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Optically Pure C_1 -Symmetric Cyclic(alkyl)(amino)carbene (CAAC) Ruthenium-Complexes for Asymmetric Olefin Metathesis

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Dedicated to our friend and colleague Professor Pierre Dixneuf for his foremost contribution to ruthenium chemistry

Supporting Information Placeholder

ABSTRACT: An expedient access to the first optically pure ruthenium complexes containing C_1 -symmetric cyclic (alkyl)(amino)carbene (CAAC) ligands is reported. They demonstrate excellent catalytic performances in asymmetric olefin metathesis with high enantioselectivities (up to 92% ee). Preliminary mechanistic insights provided by DFT models highlight the origin of the enantioselectivity.

With the discovery of the 2nd generation Grubbs catalysts, N-heterocyclic carbenes (NHCs) have become inescapable ligands in olefin metathesis, in both academic and industrial research environments.¹ This popularity has in part been attributed to their remarkable aptitude in generating more stable, yet extremely reactive ruthenium catalysts. Owing to their unique and highly modular steric environment chiral variants of diaminocarbenes have attracted interests in the field.² Indeed, following reports by Grubbs and Hoveyda, a slew of Ru-complexes featuring chiral diaminocarbene ligands, have been used with varying successes in asymmetric ring-opening cross-metathesis (AROCM)³ and ring-closing metathesis (ARCM).⁴ In 2007,⁵ a new class of carbenes namely cyclic (alkyl)(amino) carbenes (CAACs)⁶ arose as a contender to NHCs's as ligands for olefin metathesis catalysts. Since then, CAACs have been shown to achieve over 340000 TON in ethenolysis processes meanwhile achieving remarkable catalytic performances in a number of other metathesis transformations (Figure 1,a).⁷ Interestingly, despite these achievements there is still no report dealing with CAAC ligands in asymmetric metathesis. In 2019, we demonstrated that providing the right steric environment, a steroid derived chiral CAAC-copper complex ^{Cholest}CAAC-CuCl could induce Asymmetric Conjugate Borylation (ACB).⁸

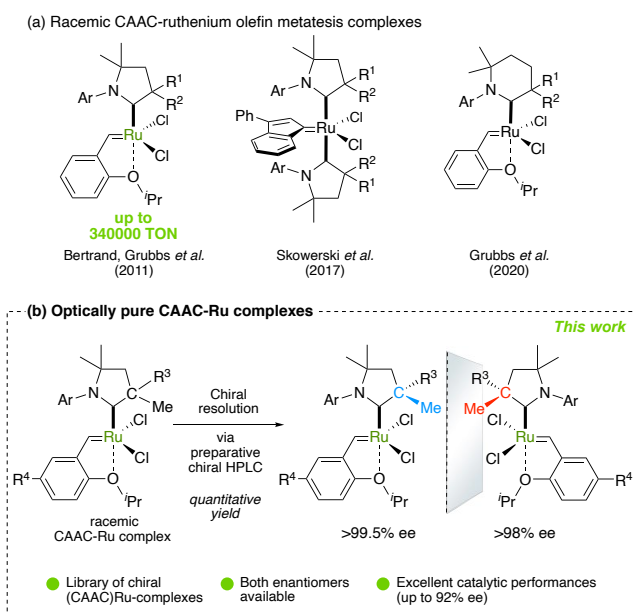
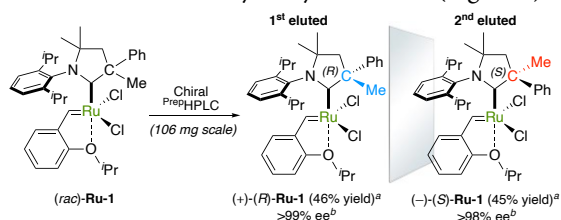


Figure 1. (a) Selected examples of known racemic CAAC-Ru olefin metathesis catalysts. (b) An expedient access to optically pure CAAC-Ru complexes (**this work**).

Encouraged by these results we set to demonstrate the potency of chiral CAAC-Ru complexes in asymmetric olefin metathesis.⁹ Despite the availability of the ligand, we reasoned that the ^{Cholest}CAAC or related chiral CAAC ligands derived from naturally abundant chiral building blocks would not provide the required structural modularity. The design of NHC chiral ligands is arguably plagued by tedious low yielding synthetic procedures, very often, resulting in the preparation of a single enantiomer (see Figure S1 in Supporting Information, SI). Eager to streamline the screening of chiral CAAC-

ruthenium catalysts, we envisaged using preparative high-performance liquid chromatographic resolution (^{Prep}HPLC), a time- and cost-effective technique extensively used in the pharmaceutical industry for bulk enantiomer resolution at the early stage of drug discovery.¹⁰ Consequently, we wish to report an expedient access to enantiomerically pure ruthenium metathesis catalysts containing *C₁*-symmetric CAAC ligands. Using ^{Prep}HPLC, optically pure (>99% ee) (*R*)- and (*S*)-CAAC-Ru complexes were obtained in almost quantitative yields (Figure 1,b). We further demonstrate that chiral CAACs yield active, but more importantly very selective catalysts for asymmetric ring-opening cross-metathesis (AROCM) reactions.

Capitalizing on the high stability of Hoveyda-Grubbs CAAC ruthenium complexes, we began our investigation with the readily accessible air-stable chiral (*rac*)-**Ru-1** catalyst (Table 1).⁵ Since to the best of our knowledge the chiral HPLC resolution of racemic Hoveyda-Grubbs ruthenium complexes had never been reported,¹¹ a range of chiral stationary phases was screened (see SI for details). Of the 10 columns evaluated using a mobile phase consisting of a heptane/isopropanol/dichloromethane mixture (70/10/20 ratio), only the amylose chiral stationary phases substituted with chloro-phenylcarbamate allowed for separations with good enantioselectivity and excellent resolution (Table 1). We selected Chiralpak IF[®] due to the shorter elution time, and good loading capacity, allowing for the antipodes separation of (*rac*)-**Ru-1** on a preparative scale (100 mg, 1 cm diameter column, flow-rate = 5 mL.min⁻¹) (Figure 2, a and b). Both (+)-**Ru-1** (first eluted) and (-)-**Ru-1** (second eluted) enantiomers were isolated in excellent yields (46 and 45%) and remarkable enantiomeric purities (>99% and >98% ee, respectively). As expected, Electronic Circular Dichroism (ECD), furnishing chiroptical properties of the Ru-complex, showed the mirror-image spectra for both enantiomers (+)-(*R*)-**Ru-1** and (-)-(*S*)-**Ru-1** (Figure 2,c). Finally, we unambiguously confirmed the absolute configuration of both enantiomers by X-ray diffraction (Figure 3).



Chiral Phase	(+)- Ru-1	<i>k</i> ₁	(-)- Ru-1	<i>k</i> ₂	α	Resolution
Chiralpak ID [®]	5.36	0.82	7.04	1.38	1.69	5.16
Chiralpak IE [®]	5.34	0.81	7.63	1.59	1.96	8.24
Chiralpak IF [®]	4.99	0.69	6.54	1.22	1.76	6.41
Chiralpak IG [®]	6.42	1.18	8.87	2.01	1.71	5.39

Table 1. Selective chiral stationary phase.

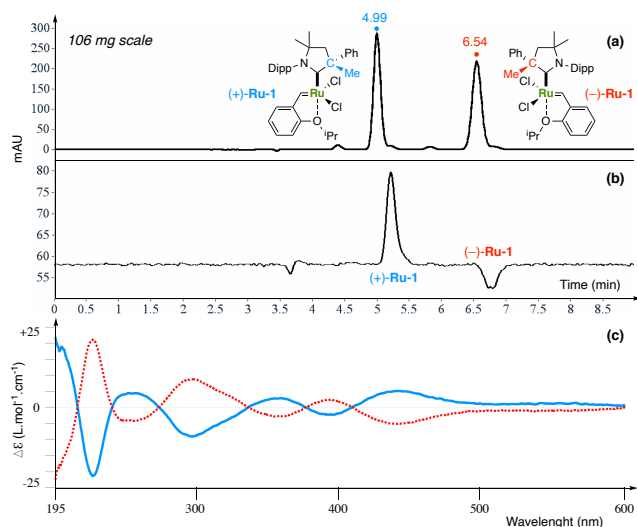


Figure 2. UV (a) and Circular Dichroism (b) chromatograms at 254 nm of (*rac*)-**Ru-1** from Chiralpak IF. (c) Electronic Circular Dichroism (ECD) spectra in acetonitrile of (+)-(*R*)-**Ru-1** (Blue) and (-)-(*S*)-**Ru-1** (Red).

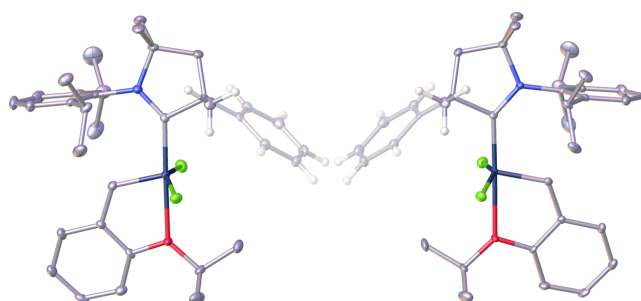
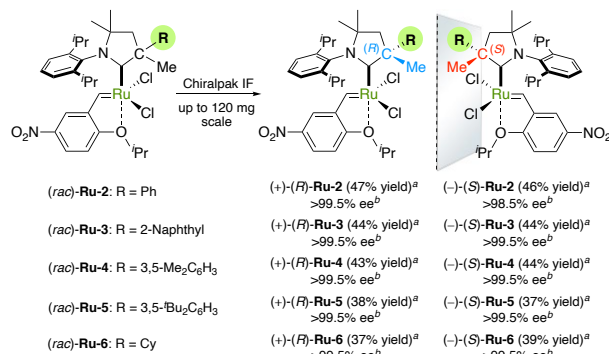


Figure 3. Solid-state structure of (+)-(*R*)-**Ru-1** (left) and (-)-(*S*)-**Ru-1** (right). Ellipsoids are drawn at 30% probability. Some hydrogens are omitted for clarity.

The latter displayed a positive ECD-active band at 220 nm ($\Delta\epsilon = +22$) and three negative ones at 250 ($\Delta\epsilon = -5$), 350 ($\Delta\epsilon = -2.5$) and 440 nm ($\Delta\epsilon = -5$), respectively. To confirm the efficiency of this chiral resolution protocol, we extended our method to Grela type CAAC-ruthenium metathesis complexes (**Ru-2-6**) (see SI, Scheme S1 for details).¹² To our delight, using the aforementioned conditions all complexes were

Scheme 1. Library of optically pure CAAC-ruthenium complexes.

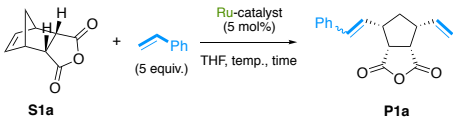


^a Isolated yield after preparative chiral resolution. ^b Determined by chiral-stationary phase HPLC analysis.

successfully resolved (up to 120 mg scale) and their respective (+)- and (-)-enantiomers isolated in good yields (from 37 to 47%) and excellent optical purities, ranging from >98.5 to >99.5% ee (Scheme 1).¹³ Here again, we unambiguously confirmed the absolute configuration of second eluted **Ru-2-6** complexes by X-ray diffraction study (see Figure S2; SI). It is worth mentioning that these complexes feature the *N*-aryl fragment of the CAAC ligand in the apical position, *syn* to the styrenyl-ether unit.⁵

Having obtained a small library of optically pure CAAC-ruthenium complexes, we investigated their catalytic performance in asymmetric olefin metathesis transformations.⁹ As a benchmark, we considered the asymmetric ring opening cross metathesis (AROCM) reaction of *meso*-norbornene derivative **S1a**.³ The reaction was performed in THF using 5 mol% of ruthenium catalyst and five equivalents of styrene (Table 2). Using (*S*)-**Ru-1** precatalyst at 50 °C, the reaction occurred slowly with a complete disappearance of the starting-material observed after 3 days (entry 1). Nevertheless, we were pleased to observe a significant enantioinduction (85% ee) for the expected metathesis product (*S,R*)-**P1a**, which was isolated in low 13% yield with a 80/20 *E/Z* ratio. With the (*S*)-**Ru-2** precatalyst, having an electron-withdrawing nitro group into the reactive arylidene ligand, the reaction was complete after 24 h (entry 2) and the (*S,R*)-**P1a** was isolated in 53% yield with a slight improvement of both *E/Z* ratio and enantioselectivity (85/15; 87% ee). Lowering the temperature to 35 °C enabled to improve the selectivity up to 90% ee, despite a prolonged reaction time (48 h, entry 3). Thanks to the preparative separation methodology, we could confirm that the opposite precatalyst enantiomer (*R*)-**Ru-2** catalyzed the formation of the (*R,S*)-**P1a** enantiomer with similar efficiencies (58%

Table 2. Evaluation of optically pure Ru-1-6 complexes in catalytic AROCM of norbornene S1a^a



Entry	Ru-cat (mol%)	T (°C) / Time	conv. ^b (yield) ^c (%)	<i>E/Z</i> ratio ^d	Ee (<i>E</i>)- P1a (%) ^e
1	(<i>S</i>)- 1 (5)	50/3d	99 (13)	80/20	85 (<i>S,R</i>)
2	(<i>S</i>)- 2 (5)	50/1d	99 (53)	85/15	87 (<i>S,R</i>)
3	(<i>S</i>)- 2 (5)	35/2d	99 (41)	85/15	90 (<i>S,R</i>) [§]
4	(<i>R</i>)- 2 (5)	35/2d	99 (58)	85/15	92 (<i>R,S</i>)
5	(<i>R</i>)- 3 (5)	35/2d	99 (55)	90/10	92 (<i>R,S</i>)
6	(<i>R</i>)- 4 (5)	35/2d	99 (49)	90/10	89 (<i>R,S</i>)
7	(<i>R</i>)- 5 (5)	50/5d	99 (18)	85/15	47 (<i>R,S</i>)
8	(<i>R</i>)- 6 (5)	35/5d	60 (45)	95/5	79 (<i>R,S</i>)

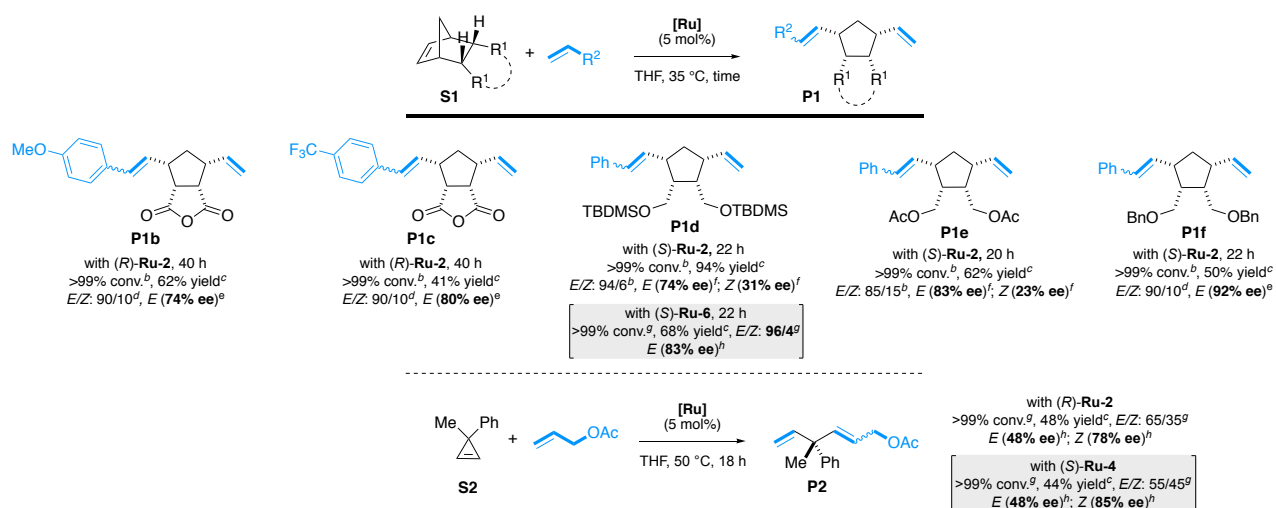
^aReaction conditions: [Ru] catalyst (5%), styrene (5 equiv.), THF (0.15 M). ^bConversions were monitored by ¹H NMR spectroscopy analysis. ^cIsolated yields after column chromatography. ^d*E/Z* ratio determined by SFC on the crude mixture. ^eee determined by SFC on a chiral stationary phase. ^fAbsolute configurations determined on the corresponding diol (see SI for details). [§]ee of (*Z*)-**P1a**: 17%.

yield; 92% ee; entry 4). Looking to improve the chiral transfer from the CAAC ligand, we next investigated precatalyst (*R*)-**Ru-3** featuring a bulkier 2-naphthyl substituent. Compared to (*R*)-**Ru-2**, similar catalytic performance and ee were obtained (92% ee, entry 5 vs 3-4). Neither 3,5-dimethylphenyl, 3,5-ditertbutylphenyl or cyclohexyl substitution at the stereogenic center led to higher chiral inductions (complexes (*R*)-**Ru-4-6**, entries 6-8). It is worth mentioning that an excellent 95/5 *E*-selectivity was achieved with (*R*)-**Ru-6** despite its lower catalytic activity (entry 8).¹⁴ We also evaluated the influence of the solvent (CH₂Cl₂, 2-MeTHF, benzene or toluene), however with no significant improvement was observed (see SI for details).

Following this optimization, we selected (*R*)-**Ru-2**, combining high productivity and decent asymmetric induction (*i.e.* >90% ee), to examine the scope of AROCM using functionalized-styrenes with norbornenes **S1d-f** and cyclopropene **S2**^{3b} (Scheme 2). To our delight, (*R*)-**Ru-2** catalyzed with similar efficiency the AROCM of **S1b,c** with methoxy and trifluoromethyl *para*-substituted styrenes. The resulting metathesis product **P1b-c** were isolated in 41-62% yield and 74-80% ee. With norbornenes **S1d-f**, (*R*)-**Ru-2** was again highly selective providing the corresponding metathesis products **P1d-f** in moderate to excellent isolated yields (50-94%) and good to excellent enantioselectivities (74, 83 and 92% ee, respectively). Of note, as reported in previous studies, a lower enantioselectivity was observed for each *Z*-stereoisomer (23-38% ee).¹⁵ Regarding the AROCM of cyclopropene **S2** with allyl acetate, both (*R*)-**Ru-2** and (*S*)-**Ru-4** gave the desired **P2b**, however in moderate yields and *E/Z* ratios. Nevertheless, good ee values were observed for *Z*-**P2b** (78-85% ee) while a moderate 48% ee was reached for the *E*-isomer.

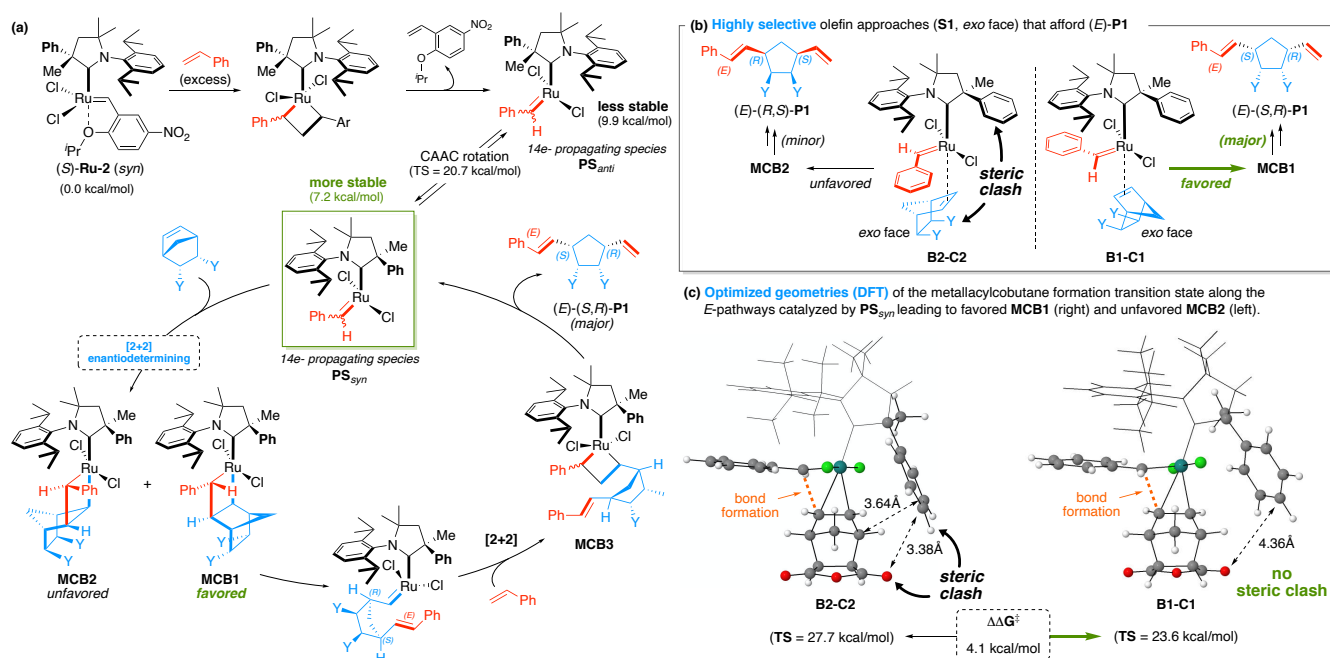
A preliminary mechanistic model for ROCM of norbornene **S1** and styrene is proposed in Scheme 3, based on DFT calculations.¹⁶ In agreement with previous studies,^{3a} the formation of the *p*-nitro styrenylether in the reaction media suggests a Ru-benzylidene **PS** as propagating species. Owing to the *C_r*-symmetry of CAAC ligands, we next considered two different geometries accessible via a metallacyclobutane with inversion at the Ru center.¹⁷ **PS_{syn}** in which the benzylidene unit is in apical position to the quaternary chiral center substituents (*syn*), and the **PS_{anti}** featuring the benzylidene in apical position to the *N*-Dipp moiety (*trans*). Using the more stable **PS_{syn}** (See SI for details), we envisaged the norbornene **S1** addition, providing the major (*E*)-**P1**, to be enantio- and diastereo-determining.^{3a} In agreement with literature precedents supporting the olefin coordination *trans* to the ancillary carbenic ligand,¹⁸ and norbornene reacting preferentially on its *exo* face, two metallacyclobutanes (MCB) were considered: **MCB1** leading to (*E*)-(*S,R*)-**P1** and **MCB2** affording the opposite enantiomer (*E*)-(*R,S*)-**P1**. In line with (*E*)-(*S,R*)-**P1** (table 2; entry 3), being unambiguously identified as the major enantiomer (see SI for details), our DFT model supports **MCB1** to be the privileged intermediate. In fact, in transition state **B1-C1**, leading to the formation of the metal

Scheme 2. Scope of AROCM catalyzed by optically pure Ru-2,4,6 complexes ^a



^a Reaction conditions: [Ru] catalyst (5 mol%), terminal olefin (5 equiv.), THF (0.1M). ^b Determined by ¹H NMR spectroscopy analysis. ^c Isolated yields after column chromatography. ^d Determined by SFC on the crude mixture. ^e Determined by SFC on a chiral stationary phase. ^f Determined on the corresponding diol by SFC on a chiral stationary phase. ^g Determined by GC-MS. ^h Determined on the corresponding alcohol by SFC on a chiral stationary phase.

Scheme 3. (a) Proposed mechanism, supported by DFT calculations, for AROCM of norbornenes S1 and styrene catalyzed by (*S*)-Ru-2 and related olefin approaches providing (*E*)-P1 (b) (c, see SI for details).

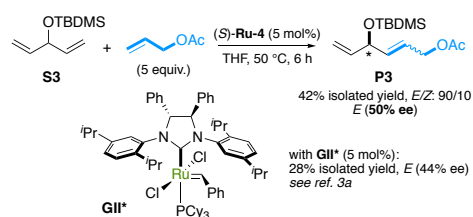


lacyclobutane MCB1, the quaternary chiral center substituents and the norbornene substrate lie quite far one from each other; at the contrary, transition state B2-C2 forming intermediate MCB2 suffers from the steric clash between the two moieties (see short distances in Scheme 3c). This model is in agreement with the lower enantioinduction observed in the bulkier (*R*)-Ru-5 (table 2; entry 7), and supports the higher selectivity of (*S*)-Ru-6 versus (*S*)-Ru-2 in the formation of (*E*)-P1d (83% vs. 74% ee, scheme 2).

To complete our study, we finally examined the challenging asymmetric cross-metathesis (ACM). As disclosed in Scheme 4, (*S*)-Ru-4 afforded P3 in 42% isolated yield and up

to 50% ee. While this result is preliminary, it already surpasses state of art selectivity obtained with chiral diaminocarbene ligand (GII* precatalyst, 44% ee).^{3a,19}

Scheme 4. Preliminary result in asymmetric cross-metathesis.



In summary, an expedient access to a range of optically pure, well-defined, ruthenium complexes containing chiral CAAC ligands was developed. It relies on an efficient resolution of their racemic mixture via chiral ^{PREP}HPLC on chiral-stationary phase. This process allowed for the isolation of air-stable (+) and (-)-enantiomers in good to nearly quantitative yields and excellent optical purity (ranging from >98 to >99.5%). Using these catalysts, excellent performances were observed in asymmetric ring-opening cross-metathesis (AROCM) with high enantioselectivities (up to 92% ee). Moreover, a promising 50% ee was reached in the more challenging asymmetric cross-metathesis (ACM), one of the highest selectivity reported so far. This novel approach paves the way for the development of more sophisticated CAAC transition-metal complexes and should create new opportunities in asymmetric catalysis.

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 X-ray crystallographic data (PDF), X-ray crystallographic data (CIF)

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REFERENCES

(1) (a) For a recent book on NHCs, see: Díez-González, S. *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, Royal Society of Chemistry: Cambridge, **2016**. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485–496. (c) For a review dealing with NHC/TM in catalysis, see: Gonzalez, S. D.; Marion, N.; Nolan, S. P. N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chem. Rev.* **2009**, *109*, 3612–3676. For review dealing with NHC/Ru in olefin metathesis. (d) Nolan, S.P.; Clavier, H. Chemoselective olefin metathesis transformations mediated by ruthenium complexes. *Chem. Soc. Rev.* **2010**, *39*, 3305–3316. (e) Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts, *Chem. Rev.* **2010**, *110*, 1746–1787. (f) Ogba, O. M.; Warner, N. C.; O’Leary, D. J.; Grubbs, R. H. Recent advances in ruthenium-based olefin metathesis. *Chem. Soc. Rev.* **2018**, *47*, 4510–4544. (2) For reviews on chiral NHC in catalysis, see: (a) Wang, F.; Liu, L.-J.; Wang, W.; Li, S.; Shi, M. Chiral NHC-Metal-Based Asymmetric Catalysis. *Coord. Chem. Rev.* **2012**, *256*, 804–853. (b) Janssen-Müller, D.; Schlep-phorst, C.; Glorius, F. Privileged Chiral N-Heterocyclic Carbene Ligands for Asymmetric Transition-Metal Catalysis. *Chem. Soc. Rev.*, **2017**, *46*, 4845–4854. (c) Zhao, M.; Zhang, Y.-T.; Chen, J.; Zhou, L. Enantioselective Reactions Catalyzed by N-Heterocyclic Carbenes. *Asian J. Org. Chem.* **2018**, *7*, 54–69. (d) Montgomery, T. P.; Johns, A. M.; Grubbs, R. H. Recent Advancements in Stereoselective Olefin Metathesis Using Ruthenium Catalysts. *Catalysts* **2017**, *7*, 87. (e) Hoveyda, A. H. Evolution of Catalytic Stereoselective Olefin Metathesis: From Ancillary Transformation to Purveyor of Stereochemical Identity. *J. Org. Chem.* **2014**, *79*, 4763–4792.

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Notes

The authors declare no competing financial interests.

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(3) Selected examples of AROCM: (a) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. Highly Active Chiral Ruthenium Catalyst for Asymmetric Cross-Metathesis and Ring-Opening Cross-Metathesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7591–7595. (b) Giudici, R. E.; Hoveyda, A. H. Directed Catalytic Asymmetric Olefin Metathesis. Selectivity Control by Enoate and Ynoate Groups in Ru-Catalyzed Asymmetric Ring-Opening/ Cross-Metathesis. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825. (c) Kannenberg, A.; Rost, D.; Eibauer, S.; Tiede, S.; Blechert, S. A Novel Ligand for the Enantioselective Ruthenium-Catalyzed Olefin Metathesis. *Angew. Chem., Int. Ed.* **2011**, *50*, 3299–3302. (d) Hartung, J.; Dornan, P. K.; Grubbs, R. H. Enantioselective Olefin Metathesis with Cyclometalated Ruthenium Complexes. *J. Am. Chem. Soc.* **2014**, *136*, 13029–13037. (e) Paradiso, V.; Bertolasi, V.; Costabile, C.; Grisi, F. Ruthenium olefin metathesis catalysts featuring unsymmetrical N-heterocyclic carbenes *Dalton Trans.*, **2016**, *45*, 561–571. (f) Rais, E.; Flörke, U.; Wilhelm, R. Reactivity of Grubbs-Hoveyda II Complexes Including Extended N-Heterocyclic Carbenes with a Bicyclic Camphor-Based Framework. *Synthesis*. **2017**, *49*, 2852–2864. (4) Selected examples of ARCM: (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. Chiral Ru-Based Complexes for Asymmetric Olefin Metathesis: Enhancement of Catalyst Activity through Steric and Electronic Modifications. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508. (b) Fournier, P.-A.; Savoie, J.; Stenne, B.; Bédard, M.; Grandbois, A.; Collins, S. K. Mechanistically Inspired Catalysts for Enantioselective Desymmetrizations by Olefin Metathesis. *Chem. Eur. J.* **2008**, *14*,

- 8690–8695. (c) Savoie, J.; Stenne, B.; Collins, S. K. Improved Chiral Olefin Metathesis Catalysts: Increasing the Thermal and Solution Stability via Modification of a *C₂*-Symmetrical N-Heterocyclic Carbene Ligand. *Adv. Synth. Catal.* **2009**, *351*, 1826–1832. (d) Paradiso, V.; Bertolasi, V.; Grisi, F. Novel Olefin Metathesis Ruthenium Catalysts Bearing Backbone-Substituted Unsymmetrical NHC Ligands. *Organometallics* **2014**, *33*, 5932–5935. (e) Paradiso, V.; Menta, S.; Pierini, M.; Della Sala, G.; Ciogli, A.; Grisi, F. Enantiopure C₁-symmetric N-Heterocyclic Carbene Ligands from Desymmetrized meso-1,2-Diphenylethylenediamine: Application in Ruthenium-Catalyzed Olefin Metathesis. *Catalysts* **2016**, *6*, 177. (f) Grisi, F.; Paradiso, V.; Caruso, T.; Bertolasi, V.; Grella, K.; Dąbrowski, M.; Costabile, C. Expanding the Family of Hoveyda–Grubbs Catalysts Containing Unsymmetrical NHC Ligands. *Organometallics* **2017**, *36*, 3692–3708. (g) Karras, M.; Dąbrowski, M.; Pohl, R.; Rybáček, J.; Vacek, J.; Bednářová, L.; Grella, K.; Starý, I.; Stará, I. G.; Schmidt, B. Helicenes as Chirality-Inducing Groups in Transition-Metal Catalysis: The First Helically Chiral Olefin Metathesis Catalyst. *Chem. Eur. J.* **2018**, *24*, 10994–10998.
- (5) Anderson, D. R.; Lavallo, V.; O’Leary, D. J.; Bertrand, G.; Grubbs, R. H. Synthesis and Reactivity of Olefin Metathesis Catalysts Bearing Cyclic (Alkyl)(Amino)Carbenes. *Angew. Chem., Int. Ed.* **2007**, *46*, 7262–7265.
- (6) (a) Lavallo, V.; Canac, Y.; Prašang, C.; Donnadiu, B.; Bertrand, G. Stable Cyclic (Alkyl)(Amino)Carbenes as Rigid or Flexible, Bulky, Electron-rich Ligands for Transition-Metal Catalysts: a Quaternary Carbon Atom Makes the Difference. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705–5709. (b) Soleilhavoup, M.; Bertrand, G. Cyclic (Alkyl)(Amino)Carbenes (CAACs): Stable Carbenes on the Rise; *Acc. Chem. Res.* **2015**, *48*, 256–266. (c) Melaimi, M.; Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (alkyl)(amino)carbenes (caacs): recent developments. *Angew. Chem. Int. Ed.* **2017**, *56*, 10046–10068. (d) Paul, U. S. D.; Radius, U. What wanzlick did not dare to dream: cyclic (alkyl)(amino)carbenes (caacs) as new key players in transition-metal chemistry. *Eur. J. Inorg. Chem.* **2017**, 3362–3375. (e) Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (alkyl)- and (aryl)-(amino)carbene coinage metal complexes and their applications. *Chem. Rev.* **2020**, *120*, 4141–4168.
- (7) Selected examples: (a) Marx, V. M.; Sullivan, A. H.; Melaimi, M.; Virgil, S. C.; Keitz, B. K.; Weinberger, D. S.; Bertrand, G.; Grubbs, R. H. Cyclic Alkyl Amino Carbene (CAAC) Ruthenium Complexes as Remarkably Active Catalysts for Ethanolysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1919–1923. (b) Zhang, J.; Song, S.; Wang, X.; Jiao, J.; Shi, M. Ruthenium-Catalyzed Olefin Metathesis Accelerated by the Steric Effect of the Backbone Substituent in Cyclic (Alkyl)(Amino) Carbenes. *Chem. Commun.* **2013**, *49*, 9491–9493. (c) Gawin, R.; Kozakiewicz, A.; Guńka, P. A.; Dąbrowski, P.; Skowerski, K. Bis(Cyclic Alkyl Amino Carbene) Ruthenium Complexes: A Versatile, Highly Efficient Tool for Olefin Metathesis. *Angew. Chem., Int. Ed.* **2017**, *56*, 981–986. (d) Gawin, R.; Tracz, A.; Chwalba, M.; Kozakiewicz, A.; Trzaskowski, B.; Skowerski, K. Cyclic Alkyl Amino Ruthenium Complexes Efficient Catalysts for Macrocyclization and Acrylonitrile Cross Metathesis. *ACS Catal.* **2017**, *7*, 5443–5449. (e) Nascimento, D. L.; Gawin, A.; Gawin, R.; Gunka, P. A.; Zachara, J.; Skowerski, K.; Fogg, D. E. Integrating Activity with Accessibility in Olefin Metathesis: An Unprecedentedly Reactive Ruthenium-Indenylidene Catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 10626–10631. (f) Samkian, A. E.; Xu, Y.; Virgil, S. C.; Yoon, K.-Y.; Grubbs, R. H. Synthesis and Activity of Six-Membered Cyclic Alkyl Amino Carbene–Ruthenium Olefin Metathesis Catalysts. *Organometallics* **2020**, *39*, 495–499.
- (8) Pichon, D.; Soleilhavoup, M.; Morvan, J.; Junor, G.; Vives, T.; Crévisy, C.; Campagne, J.-M.; Mauduit, M.; Jazzar, R.; Bertrand, G. The Debut of Cyclic (Alkyl)(Amino)Carbenes (CAACs) in Enantioselective Catalysis. *Chem. Sci.* **2019**, *10*, 7807–7811.
- (9) Selected book chapter on Ru-AOM, see: Stenne, B.; Collins, S. K. Enantioselective Olefin Metathesis in Olefin Metathesis: Theory and Practice (Ed.: K. Grella), Wiley-VCH, Weinheim (Germany), 2014.
- (10) Okamoto, Y.; Ikai, T. Chiral HPLC for efficient resolution of enantiomers. *Chem. Soc. Rev.* **2008**, *37*, 2593–2608.
- (11) The chiral HPLC resolution of chiral transition-metal complexes was scarcely reported, see: (a) Norel, L.; Rudolph, M.; Vanthuyne, N.; Williams, J. A. G.; Lescop, C.; Roussel, C.; Autschbach, J.; Crassous, J.; R. Réau, R. Metallahelicenes: Easily Accessible Helicene Derivatives with Large and Tunable Chiroptical Properties. *Angew. Chem. Int. Ed.* **2010**, *49*, 99–102. (b) Hellou, N.; Jahier-Diallo, C.; Baslé, O.; Srebro-Hooper, M.; Toupet, L.; Roisnel, T.; Caytan, E.; Roussel, C.; Vanthuyne, N.; Autschbach, J.; Mauduit, M.; Crassous, J. Electronic and Chiroptical Properties of Chiral Cycloiridiated Complexes Bearing Helicenic NHC Ligands. *Chem. Commun.* **2016**, *52*, 9243–9246. (c) Hellou, N.; Srebro-Hooper, M.; Favereau, L.; Zinna, F.; Caytan, E.; Toupet, L.; Dorcet, V.; Jean, M.; Vanthuyne, N.; Williams, J. A. G.; Di Bari, L.; Autschbach, J.; Crassous, J. Enantiopure Cycloiridiated Complexes Bearing a Pentahelicenic N-Heterocyclic Carbene and Displaying Long-Lived Circularly Polarized Phosphorescence. *Angew. Chem. Int. Ed.* **2017**, *56*, 8236–8239. (d) Kong, L.; Morvan, J.; Pichon, D.; Jean, M.; Albalat, M.; Vives, T.; Colombel-Rouen, S.; Giorgi, M.; Dorcet, V.; Roisnel, T.; Crévisy, C.; Nuel, D.; Nava, P.; Humbel, S.; Vanthuyne, N.; Mauduit, M.; Clavier, H. From Prochiral N-Heterocyclic Carbenes to Optically Pure Metal Complexes: New Opportunities in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 93–98.
- (12) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grella, K. Nitro-Substituted Hoveyda–Grubbs Ruthenium Carbenes: Enhancement of Catalyst Activity through Electronic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.
- (13) The synthesis of Ru-2 was previously reported but in a lower 13% isolated yield, see ref. 5d.
- (14) Blechert and co-workers reported up to >30:1 *E*-selectivity with chiral monodentate NHC-Ru precatalysts, see: Tiede, S.; Berger, A.; Schlesiger, D.; Rost, D.; Lühl, A.; Blechert, S. Highly Active Chiral Ruthenium-Based Metathesis Catalysts through a Monosubstitution in the N-Heterocyclic Carbene. *Angew. Chem. Int. Ed.* **2010**, *49*, 3972–3975.
- (15) A significant lower enantioselectivity for *Z*-products was already reported by Grubbs and co-workers; see ref. 3a and 14.
- (16) A full DFT study has been disclosed in the SI and involves: i) the initiation pathway for the formation of the Ru-benzylidene propagating species, ii) the possible pathways for the interconversion of the two 14e⁻ rotamers and iii) energy profiles for AROCM of S1 catalyzed by (**S**)-Ru-2.
- (17) (a) Bornand, M.; Chen, P. Mechanism-Based Design of a ROMP Catalyst for Sequence-Selective Copolymerization. *Angew. Chem., Int. Ed.* **2005**, *44*, 7909–7911. (b) Khan, R. K. M.; Zhugralin, A. R.; Torke, S.; O’Brien, R. V.; Lombardi, P. J.; Hoveyda, A. H. Synthesis, Isolation, Characterization, and Reactivity of High-Energy Stereogenic-at-Ru Carbenes: Stereochemical Inversion through Olefin Metathesis and Other Pathways. *J. Am. Chem. Soc.* **2012**, *134*, 12438–12441.
- (18) (a) Tallarico, J. A.; Bonitatebus, P. J.; Snapper, M. L. Ring-Opening Metathesis. A Ruthenium Catalyst Caught in the Act. *J. Am. Chem. Soc.* **1997**, *119*, 7157–7158. (b) Cavallo, L. Mechanism of Ruthenium-Catalyzed Olefin Metathesis Reactions from a Theoretical Perspective. *J. Am. Chem. Soc.* **2002**, *124*, 8965–8973. (c) Costabile, C.; Cavallo, L. Origin of Enantioselectivity in the Asymmetric Ru-Catalyzed Metathesis of Olefins. *J. Am. Chem. Soc.* **2004**, *126*, 9592–9600. (d) Adlhart, C.; Chen, P. Mechanism and Activity of Ruthenium Olefin Metathesis Catalysts: The Role of Ligands and Substrates from a Theoretical Perspective. *J. Am. Chem. Soc.* **2004**, *126*, 3496–3510. (e) Romero, P. E.; Piers, W. E. Direct Observation of a 14-Electron Ruthenacyclobutane Relevant to Olefin Metathesis. *J. Am. Chem. Soc.* **2005**, *127*, 5032–5033. (f) Nascimento, D. L.; Fogg, D. E. Origin of the Breakthrough Productivity of Ruthenium-Cyclic Alkyl Amino Carbene Catalysts in Olefin Metathesis. *J. Am. Chem. Soc.* **2019**, *141*, 19236–19240. (g) Ton, S. J.; Fogg, D. E. Origin of the Breakthrough Productivity of Ruthenium-Cyclic Alkyl Amino Carbene Catalysts in Olefin Metathesis. *ACS Catal.* **2019**, *9*, 11329–11334. (g) Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. Key processes in ruthenium-catalyzed olefin metathesis. *Chem. Commun.* **2014**, *50*, 10355–10375. (h) Sanford, M. S.; Love, J. A.; Grubbs, R. H. Mechanism and Activity of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (19) Note that the *Z*-selective ACM variant (35% yield, 50% ee) has been reported by Grubbs *et al.* using a cyclometalated NHC-ruthenium complexes; see ref. 3d.

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