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Journal

ACS Catalysis, 13(9)

ISSN

2155-5435

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Publication Date

2023-05-05

DOI

10.1021/acscatal.3c01208

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

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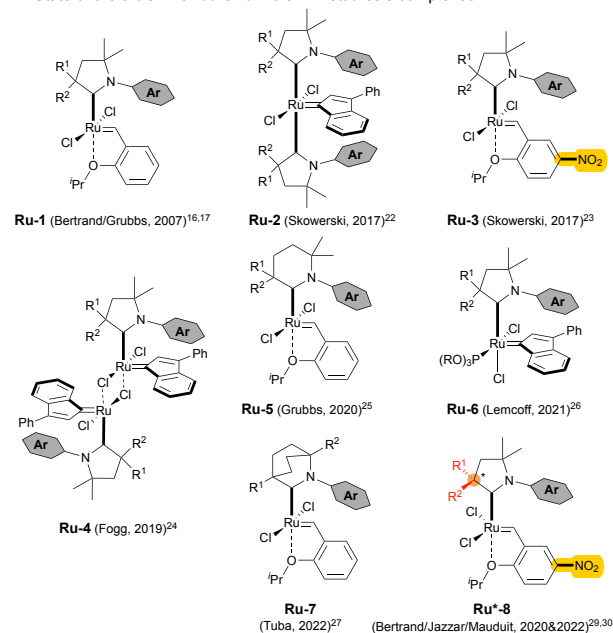
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ABSTRACT: The first Blechert-type ruthenium complexes containing cyclic(alkyl)(amino)carbene (CAAC) ligands are reported. These catalysts demonstrate remarkable thermal stability in solution and excellent catalytic performances at low catalytic loading (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.^{1,2} Thanks to the development of bench stable and well-defined ruthenium-arylidene complexes, this catalytic reaction is intensively used in polymer chemistry^{3,4} and fine chemistry⁵, and has also found applications in the valorisation of biomasses⁶ and the depolymerisation of polyethylene.⁷ Despite these remarkable achievements, the quest for more efficient Ru-complexes remains a very active research topic across academia and industry.^{1,2} A significant breakthrough was accomplished in 2007 when it was reported that the use of cyclic(alkyl)(amino)carbene (CAAC) ligands^{8–15} could provide very active catalysts for the ethenolysis of vegetable oils (0.0001 mol% **Ru-1**; TON up to 390.000).^{16,17} This peculiar behaviour, surpassing state-of-the art N-heterocyclic carbene (NHC) analogues,¹⁸ was shown to result from the improved stability of the corresponding Ru-methylidene intermediate; imparting resilience toward bimolecular decomposition.^{19–21} 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),^{22–28} including optically pure congeners **Ru*-8** recently developed by our groups.^{29–31} 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 NO₂ 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)

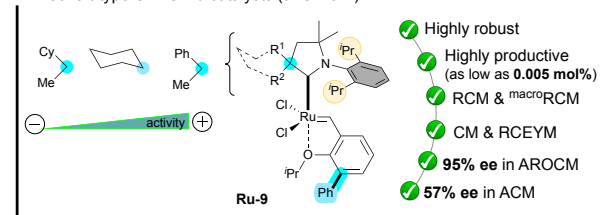
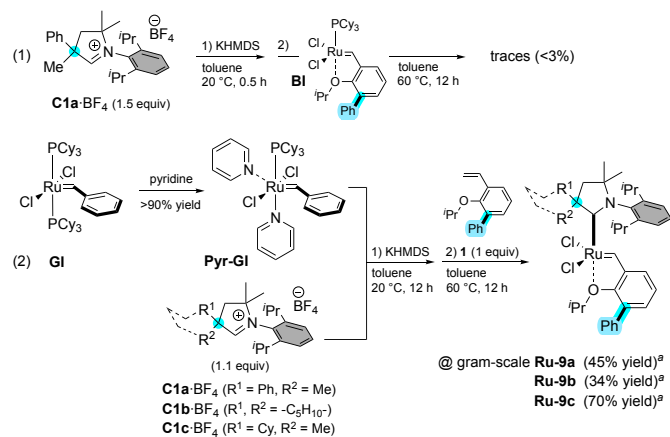


Figure 1 (A) Previously developed CAAC-Ru complexes. (B) Blechert-type CAAC-Ru complexes (this work).

Thus, CAAC-catalysts featuring a 2,6-diethylphenyl (DEP) *N*-substituent (^{DEP}CAAC) and a NO₂ 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**).²²⁻²⁴ 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 (^{DIPP}CAAC) which are readily accessible in good to excellent yield from 1st generation Hoveyda precursors (70-91%), ^{DEP}CAAC appears to be more challenging with yields (when reported) range from 15 to 45%.³² This problem extends to nitro-Grela derivatives which are isolated in poor to moderate yields (14 to 50%).³² Given importance of CAAC-Ru complexes for the industrial sector, we investigated the preparation of Blechert-type Ru-complexes **Ru-9** (Figure 1, B).^{33,34} Herein we disclose a new class of CAAC catalysts readily accessible from the commercially available Grubbs 1st generation complex **GI**³⁵ 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 ^{DIPP}CAAC **Ru-9** complexes starting from the phosphine-based Blechert precursor **BI** (Scheme 1, Eq. 1).³⁶ Unfortunately, in this case only trace amount of ^{DIPP}CAAC **Ru-9a** was observed (<3%) which we attributed to the relative instability of **BI** in solution. In contrast, deprotonation of **C1a**·BF₄ with potassium hexamethyldisilazide (KHMDs) in presence of **Pyr-GI**,¹⁶ afforded the expected ^{DIPP}CAAC **Ru-9a** in 45% yield (over two step) on gram-scale.



Scheme 1 Synthesis of Blechert-type CAAC **Ru-9a-c**. ^a Isolated yield over 2 steps.

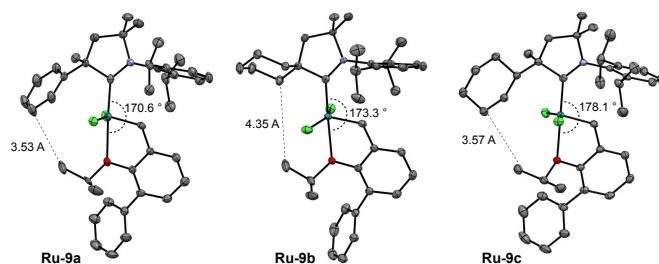


Figure 2 Solid-state structure of complexes **Ru-9a,b,c** from single crystal X-ray diffraction. Displacement ellipsoids are drawn at 30% probability. Hydrogen atoms have been omitted for clarity.

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).³⁷ Similarly, ^{DIPP}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).^{38,39} Blechert-type NHC-catalysts often lack stability in solution.³⁸ As shown in Figure 3, ^{DIPP}CAAC-Blechert **Ru-9a** demonstrated a remarkable stability in presence of air at 80 °C in toluene-*d*₈ (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).

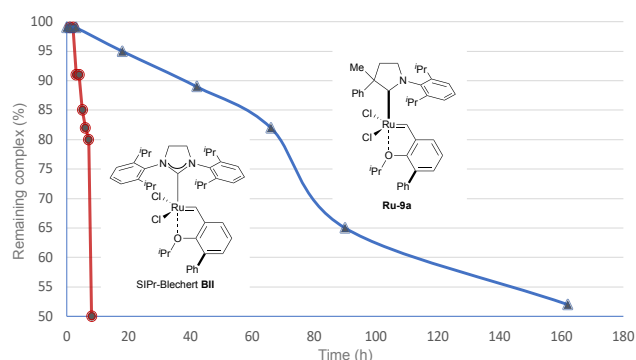
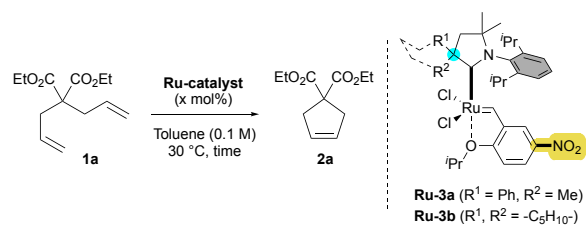


Figure 3 Thermal stability of ^{DIPP}CAAC-Blechert **Ru-9a** (blue) and SiPr-Blechert **BII** (red) in toluene-*d*₈ (0.1M) at 80 °C. Pre-catalyst decomposition was monitored by ¹H-NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

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 ^{DIPP}CAAC **Ru-9b,c** showed a poor reactivity (5-10% conv., entries 3,5, after 2h) comparable to that of nitro-Grela ^{DIPP}CAAC **Ru-3a,b** (entries 1-2).⁴⁰ 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).^{41,42}

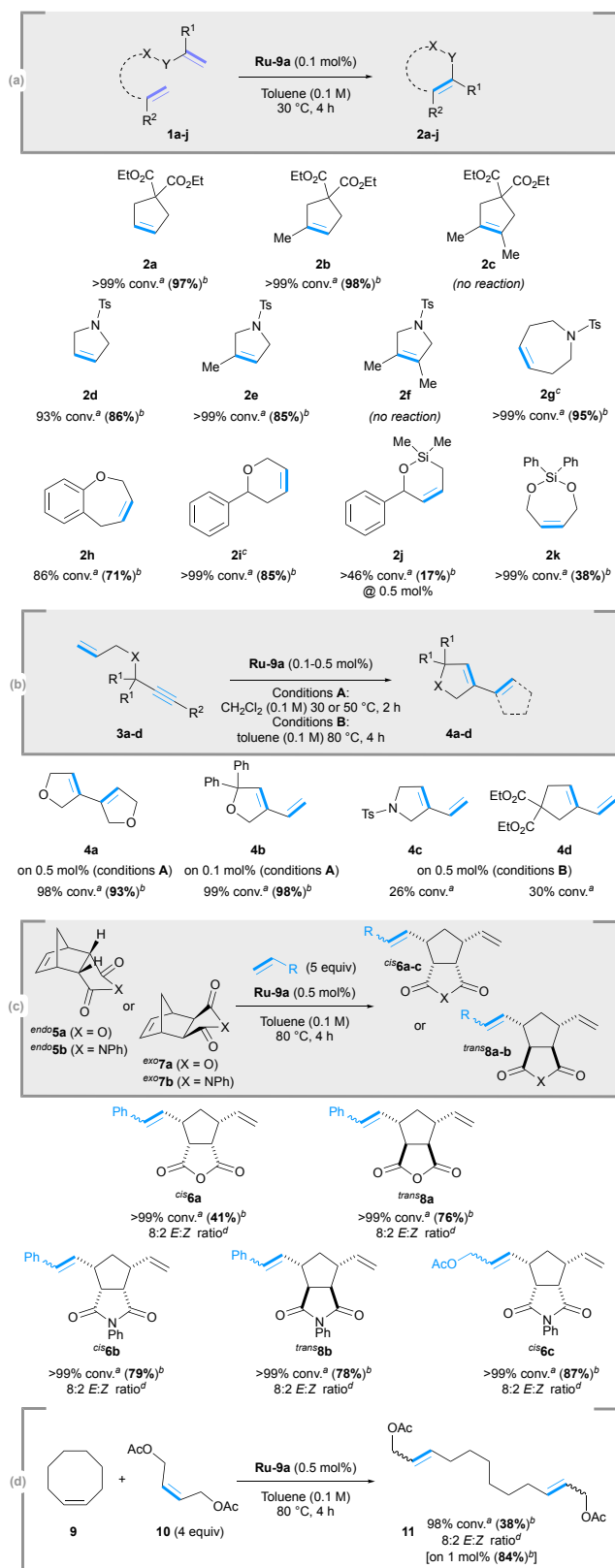
Table 1 Catalytic performances of Blechert-type CAAC **Ru-9a-c** in ring-closing metathesis of DEDAM **1a** and comparison with nitro-Grela congeners **Ru-3a,b** and SIPr-Blechert **BII**.



Entry	Catalyst	Mol%	Time (h)	Conv./Yield (%) ^a
1	Ru-3a	0.1	1	10 (ref. 21)
2	Ru-3b	0.1	1	5 (ref. 21)
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)
9	Ru-9a	0.05	4	99 (96)
10	Ru-9a	0.01	4	50 (48)
11 ^b	Ru-9a	0.01	4	96 (94)
12 ^{b,c}	Ru-9a	0.005	4	90 (85)
13 ^{b,c}	Ru-9a	0.0025	4	23 (12)

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

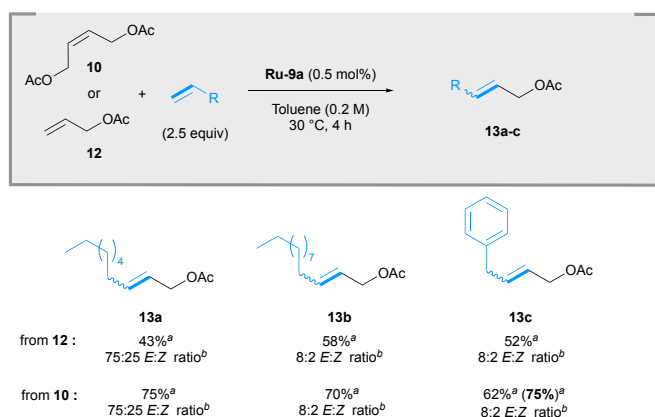
Having identified Blechert ^{DIPP}CAAC **Ru-9a** as the most efficient catalyst, we then investigated its performances in various olefin metathesis transformations at 0.1 to 0.5 mol%. In ring-closing metathesis (Scheme 2, a), full conversions and good to excellent yields (86-98%) were obtained for the 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 ^{DIPP}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. ^a Conversions were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. ^b NMR yield. ^c Reaction performed at 80 °C. ^d *E/Z* ratio were monitored by ¹H 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).

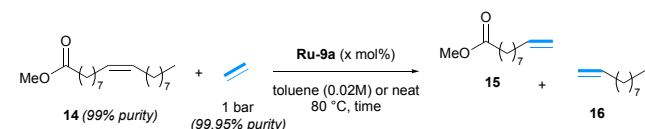
Shifting our investigation to cross-metathesis (CM) with various cross-olefin partners (Scheme 3), we found that the reaction between allyl acetate **12** and 1-nonene or 1-dodecene led to the expected linear alkenes **13a,b** in 43 and 58% isolated yield with a 75:25 and 8:2 *E:Z* ratio, respectively (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. ^a Isolated yield. ^b *E/Z* ratio were monitored by ¹H NMR analysis. ^c 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.¹⁷ 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.



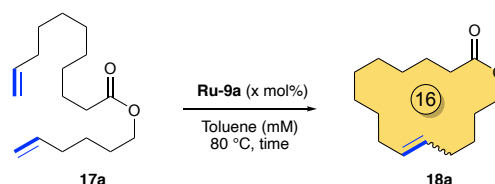
Entry	Ru-9a (mol%)	Condition	Time (h)	Yield (%) ^a	TON
1	0.1	Tol (0.02M)	3	97	970
2	0.01	Tol (0.02M)	3	7	-
3	0.01	neat	3	36	3600
4	0.001	neat	6	10	10000
5	0.0005	neat	6	8	16000
6 ^b	0.0005	neat	6	3	6000

^a Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (see SI). ^b 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 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.^{43,44}

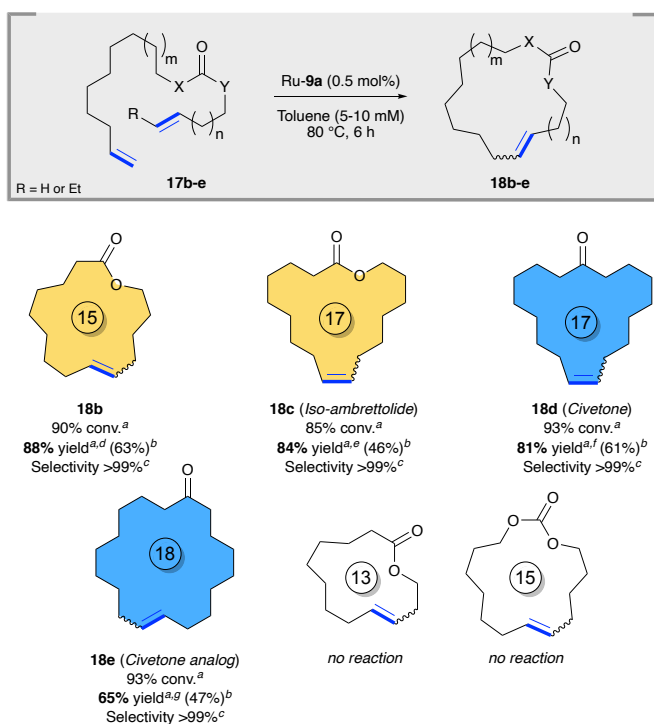
Table 3 Catalytic performances of Blechert-CAAC **Ru-9a** in macro-RCM of hex-5-enyl undec-10-enoate **17a** furnishing 16-membered Exaltolide precursor **18a**.



Entry	Catalyst loading (mol%)	Conc. (mM)	Time (h)	Conv. (Yield)% ^{a,b}	Purity (%) ^c
1	0.1	5	6	99 (87) ^d	>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

^a Conversions and yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. ^b *E/Z* ratio: 7/3 (determined by GC analysis). ^c Determined by GC analysis (see SI for details). ^d Isolated yield after SiO₂ purification.

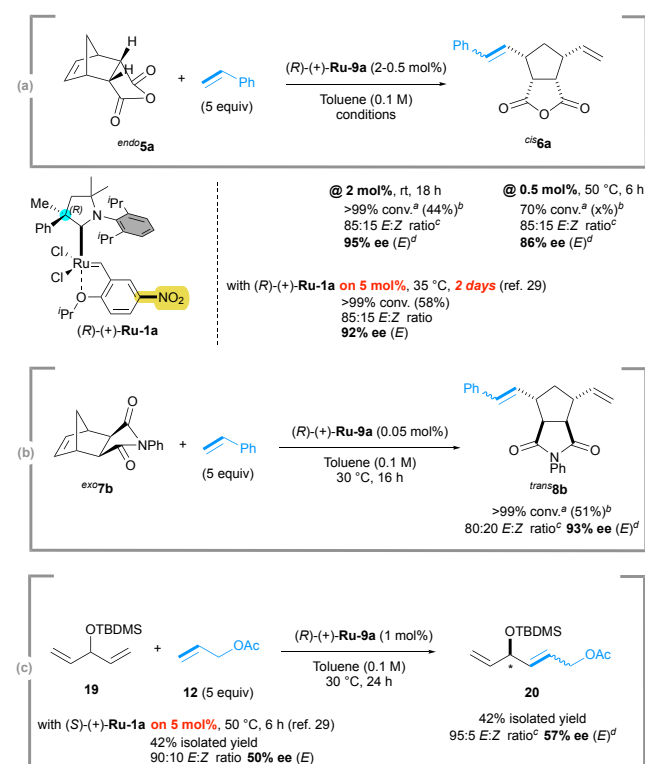
We first investigated the catalytic performance of Blechert ^{DIPP}CAAC **Ru-9a** (0.1 mol%, 5 mM in toluene, Table 3, entry 1) in the cyclisation of hex-5-enyl undec-10-enoate **17a**. In this case, the resulting 16-membered macrocycle **18a** – a precursor of Exaltolide⁴⁵ – was obtained in a *E/Z* 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)^{46–49} 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).⁵⁰ 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)⁵¹ 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**. ^a Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. ^b Isolated yields after SiO₂ purification. ^c Determined by GC analysis (see SI for details). ^d *E/Z* ratio: 4/6. ^e *E/Z* ratio: 8/2. ^f *E/Z* ratio: 7/3. ^g *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*),^{52–54} up to 81% NMR yield was obtained (61% isolated yield) while its 18-membered analogue **18e**⁵⁵ was formed in lower yield (isolated: 47%; NMR: 65%). Of note, Blechert ^{DIPP}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,^{29–31,56} we also considered the enantiopure variant of ^{DIPP}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^{36,57–61} 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-^{DIPP}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. ^a Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. ^b Isolated yields after SiO₂ purification. ^c Determined by GC-MS analysis. ^d 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,⁶² for which the best ee reported so far is <54%.⁴⁴ (*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).²⁹

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 conditions⁶³ as well as in relevant enantioselective metathesis transformations, more specifically toward the highly challenging asymmetric ring-closing enyne metathesis (ARCEYM).^{64,65}

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

ACKNOWLEDGMENT

We are grateful to the CNRS, the Ecole Nationale Supérieure de Chimie de Rennes and the University of California San Diego. This work was supported by the “prematuration program” of CNRS (grant to J.L.), the Agence Nationale de la Recherche (ANR-19-CE07-0017 ChiCAAC, grant to J.T.), “France Relance” (for fellowship to A.D.V.) and the U.S. Department of Energy, Office of Science, Basic Energy Sciences, Catalysis Science Program, under Award # DE-SC0009376. The generous gift of ruthenium complexes by Umicore AG & Co is gratefully acknowledged. We thank P. Jehan for HRMS analysis

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

