JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Article

Merging Central and Axial Chirality in Cyclic(alkyl)(amino)carbenes: The Keystone for High Enantioselectivities in Ru-Catalyzed Asymmetric Olefin Metathesis

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Cite This: JACS Au 2025, 5, 5170−5183

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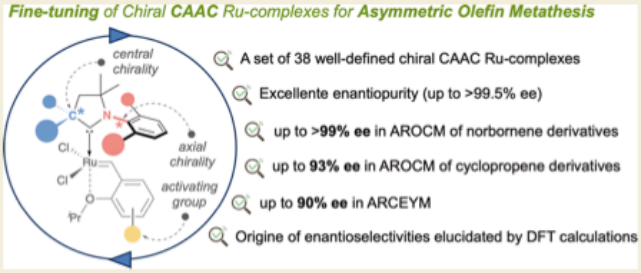
ABSTRACT: A series of 38 chiral ruthenium complexes containing cyclic(alkyl)(amino)carbene (CAAC) ligands with axial C−N chirality have been developed. By merging axial and central chirality, very high enantioselectivity (up to >99% ee) as well as good to high *E*-selectivity (up to 98%) were achieved in the asymmetric ring-opening cross-metathesis (AROCM) of various norbornene and cyclopropene derivatives. Furthermore, these catalysts are efficient in challenging asymmetric ring-closing ene-yne metathesis (ARCEYM), providing valuable enantioenriched building blocks (up to 90% ee). Mechanistic insights from density functional theory (DFT) calculations highlight the crucial role of axial chirality in CAAC ligands in governing both enantio- and diastereo-selectivity in the metathesis reaction.



KEYWORDS: *asymmetric catalysis, olefin metathesis, ruthenium, CAAC, ligand design, DFT calculation*

INTRODUCTION

Since the first successful application of chiral *N*-Heterocyclic carbenes (NHC) in transition-metal (TM) asymmetric catalysis by Burgess and co-workers in 2001,[1] this class of ancillary ligands[2] has gained increasing popularity, as witnessed by the extensive variety of chiral NHCs developed so far.[3] Thanks to their modularity and ease of access, many strategies for asymmetric induction have been investigated, from central[4] to helicenic chirality,[5] with numerous catalytic transformations displaying high enantioselectivity (>90% ee).[3] While chiral mono- or bidentate diamino-carbenes (DACs) have been intensively studied (Figure 1A), cyclic(alkyl)(amino)carbene (CAAC) ligands discovered in 2005 by Bertrand and colleagues,[6] still remain comparatively underexplored (Figure 1A). CAACs, owing to the presence of an α-quaternary carbon adjacent to the carbene center, exhibit high ambiphilic electronic properties (e.g., both strong σ-donors and strong π-acceptors), which explains the remarkable robustness of their organometallic complexes.[7] When the α-quaternary carbon is stereogenic, this scaffold creates a chiral environment in close proximity to the carbene−metal bond, making CAACs promising candidates for transition-metal asymmetric catalysis. In 2019, our groups reported the first asymmetric application (a copper-catalyzed asymmetric conjugate borylation: 55% ee) for this class of ligands by capitalizing on a CAAC motif derived from cholestanone (**Cu1**, Figure 1B).[8] To streamline the preparation of a library of chiral CAACs complexes, we devised an alternative strategy involving preparative chiral HPLC resolution of racemic TM-complexes.[9] An approach that also offers the advantage of accessing both enantiomers with high enantiomeric purity (>98% ee) in one single method. Successfully applied to well-known, robust, and commercially available CAAC-ruthenium complexes,[10] the methodology provided access to (^{Chi}CAAC)Ru-complexes (*R*)-**Ru1** and (*S*)-**Ru1** in nearly quantitative yields and excellent enantiomeric purity (up to >99.5% ee) (Figure 1C).[11] The latter demonstrated high efficiency in asymmetric ring-opening cross-metathesis (AROCM)[12,13] affording *cis*-cyclopentanes **A** with up to 92% ee, and up to 50% ee in the highly sought-after asymmetric cross-metathesis (ACM).[14] To expand the scope of AROCM to less reactive *exo*-norbornene derivatives,[15] we also developed (^{Chi}CAAC)Ru-complexes **Ru2** and **Ru3** incorporating the less bulky *N*-DEP (DiEthylPhenyl) substituent or Blechert's styrenylether ligand, respectively (Figure 1C). Interestingly, while (*R*)-**Ru2** gave moderate ees

Received: August 26, 2025
Revised: September 22, 2025
Accepted: September 23, 2025
Published: October 13, 2025

https://doi.org/10.1021/jacsau.5c01098
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