup>st</sup> generation Hoveyda precursors (70-91%), <sup>DEP</sup>CAAC appears to be more challenging with yields (when reported) range from 15 to 45%.<sup>32</sup> This problem extends to nitro-Grela derivatives which are isolated in poor to moderate yields (14 to 50%).<sup>32</sup> Given importance of CAAC-Ru complexes for the industrial sector, we investigated the preparation of Blechert-type Ru-complexes **Ru-9** (Figure 1, B).<sup>33,34</sup> Herein we disclose a new class of CAAC catalysts readily accessible from the commercially available Grubbs 1<sup>st</sup> generation complex **GI**<sup>35</sup> in good yields (Scheme 1, Eq. 2). These catalysts demonstrate remarkable catalytic activity (as low as 0.001 mol%) towards 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 <sup>DIPP</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 trace amount of <sup>DIPP</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 presence of **Pyr-GI**,<sup>16</sup> afforded the expected <sup>DIPP</sup>CAAC **Ru-9a** in 45% yield (over two step) on gram-scale.

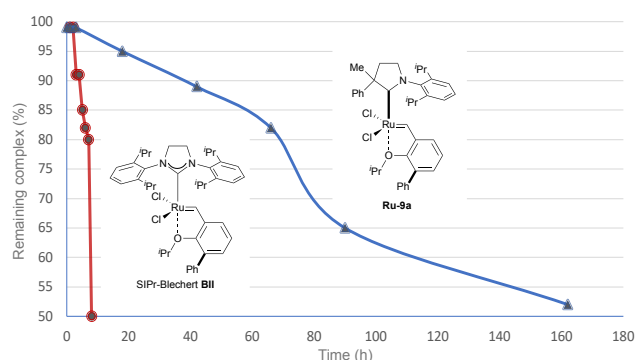


**Scheme 1** Synthesis of Blechert-type CAAC **Ru-9a-c**. <sup>a</sup> Isolated yield over 2 steps.



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

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, <sup>DIPP</sup>CAAC-Blechert complexes, bearing a spirocyclohexyl (**Ru-9b**) and methyl/cyclohexyl (**Ru-9c**) at the quaternary centre were isolated in 34 and 70% yield, respectively. We confirmed the structure of **Ru-9a,b,c** by X-ray diffraction analysis (Figure 2).<sup>38,39</sup> Blechert-type NHC-catalysts often lack stability in solution.<sup>38</sup> As shown in Figure 3, <sup>DIPP</sup>CAAC-Blechert **Ru-9a** demonstrated a remarkable stability in presence of air at 80 °C in toluene-*d*<sub>8</sub> (0.1 M), with up to 52% remaining complex after seven days and a complete decomposition over 28 days (see Figure 3 and 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 hours and a full decomposition after 3.5 days (see SI for details).

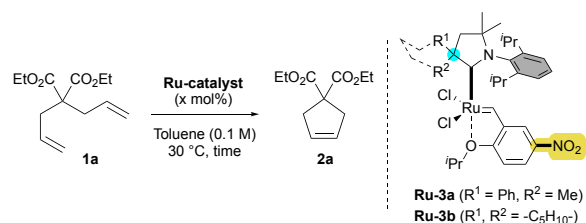


**Figure 3** Thermal stability of <sup>DIPP</sup>CAAC-Blechert **Ru-9a** (blue) and SiPr-Blechert **BII** (red) in toluene-*d*<sub>8</sub> (0.1M) at 80 °C. Pre-catalyst decomposition was monitored by <sup>1</sup>H-NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

Having confirmed the stability of these catalysts, we next investigated their catalytic performances of Blechert-CAAC **Ru-9a,b,c** in the RCM of DEDAM **1a** (Table 1). At 0.1 mol% catalyst loading <sup>DIPP</sup>CAAC **Ru-9b,c** showed a poor reactivity (5-10% conv., entries 3,5, after 2h) comparable to that of nitro-Grela <sup>DIPP</sup>CAAC **Ru-3a,b** (entries 1-2).<sup>40</sup> As expected, higher catalyst concentration led to nearly full conversions (entries 4,6). To our surprise **Ru-9a** displaying bearing Me/Ph substituents at the quaternary centre showed significantly higher

reactivity within 2 hours at 0.1 mol%, affording the desired cyclopentene **2a** in 97% yield after 2 hours at 0.1 mol% loading, thus surpassing the SIPr-Blechert **BII** (entry 7 vs 8). 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). Note that under these conditions a 20-fold higher solvent concentration (2 M) was required to improve the mass transfer (entry 10 vs 11).<sup>41,42</sup>

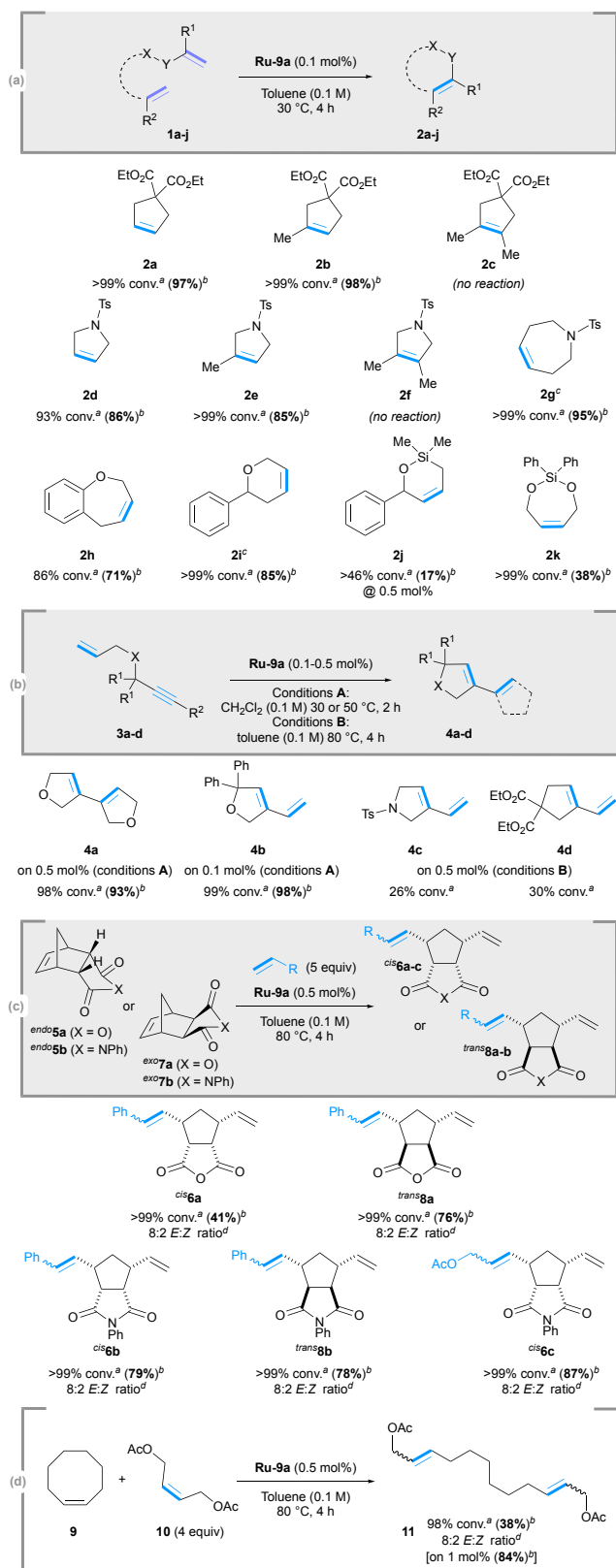
**Table 1** Catalytic performances of Blechert-type CAAC **Ru-9a-c** in ring-closing metathesis of DEDAM **1a** and comparison with nitro-Grela congeners **Ru-3a,b** and SIPr-Blechert **BII**.



Entry	Catalyst	Mol%	Time (h)	Conv./Yield (%) <sup>a</sup>
1	<b>Ru-3a</b>	0.1	1	10 (ref. 21)
2	<b>Ru-3b</b>	0.1	1	5 (ref. 21)
3	<b>Ru-9b</b>	0.1	2	4 (4)
4	<b>Ru-9b</b>	1	2	99 (96)
5	<b>Ru-9c</b>	0.1	2	7 (7)
6	<b>Ru-9c</b>	1	2	83 (72)
7	<b>Ru-9a</b>	0.1	2	99 (97)
8	<b>BII</b>	0.1	4	75 (73)
9	<b>Ru-9a</b>	0.05	4	99 (96)
10	<b>Ru-9a</b>	0.01	4	50 (48)
11 <sup>b</sup>	<b>Ru-9a</b>	0.01	4	96 (94)
12 <sup>b,c</sup>	<b>Ru-9a</b>	0.005	4	90 (85)
13 <sup>b,c</sup>	<b>Ru-9a</b>	0.0025	4	23 (12)

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (see SI). <sup>b</sup> Toluene (2 M). <sup>c</sup> Reaction performed at 40 °C.

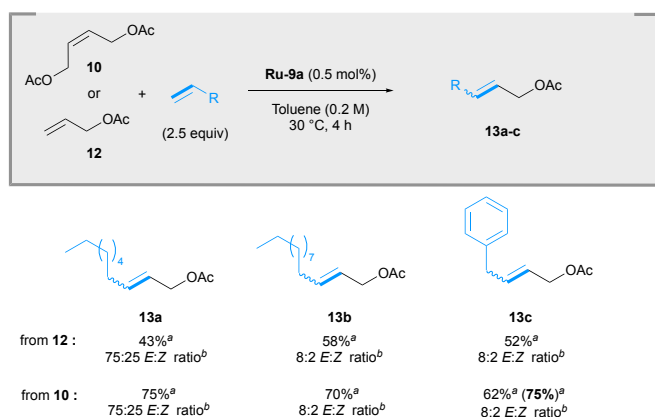
Having identified Blechert <sup>DIPP</sup>CAAC **Ru-9a** as the most efficient catalyst, we then investigated its performances in various olefin metathesis transformations at 0.1 to 0.5 mol%. In ring-closing metathesis (Scheme 2, a), full conversions and good to excellent yields (86-98%) were obtained for the formation of di- or tri-substituted cyclopentenes **2a,b,d,e**. Unfortunately, no reaction was obtained with the more challenging tetrasubstituted cyclopentenes **2c** and **2f**. To our delight, seven-membered rings were also formed in good yields (**2g,h,i** : 71-95%), while cyclic silanes **2j** and **2k** were obtained in low to moderate yields (17-38%). We also considered ring-closing enyne metathesis (RCEYM), in which <sup>DIPP</sup>CAAC **Ru-9a** showed good activity at 0.1-0.5 mol%, affording **4a,b** in 93-98% yield respectively (Scheme 2, b). However, lower conversions (26-30%) were observed for products **4c,d** despite the use of more drastic conditions.



**Scheme 2** Scope of RCM (a), RCEYM (b) and ROCM (c,d) catalyzed by Blechert-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> Reaction performed at 80 °C. <sup>d</sup> *E/Z* ratio were monitored by <sup>1</sup>H NMR analysis.

We next considered the ring-opening cross-metathesis (ROCM) of *endo*-norbornenes **5a,b** and *exo*-norbornenes **7a,b** with styrene which afforded the corresponding *cis*-cyclopentanes **6a,b** and *trans*-cyclopentanes **8a,b** in moderate to good yield (41-79%) and a 8:2 *E:Z* ratio (Scheme 2, c). In contrast, ROCM of *endo*-**5b** with allyl acetate gave the expected *cis*-cyclopentane **6c** in 87% yield and a similar 8:2 *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 2, d). Fortunately, the latter can be improved reaching 84% with 1 mol% catalyst loading. It is worth mentioning that all ROCM transformations required thermal activation (80 °C).

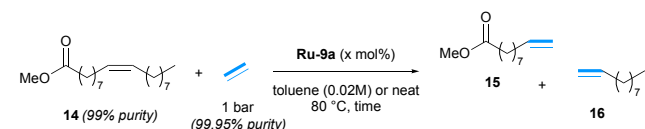
Shifting our investigation to cross-metathesis (CM) with various cross-olefin partners (Scheme 3), we found that the reaction between allyl acetate **12** and 1-nonene or 1-dodecene led to the expected linear alkenes **13a,b** in 43 and 58% isolated yield with a 75:25 and 8:2 *E:Z* ratio, respectively (Scheme 3). A similar 52% yield and *E:Z* ratio was 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 irrespectively of cross-olefin partners (62-75%).



**Scheme 3** Scope of CM catalyzed by Blechert-CAAC **Ru-9a** complex. <sup>a</sup> Isolated yield. <sup>b</sup> *E/Z* ratio were monitored by <sup>1</sup>H NMR analysis. <sup>c</sup> 1 mol% of catalyst was used.

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 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 hours at 80 °C in toluene (entry 1). Importantly, despite the use of low pressure of ethylene gas, no trace of self-metathesis products was detected by GC (see 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).

**Table 2** Low-pressure ethenolysis of methyloleate **14** catalyzed by Blechert-CAAC **Ru-9a** complex.



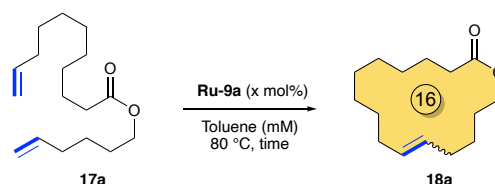
Entry	<b>Ru-9a</b> (mol%)	Condition	Time (h)	Yield (%) <sup>a</sup>	TON
1	0.1	Tol (0.02M)	3	97	970
2	0.01	Tol (0.02M)	3	7	-
3	0.01	neat	3	36	3600
4	0.001	neat	6	10	10000
5	0.0005	neat	6	8	16000
6 <sup>b</sup>	0.0005	neat	6	3	6000

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

In neat conditions, the reactivity was improved affording **15** and **16** in 36% yield (TON 3600, entry 3). Noteworthy, a large amount of methyl elaidate – the *E* isomer of the Ru starting material resulting from the reverse cross-metathesis – was also detected (see SI for details). Finally, the best TON (16000) 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 (entry 5 vs 6).

At last, we focused our attention toward macrocyclic ring-closing metathesis (macro-RCM) which is used in the production of macrocyclic odorant molecules frequently used in perfumery for their strong musk fragrance.<sup>43,44</sup>

**Table 3** Catalytic performances of Blechert-CAAC **Ru-9a** in macro-RCM of hex-5-enyl undec-10-enoate **17a** furnishing 16-membered Exaltolide precursor **18a**.

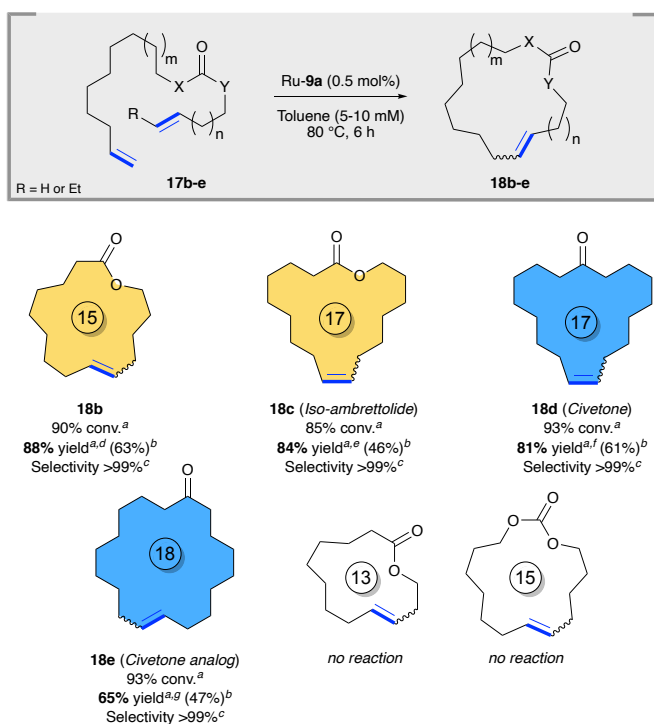


Entry	Catalyst loading (mol%)	Conc. (mM)	Time (h)	Conv. (Yield)% <sup>a,b</sup>	Purity (%) <sup>c</sup>
1	0.1	5	6	99 (87) <sup>d</sup>	>99
2	0.05	10	6	87 (87)	>99
3	0.01	10	6	55 (55)	>99
4	0.01	25	6	49 (45)	>99
5	0.01	50	6	50 (25)	>99
6	0.01	100	6	49 (25)	>99

<sup>a</sup> Conversions and yields were determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup> *E/Z* ratio: 7/3 (determined by GC analysis). <sup>c</sup> Determined by GC analysis (see SI for details). <sup>d</sup> Isolated yield after SiO<sub>2</sub> purification.



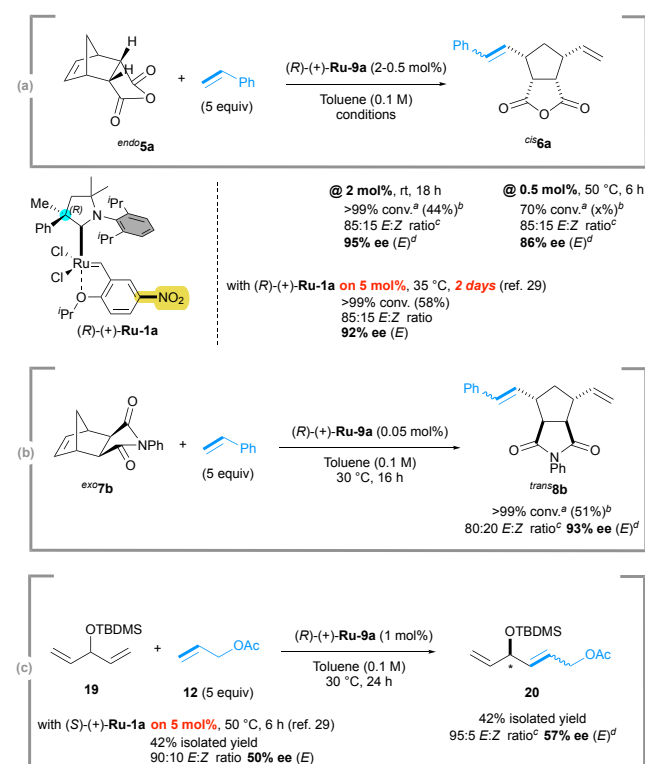
We first investigated the catalytic performance of Blechert <sup>DIPP</sup>CAAC **Ru-9a** (0.1 mol%, 5 mM in toluene, Table 3, entry 1) in the cyclisation of hex-5-enyl undec-10-enoate **17a**. In this case, the resulting 16-membered macrocycle **18a** – a precursor of Exaltolide<sup>45</sup> – was obtained in a *E/Z* mixture (7/3 ratio) and 87% isolated yield after silica gel purification. Noteworthy, **21b** showed an excellent purity (>99%) with no by-products (*i.e.* ring-contraction resulting from isomerisation of starting material)<sup>46–49</sup> detected by GC. Interestingly, a similar 87% yield and >99% purity was obtained at lower dilution (10 mM) and catalyst loading (0.05 mol%; entry 2). Attempts to decrease the latter to 0.01 mol% resulted in a significant drop of conversion/yield (55%; entry 3), meanwhile increasing reaction concentration (up to 100 mM) improve the yield significantly (entries 5–6).<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 to 10 mM, 0.5 mol% 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 4/6 *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%).



**Scheme 4** Scope of macrocyclic RCM of dienic substrates **17b-e** catalyzed by Blechert-CAAC **Ru-9a** complex leading to the corresponding macrocyclic **21b-e**. <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup> Isolated yields after SiO<sub>2</sub> purification. <sup>c</sup> Determined by GC analysis (see SI for details). <sup>d</sup> *E/Z* ratio: 4/6. <sup>e</sup> *E/Z* ratio: 8/2. <sup>f</sup> *E/Z* ratio: 7/3. <sup>g</sup> *E/Z* ratio: 7/3.

Here also, no trace of by-products was detected (purity >99%). Using the 17-membered macrocyclic ketone **18d** (namely *Civetone*),<sup>52–54</sup> up to 81% NMR yield was obtained (61% isolated yield) while its 18-membered analogue **18e**<sup>55</sup> was formed in lower yield (isolated: 47%; NMR: 65%). Of note, 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 SI for details). In the AROCM<sup>36,57–61</sup> between *endo*-norbornene **5a** and styrene (Scheme 5, a), the expected *cis*-cyclopentane **6a** was isolated in 44% yield and an excellent 95% ee using 2 mol% of (*R*)-(+)-**Ru-9a**. In contrast, larger catalyst loading (5 mol%), longer reaction time (48h) and higher temperature were required to reach similar nitro-<sup>DIPP</sup>CAAC (*R*)-(+)-**Ru-1a**. To our delight, the chiral Blechert catalyst remained highly performant even at lower catalyst loading (0.5 mol%), affording **6a** in 86% ee. More interestingly, (*R*)-(+)-**Ru-9a** catalysed the AROCM of *exo*-norbornene **7b** with only 0.05 mol% leading to the corresponding *trans*-cyclopentane **8b** in 51% yield and up to 93% ee (Scheme 5, b).



**Scheme 5** Asymmetric olefin metathesis catalyzed by optically pure Blechert-CAAC (*R*)-(+)-**Ru-9a** complex. <sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as 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 ESI for details).

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> (*R*)-(+)-**Ru-9a** (1 mol%) efficiently catalysed 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). It is worth mentioning that these results also surpass those of nitro-DIPP-CAAC (*S*)-(+)-**Ru-1a** 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. DIPP-CAAC **Ru-9a** featuring a quaternary centre 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 to 0.005 mol%). Moderate to good yields were obtained in various RCM, ROCM, CM and ethenolysis reactions. Blechert-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 to 0.05 mol%) in 93% and 57% ee, respectively. Future work will focus on the use of **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 on the ACS Publications website. NMR spectra of products, GC analyses, experimental procedures and details about DFT calculations are provided. X-ray crystallographic data (CIF) are available on the CCDC website.

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### Author Contributions

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 and reviewed by G. B., R. J. and M. M. The ESI was written by A. D.V., J. T. and S. C.-R.

## Notes

The authors declare no conflict of interest

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Ring-Closing - Ring-Closing Enyne - Macrocyclization - Ethenolysis - (Asymmetric) Cross - Ring-Opening-Cross Metathesis

