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Communication

Efficient *Z*-Selective Olefin-Acrylamide Cross-Metathesis Enabled by Sterically Demanding Cyclometalated Ruthenium Catalysts

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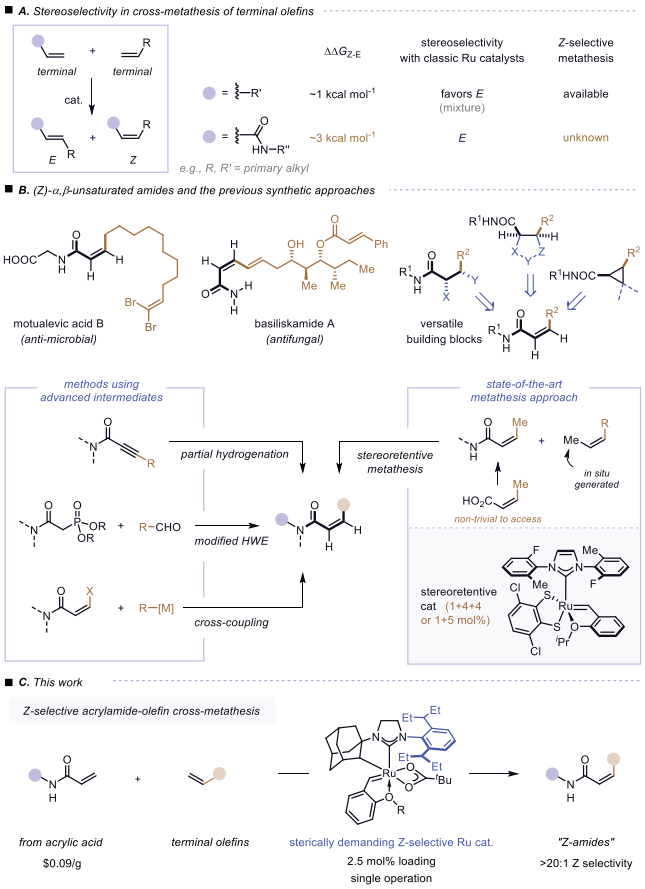
ABSTRACT: The efficient *Z*-selective cross-metathesis between acrylamides and common terminal olefins has been developed by the use of novel cyclometalated ruthenium catalysts with bulky N-heterocyclic carbene (NHC) ligands. Superior reactivity and stereoselectivity are realized for the first time in this challenging transformation, allowing streamlined access to an important class of *cis*-Michael acceptors from readily available feedstocks. The kinetic preference for cross-metathesis is enabled by a pivalate anionic ligand, and the origin of this effect is elucidated by density functional theory calculations.

Olefin metathesis is a versatile method to access complex structures from simple, readily available feedstocks,[1,2] and the precise control over the stereochemistry of the generated double bonds adds critical value to allow selective and divergent synthesis.[3] Among various metathesis transformations, the acrylamide-olefin metathesis represents a highly streamlined approach to α,β-unsaturated amides, but full control over the stereoselectivity has been a long-standing challenge in this important transformation (Scheme 1a).[4] Consistent with a larger thermodynamic gap between the *Z*- and *E*-alkenyl amides compared to common internal olefins,[5] substrate-controlled, high *E* selectivity (usually >25:1) is generally obtained in the acrylamide-olefin metathesis using classic catalysts.[4b] However, the *Z*-selective acrylamide-olefin metathesis has been substantially difficult, even though efficient *Z*-selective metathesis protocols have been established for common terminal olefins.[6] With high *Z*-selectivity adversely impacted by a strong thermodynamic preference for the *E* isomers, access to a useful turnover number (TON) is further hampered by the limited compatibility between acrylamides and the known *Z*-selective catalysts, including the cyclometalated **Ru-1**[7] and **Ru-2**[8] (*vide infra*) and those based on Mo[9] or W.[10] The streamlined access to (*Z*)-α,β-unsaturated amides is highly desirable because of their versatile utility as synthetic intermediates and bioactive molecules, e.g., covalently acting protein modulators (Scheme 1b).[11] Only a few conventional methods are available to date, but all rely on the use of prefunctionalized, advanced intermediates.[12] An alternative, stereoretentive cross-metathesis approach was recently achieved using (*Z*)-but-2-enamides and *in situ*-formed (*Z*)-2-alkenes, but access to these internal alkene starting materials, especially the (*Z*)-but-2-enamides, is nontrivial.[13−15]

Scheme 1. Challenge in *Z*-Selective Acrylamide-Olefin Cross-Metathesis and the Synthesis of (*Z*)-α,β-Unsaturated Amides



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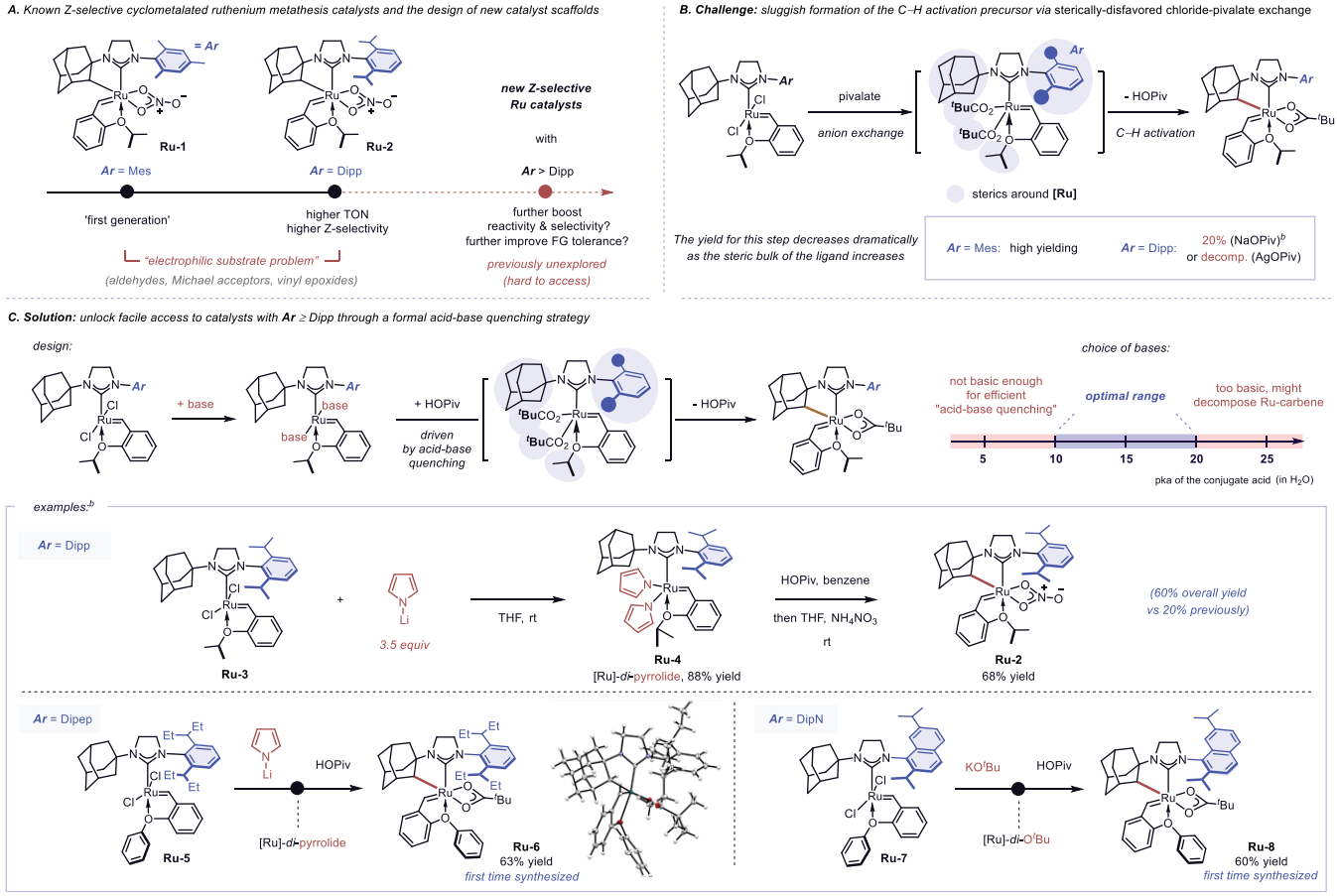
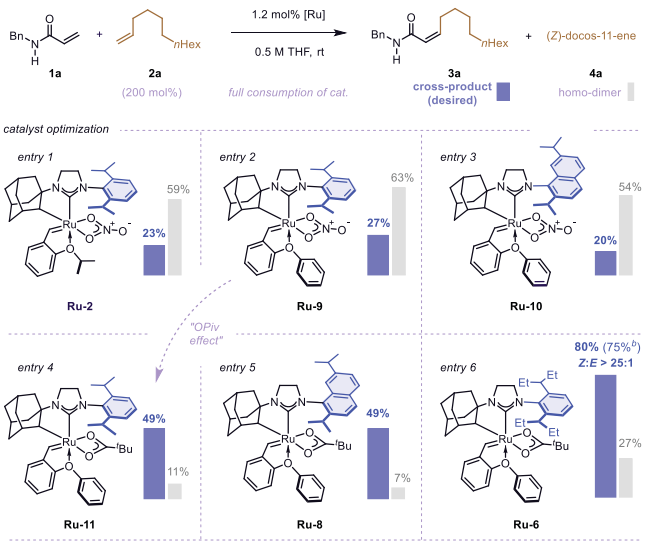
Scheme 2. Design and Development of Novel *Z*-Selective Cyclometalated Ruthenium Metathesis Catalysts with Bulky Ligands[a]



[a]All yields are isolated yields. [b]Isolated as the ruthenium nitrate via further anion exchange with ammonium nitrate. For details, see SI.

Scheme 3. Catalyst Screening[a]



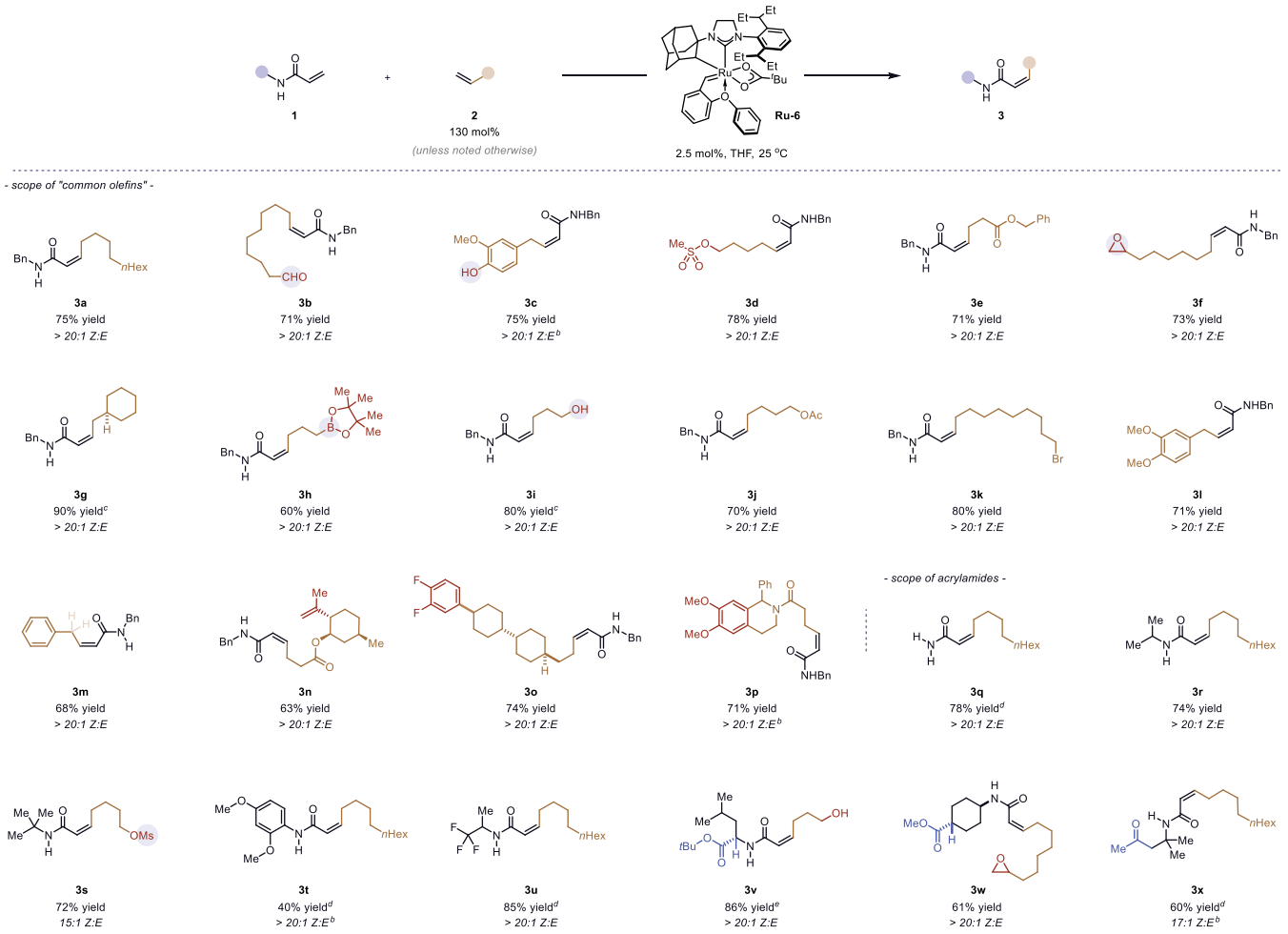
[a]Yields determined by ^{1}H NMR using anthracene as an internal standard. [b]Isolated yields of the *Z*-product. For details, see SI.

We now report efficient *Z*-selective acrylamide-olefin metathesis by a novel, sterically demanding cyclometalated Ru catalyst that features high yield, high *Z*-selectivity, single operation (i.e., without adding the catalyst in portions), and use of readily available feedstocks (Scheme 1c).

To enable this challenging *Z*-selective metathesis, new catalyst scaffolds beyond the known platform are needed (Scheme 2a). In 2011, our group discovered that a type of cyclometalated Ru-carbene complexes kinetically favors *Z*-products in the metathesis of two terminal olefins via a unique, side-bound cycloaddition pathway.[7a,16] The initial *Z*-selective catalysts feature a 2,4,6-mesityl (Mes) side arm on the N-heterocyclic carbene (NHC) ligand (e.g., **Ru-1**),[7] and replacing the Mes with the bulkier 2,6-diisopropylphenyl (Dipp) led to the second-generation catalysts (e.g., **Ru-2**) with superior TONs and *Z*-selectivity.[8] Despite their synthetic utility, both generations of catalysts are less compatible with electrophilic substrates such as aldehydes and Michael acceptors,[9c,14c,17] and the TONs and *Z*-selectivity require further improvement. We hypothesized that the introduction of new NHC side arms that are not only bulkier than Dipp but also sufficiently flexible may further boost the major catalyst parameters including the functional group (FG) compatibility, thus providing a vital opportunity with challenging substrates.[18]

Such a design, however, faces a significant synthetic difficulty (Scheme 2b). The conventional anion exchange that generates the key ruthenium dipivalate intermediates for the carboxylate-assisted C−H activation is only high yielding when the NHC ligand is relatively small (e.g., with Mes as the side arm), which

Scheme 4. Substrate Scope with Various Common Olefins and Acrylamides

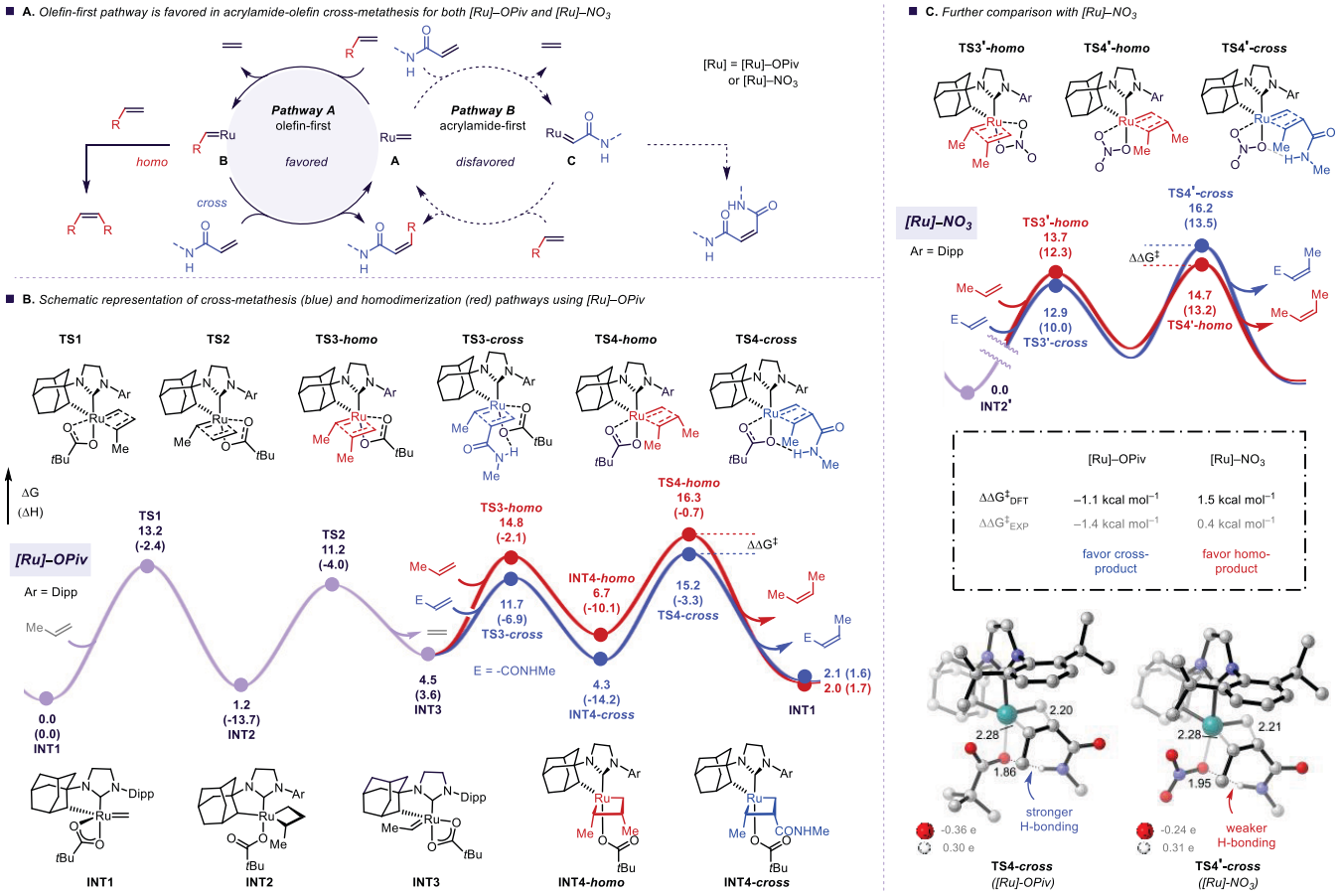


[a]General reaction conditions: **1** (0.25 mmol), **2** (0.325 mmol), and **Ru-6** (0.00625 mmol) in THF (0.4 mL). All yields are isolated yields of the *Z*-products. The stereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture unless otherwise noted. [b]Stereoselectivity determined by isolation. [c]**2** was used in 1.6 equiv. [d]**2** was used in 2 equiv. [e]**2** was used in 1.8 equiv. For details, see SI.

is consistent with a sterically disfavored process leading to a highly congested organometallic species.[19] Even in the preparation of known cyclometalated catalysts equipped with the Dipp ligand (e.g., **Ru-2**), the yield for this key transformation is only 20%,[8] indicating a slightly favored productive pathway over metallocarbene decomposition, as the steric bulk increases.[20] To overcome this long-existing limitation and to unlock unprecedented catalyst scaffolds with even bulkier side-arms, we envisioned the use of formal acid−base quenching to bypass the challenging salt metathesis, in which a ruthenium halide precursor is first treated with a base whose conjugated acid's pK_a is between 10 and 20 to generate a ruthenium-base complex and then pivalic acid to remove the basic ligands and yield a ruthenium dipivalate (Scheme 2c).[21] A variety of bases were tested, yet most led to either no reaction, *mono*-exchange, or metallocarbene decomposition.[22] Finally, lithium pyrrolide[23] was identified as a suitable base in a model reaction with **Ru-3**, successfully furnishing **Ru-2** in a much improved, 60% isolated yield (vs 20% previously). Moreover, using this strategy, new catalyst scaffolds with bulky side-arms, such as 2,6-diisopentylphenyl[24] (Dipep, in **Ru-6**, bulkier than Dipp) and 2,7-diisopropylnaphthalen-1-yl[18b] (DipN, in **Ru-8**), could be obtained for the first time.[25] A less-electron-rich phenoxy group is also incorporated in **Ru-6** and **Ru-8** in place of the common Hoveyda auxiliary to allow fast catalyst initiation (*vide infra*) and potentially help with the accommodation of bulky NHCs.[26]

N-Benzyl acylamide (**1a**) and 1-dodecene (**2a**) were selected as model substrates to test the *Z*-selective acrylamide-olefin cross-metathesis with various catalyst scaffolds (Scheme 3). The initial study revealed that the classic *Z*-selective catalysts (e.g., **Ru-1** and **Ru-2**) are largely inefficient for this transformation. The use of the state-of-the-art **Ru-2** achieved < 20 turnovers, together with a sluggish turnover frequency that required 2 days to reach full catalyst consumption. While the desired product **3a** was obtained in only 23% yield, the homoproduct **4a** was furnished in 59% yield, further indicating an undesired kinetic preference for the homodimerization (entry 1). **Ru-9** with a fast-initiating phenoxy auxiliary was then tested, which indeed shortened the reaction time to ∼8 h and resulted in a slightly improved yield (entry 2). While manipulating the side arm of **Ru-9** alone appeared to be less fruitful (**Ru-10**, entry 3), we discovered that the kinetic preference between the cross- and the homometathesis could be further tuned by switching the anionic ligands. When the nitrate was replaced by pivalate, more than 10-fold change in the kinetic preference and a much higher yield of the desired product **3a** was obtained (49% yield, **Ru-11**, entry 4). Further

Scheme 5. Computational Studies on the Reaction Pathways and the Kinetic Selectivity between Cross- and Homometathesis



[a]All energies are reported in kcal/mol and are with respect to the lowest-energy intermediates in the olefin-first pathways (i.e., **INT1** for [Ru]−OPiv and **INT2′** for [Ru]−NO_3). All distances are reported in Å. $\Delta\Delta G_{DFT}^{\ddagger}$ values were calculated by subtracting the $\Delta G^{\ddagger}$ for the homometathesis pathway from the $\Delta G^{\ddagger}$ for the cross-metathesis pathway. $\Delta\Delta G_{exp}^{\ddagger}$ values were derived from the experimental relative rate constants at an early stage. Calculations were carried out at the M06/6-311++G(d,p)-SDD(Ru), SMD(THF)//B3LYP-D3/6-31G(d)-SDD(Ru) level of theory with vibrational frequencies calculated using the Grimme quasi-rigid rotor-harmonic oscillator approximation (see SI for details).

improvement of the TONs and the *Z*-selectivity was realized by exploring cyclometalated ruthenium pivalate catalysts with more sterically demanding ligands. While the introduction of a DipN side arm (**Ru-8**) led to a similar yield as **Ru-11**, the use of **Ru-6** with a Dipep side arm successfully increased the yield of **3a** to 80%, together with >25:1 *Z*/*E* ratio. Compared with the classic metathesis catalysts (e.g., G-II catalyst) that predominately form (*E*)-*α*,*β*-unsaturated amides, the facile access to the *Z* products with **Ru-6** represents a more than 500-fold change in the stereoselectivity, providing a valuable, complementary method to stereodivergent synthesis.[4b]

Using 2.5 mol % of the optimal **Ru-6**, the substrate scope of the *Z*-selective acrylamide-olefin cross-metathesis was further examined (Scheme 4). The common olefins were used in slight excess (unless volatile or otherwise noted), but they could also be used in stoichiometric amounts relative to the acrylamide substrates without a significant decrease in the yield (see Scheme S3 in SI). Various acrylamides, including those with primary, secondary, and tertiary alkyl substituents, could be readily used as the substrates, through reacting with a large array of terminal olefins furnishing high-value-added products in decent yields. *N*-Aryl acrylamides could also be used despite a lower efficiency (**3t**). The *Z*-selectivity is in general over 20:1, except for secondary acrylamides bearing tertiary substituents (**3s**, 15:1, and **3x**, 17:1). A wide range of FGs are readily compatible, including sulfonates (**3d**), epoxides (**3f**), boronic esters (**3h**), alcohols (**3i**), alkyl and aryl halides (**3k** and **3o**), and ketones (**3x**). Aldehydes (**3b**) and phenols (**3c**) are reportedly less compatible with **Ru-1** and **Ru-2** by significantly decreasing their TONs,[14c] but are well-tolerated by the new catalyst. No olefin migration was noticed with allylbenzene (**3m**), and 1,1-disubstituted olefins remained untouched in **3n**.[27] No intramolecular cyclization or notable erosion of the *Z*-selectivity was observed with substrates bearing tethered nucleophiles (**3c**, **3h**, and **3i**), further showcasing a very mild reaction condition. Many densely functionalized amide products are challenging to access by other methods (**3v**, **3w** and **3x**), which highlights the advantage of this method in accessing complex and biologically relevant molecules containing amide-based *cis*-Michael acceptors.

We then sought to further understand the intriguing role of pivalate, a key factor that significantly increases the kinetic preference for forming the desired cross-products and enables efficient *Z*-selective acrylamide-olefin metathesis. Using the Dipp-NHC as a model ligand, computational studies were performed to depict detailed mechanistic profiles with *Z*-selective ruthenium catalysts bearing different anionic ligands.

First, it was found that the "olefin-first" pathway is favored by both the ruthenium pivalate and nitrate catalysts (Scheme 5a), in which a ruthenium methylidene (**A**) first reacts with a common olefin to form a ruthenium alkylidene (**B**) and then with an acrylamide or another molecule of common olefin to form the cross- or homoproduct. Proceeding through intermediate **C**, an alternative "acrylamide-first" pathway is higher in energy and thus disfavored. A schematic representation for the key intermediates and transition states of the "olefin-first" pathway was further depicted for a model cyclometalated ruthenium pivalate catalyst (Scheme 5b), and the cycloreversion of the most sterically congested, trisubstituted ruthenacyclobutanes was found to be the turnover-limiting and the selectivity-determining step. Cross-metathesis and homodimerization have barriers of 15.2 kcal/mol (**TS4**-*cross*) and 16.3 kcal/mol (**TS4**-*homo*), respectively, which align well with the observed experimental results, favoring cross-metathesis by 1.1 kcal/mol. As a comparison, when a model ruthenium nitrate catalyst was employed (Scheme 5c), the cross- and homometathesis are calculated to have barriers of 16.2 kcal/mol (**TS4′**-*cross*) and 14.7 kcal/mol (**TS4′**-*homo*), respectively. This leads to a reversed selectivity favoring homometathesis by 1.5 kcal/mol, which is also consistent with experimental observations. Using the corresponding activation energy of the homometathesis as a benchmark, it appears that the pivalate ligand is superior to the nitrate ligand in stabilizing the key cycloreversion transition state for the desired cross-metathesis. Analysis of the transition-state structure **TS4**-*cross* revealed a strong hydrogen-bonding interaction between the oxygen of the pivalate ligands and the N−H bond of the amide motif, which is shown by a short H···O distance (1.86 Å). The CM5 charge calculations indicate the oxygen has a negative charge of −0.36 and the hydrogen has a positive charge of +0.30, supporting favorable electrostatic interactions. When the pivalate ligand is replaced by a nitrate (**TS4′**-*cross*), such a hydrogen-bonding interaction is notably weakened, as seen by a longer H···O distance (1.95 Å) and a smaller negative charge on the oxygen (−0.24). As such, the observed kinetic preference of acrylamide-olefin cross-metathesis with the *Z*-selective ruthenium pivalate catalysts could be rationalized by a more favorable hydrogen-bonding interaction between the pivalate ligand and the amide N−H bond in the key cycloreversion step. This is further supported by the experimental observation of a reversed kinetic preference with the pivalate catalysts when acrylamides are replaced by acrylates (favoring homometathesis), a type of substrates with similar electronic properties but unable to serve as the hydrogen-bond donor.[28]

In summary, we have developed a novel synthesis of cyclometalated *Z*-selective ruthenium olefin metathesis catalysts by using a formal acid−base quenching protocol to bypass challenging salt metathesis, which ultimately unlocked facile access to sterically demanding catalysts that were previously hard to obtain or even unexplored. By using a novel catalyst featuring a bulky Dipep side arm and a pivalate bidentate anionic ligand, we successfully realized the first efficient *Z*-selective cross-metathesis between terminal acrylamides and common olefins, providing efficient access to an important class of *cis*-Michael acceptors from readily available feedstocks. A detailed reaction pathway and an intriguing "pivalate effect" were further elucidated by computational studies. Following this, efforts to develop more advanced *Z*-selective catalysts are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11334.

Crystallographic data (CIF)

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2024207 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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