Ring-Opening Olefin Metathesis of Twisted Amides: Activation of Amide Bonds by C=C Cleavage

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Supporting Information Placeholder

ABSTRACT: Selective C=C bond cleavage in twisted amides by ring-opening olefin metathesis (ROM) has been accomplished. The reaction represents the third mechanism for ring opening of non-planar amide bonds discovered to date. Adding to the facile hydrolytic cleavage of non-planar N–C(O) amide bonds and σ N–C bond scission reactions, this reaction manifold engages a peripheral reactivity principle that hinges upon ring strain energy enforced by the twisted amide bond. Considering the wide utility of ring-opening olefin metathesis reactions in various aspects of chemistry, we anticipate that this ring opening methodology will be of broad interest and could lead to the development of ROM reactions of twisted amides as a powerful synthetic tool.

KEYWORDS: *twisted amides, olefin metathesis, amide bonds, ring opening, ring-opening metathesis, ROMP*

The profound importance of amide bonds in chemistry and biology has spurred an intense research interest in the synthesis and properties of amides.[1–3] Twisted amides in which the amide bond is distorted from planarity due to steric constraints, thus disrupting the classic $n_N \rightarrow \pi^*_{C=O}$ conjugation, have played a central role in understanding the fundamental properties of amides (Figure 1A).[4,5] In addition to the central biological role, including cis/trans isomerization of peptides,[6–8] twisted amides provide a frozen frame of the rotation around the N–C(O) axis that in principle could be translated into planar amides by a judicious choice of frameworks and catalysts.[9,10]

Two modes of ring opening of twisted amides have been reported to date: (1) strain-induced instantaneous hydrolysis of twisted N–C(O) amide bonds exemplified by 2-quinuclidone (Winkler-Dunitz distortion: $\tau = 89.1°$, $\chi_N = 59.5°$) and 1-aza-2-adamantanone ($\tau = 85.9°$, $\chi_N = 61.7°$) (Figure 1B);[11,12] (2) facile σ N–C cleavage of the bond adjacent to the twisted amide bond induced by the distortion from the carbonyl plane exemplified by tricyclic bridged lactams ($\tau = 51.5°$, $\chi_N = 36.1°$) (Figure 1C).[13,14] Herein, we report the third mechanism for ring opening of twisted amide bonds discovered to date,[15] which hinges upon the amide bond ring strain[16] as a driving force for ring-opening olefin metathesis of bicyclic amides (Figure 1D). Since ring-opening olefin metathesis is a widely used method in organic synthesis as well as a valuable strategy in the preparation of synthetic and bio-derived polymers,[17,18] we anticipate that the capacity of twisted amides to selectively engage in ring-opening metathesis will be of broad interest.

Mechanistically, ring-opening metathesis is limited to highly strained cycloalkenes due to competing ring-opening/ring-closing equilibrium and the formation of side products through ring-opening metathesis polymerization (ROMP). Classic examples of ROM

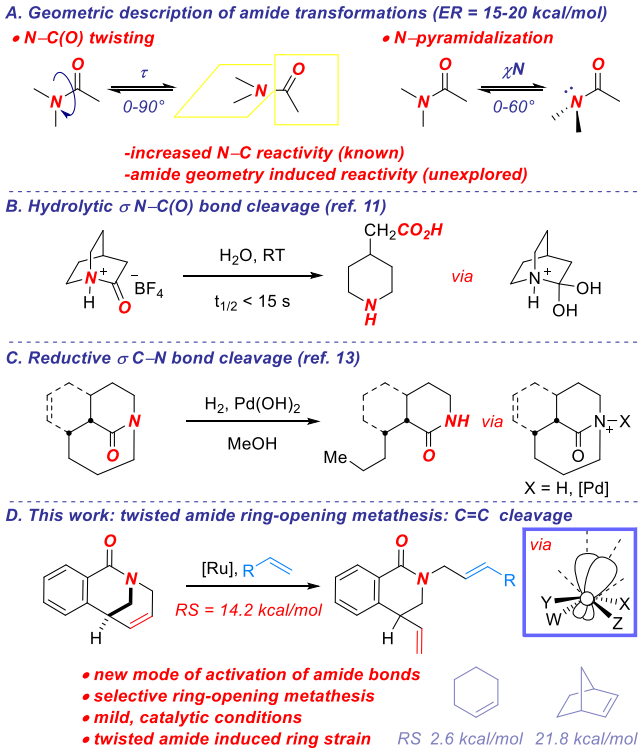
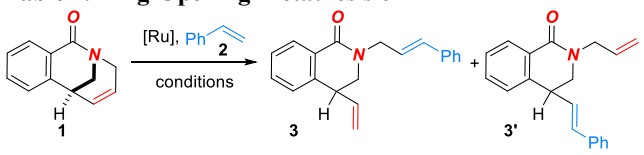


Figure 1. (a) Description of amide bond transformations. (b) Hydrolytic σ N–C(O) cleavage. (c) Reductive σ N–C cleavage. (d) This work: Ring-opening olefin metathesis: C=C cleavage. The inset shows increased distortion of the olefin provoked by amide bond twisting. RS = ring strain.

substrates include norbornene (RS = 21.8 kcal/mol, RS = ring strain) and cyclobutene (RS = 32.0 kcal/mol), while cyclohexene (RS = 2.6 kcal/mol), a classic six-membered ring in organic synthesis, represents a very challenging substrate due to low strain energy. In this vein, bicyclic alkenes, such as norbornenes, have greatly broadened the utility of ring-opening metathesis due to high ROM activity of the ring and the ease of incorporation of substituents onto the scaffold.[17,18] Continuing our interest in the chemistry of non-planar amides,[9,14] we hypothesized that readily-available bridged bicyclic twisted amides containing six-membered cyclohexene ring could enable ring-opening metathesis with high C=C bond cleavage selectivity similar to the prototypal norbornene.

More broadly, the reactivity of twisted amides has been hindered by their propensity for polymerization as exemplified by the initial unsuccessful attempts to reproduce the synthesis of 2-quinuclidone

Table 1. Ring-Opening Metathesis of 1[a]



entry	catalyst	solvent	**1**:**2**	*T* (°C)	yield (%)[b,c]	**3**:**3'**
1	G2	$CHCl_3$	1:5	23	85	6.3:1
2	G2	$CHCl_3$	1:2	23	78	6.1:1
3	G2	$CHCl_3$	2:1	23	72	6.2:1
4	G2	$CHCl_3$	1:5	0	59	5.6:1
5	G2	$CHCl_3$	1:5	60	90	6.3:1
6[d]	G2	$CHCl_3$	1:5	23	63	5.4:1
7	HG2	$CHCl_3$	1:5	23	85	5.3:1
8	G2	$PhCH_3$	1:5	23	70	3.2:1
9	G2	CH_2Cl_2	1:5	23	74	4.2:1
10	G2	dioxane	1:5	23	73	2.1:1
11	G2	$PhCH_3$	1:5	60	77	3.2:1
12	G2	$PhCH_3$	1:5	100	78	3.6:1
13	HG2	$PhCH_3$	1:5	23	71	2.4:1
14[e]	G2	$CHCl_3$	1:5	23	82	6.1:1
15[f]	G2	$CHCl_3$	1:5	23	84	6.3:1

[a]Conditions: amide (1.0 equiv), **2** (x equiv), catalyst (5.0 mol%), solvent (0.30 M), *T*. [b]Yields determined by ^{1}H NMR and/or GC-MS. [c]Combined yield of **3** and **3'**. [d]Catalyst (1.0 mol%). [e]$CHCl_3$ (0.15 M). [f]$CHCl_3$ (1.5 M). Double cross-metathesis product not observed in all entries. Note: *E*/*Z* >95:5 in all entries. G2 = Grubbs catalyst 2nd generation; HG2 = Hoveyda-Grubbs catalyst 2nd generation. See Figure 2 for structures of G2 and HG2.

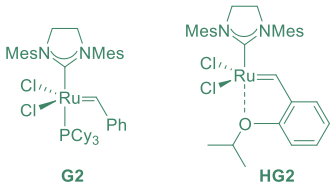
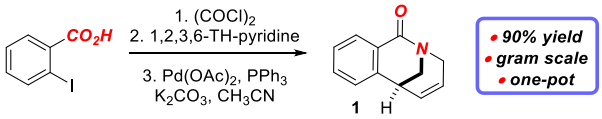


Figure 2. Ring-opening metathesis catalysts. Mes = 2,4,6-triphenylmethyl.

Scheme 1. Facile Synthesis of Twisted Amide 1[a]

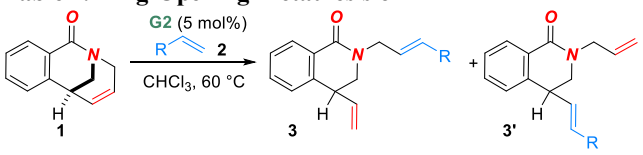


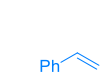
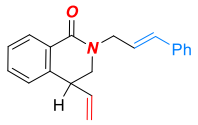
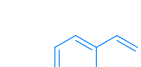
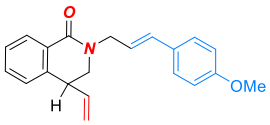
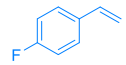
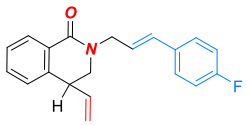
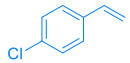
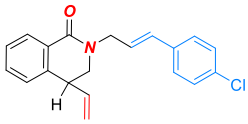
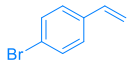
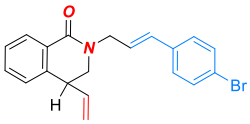
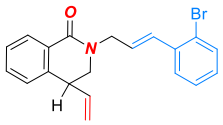
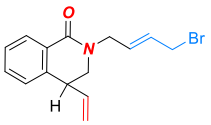
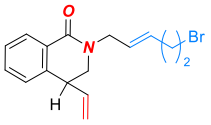
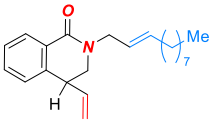
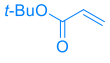
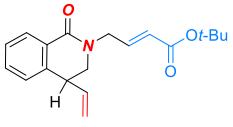
[a]See SI for details.

by Yakhontov[11a] and the β-lactam assignment by Robinson.[19] The selective ring-opening metathesis is significantly more challenging than polymerization reported by Gutenkust[20] that appeared just before the submission of this manuscript.

Our studies began with an examination of ring-opening metathesis of the parent amide **1** using styrene as a model donor alkene (Table 1). Twisted amide **1** is readily prepared on gram scale from 2-iodobenzoic acid in a one-pot procedure,[21] which enables facile access to this scaffold (Scheme 1). We were delighted to find that the use of Grubbs 2 catalyst (5 mol%) in $CHCl_3$ as a solvent at room temperature delivered the desired ring-opening metathesis product in 85% yield as a 6.3:1 ratio of regioisomers (Table 1, entry 1). The products were observed as single *E* isomers (*E*:*Z* >95:5). The double cross-metathesis was not observed. Strikingly, we did not

Table 2. Ring-Opening Metathesis of 1[a]



entry	**2**	**3**	yield (%)[b]	**3**:**3'**[c]
1			83	6.3:1
2			74	>10:1
3			68	4.7:1
4			66	8.1:1
5			62	5.6:1
6			66	8.3:1
7			55	>20:1
8			66	>20:1
9			63	4.2:1
10			44	>20:1

[a]Conditions: amide (1.0 equiv), **2** (5 equiv), G2 (5.0 mol%), $CHCl_3$ (0.30 M), 60 °C. [b]Isolated yields of **3** and **3'**. [c]Determined by ^{1}H NMR and/or GC-MS of crude reaction mixtures. See SI for details.

observe any products resulting from N–C(O)[11] or σ N–C bond cleavage[12] under these mild Ru-catalyzed conditions.

Key optimization results are outlined in Table 1. Decreasing the olefin loading from 5 to 2 equiv resulted in a minimal decrease in the reaction efficiency (entries 1-3), consistent with a facile ring-

opening and irreversibility of the reaction (*vide infra*). It worthwhile to note that the reaction was efficient with olefin as the limiting reagent (entry 3). Increasing the reaction temperature had a negligible effect on the reaction efficiency and the isomer ratio, while a considerable conversion was still observed at 0 °C (entries 4-5). The reaction resulted in a substantial conversion using 1 mol% of the catalyst (entry 6). The use of Hoveyda-Grubbs catalyst resulted in a comparable reaction efficiency (entry 7). A solvent screen indicated $CHCl_3$ as the preferred solvent for the reaction (entries 8-13). Interestingly, a decrease in the isomer ratio was observed using toluene, dioxane and CH_2Cl_2, indicative of a lower selectivity in the [2+2] cycloaddition step. Finally, changes in the reaction concentration had a negligible effect on the reaction efficiency (entries 14-15). Taken together, the optimization results are consistent with the facile ring-opening metathesis of the six-membered cyclic olefin embedded in the twisted amide scaffold.

Having identified optimal conditions for the ROM, we next investigated the scope of the reaction (Table 2). As outlined in Table 2, various olefins were found to be compatible with this novel ring-opening metathesis process. Neutral (entry 1) and electron-rich olefins (entry 2) furnished the corresponding ring-opening metathesis products with high efficiency. Electron-deficient aromatic olefins were found to be well-compatible (entry 3). Importantly, halides proved to be well-tolerated, thus providing synthetic handles that for further derivatization by the traditional cross-coupling methodologies (entries 4-5). Notably, even sterically-hindered olefins containing halides, such as 2-bromo were found to be suitable donor olefin partners (entry 6). In these cases, the regioisomer ratio (**3**:**3'**) is consistent with electronic stabilization of the olefin. We hypothesize that the slightly lower ratio using 4-F-styrene results from a fluorine-ruthenium interaction. Furthermore, we were pleased to find that the reaction is not limited to aromatic olefins and the scope could be extended to electron-rich aliphatic olefins (entries 7-10). It should be noted that functionalized aliphatic olefins, such as allyl bromide (entry 7) as well as 4-bromobut-1-ene (entry 8), provided the ring-opening metathesis adducts in good yields. Moreover, unsubstituted aliphatic alkenes, such as dec-1-ene are compatible (entry 9). Finally, electron-deficient conjugated alkenes, such as *t*-Bu acrylate, are also amenable to this ring-opening metathesis protocol, albeit the product was obtained with lower reaction efficiency (entry 10). The reactions were selective for the formation of *E* alkenes. In general, electron-deficient olefins resulted in a higher regioisomer ratio than their electron-rich counterparts, which is consistent with their relative reactivity in olefin cross-metathesis. It should be noted that under these conditions the propensity of twisted amide **1** to engage in the polymerization is minimized, resulting in a synthetically useful process. It is important to compare the difference between ring opening and polymerization as the preferred pathway.[20] Cross-metathesis following the ring-opening of strained olefins is in competition with the polymerization process. Typically, polymerization can be suppressed by an excess olefin, while **G3** initiators are advantageous for polymerization.[17a,b]

To gain insight into the driving force behind this novel process, we conducted extensive computational studies on the properties of the bridged systems relevant to the ring opening (Figure 3). We originally hypothesized that the high reactivity of the scaffold would originate from the presence of a unique bicyclo[3.3.1]non-2-ene bridged system, wherein the olefin would be strained by virtue of the bicyclic ring strain,[16] while the amide would provide a facile avenue for the scaffold assembly. Strikingly, we found that the twisted amide plays a key role enabling the ring-opening metathesis reactivity:

(1) To understand the role of the twisted amide bond, ring strain energies of the twisted amide and corresponding hydrocarbon, ketone and amine were calculated by homodesmotic equations.[22,23]

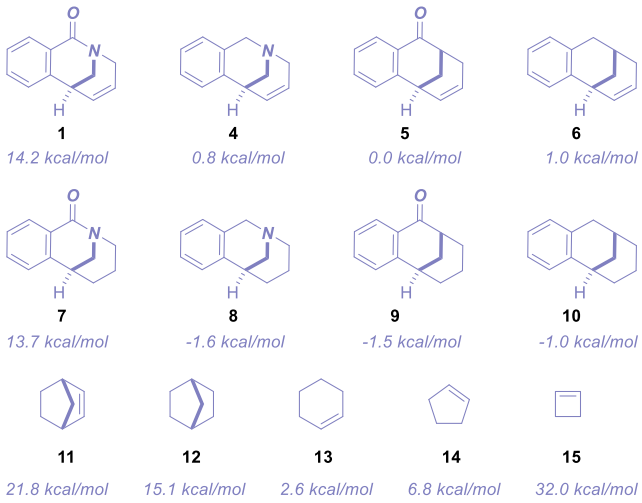
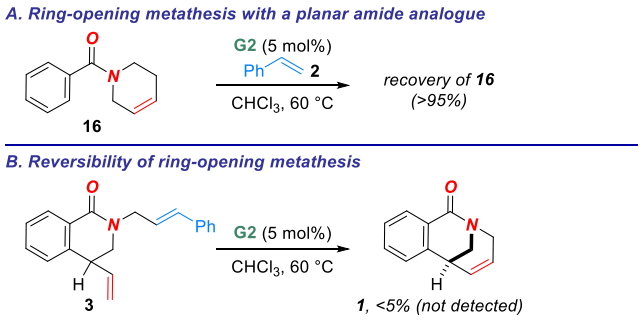
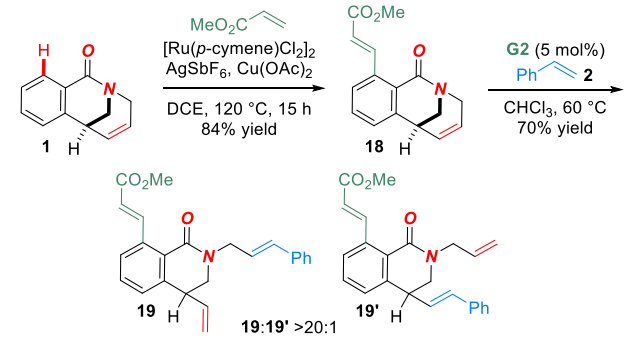


Figure 3. Ring strain energy calculated using homodesmotic equations at the B3LYP/6-311++G(d,p) level. See SI for details.

Scheme 2. Mechanistic Studies



Scheme 3. Sequential C–H Activation/Twisted Amide Ring-Opening Metathesis



(2) Likewise, ring strain energies of fully saturated twisted amide, hydrocarbon, ketone and amine counterparts were determined by homodesmotic equations at the same level.

(3) For comparison, ring strain energies of representative cyclic olefins commonly used in ROM processes (cyclobutene, cyclopentene, cyclohexene, norbornene) were determined at the same level.

(4) Finally, olefin strain energies of the twisted amide, hydrocarbon, ketone and amine were calculated.

The data in Figure 3 clearly indicate that ring strain of amide **1** (14.2 kcal/mol) is much higher than that of amine **4** (0.8 kcal/mol), ketone **5** (0.0 kcal/mol) and hydrocarbon **6** (1.0 kcal/mol). Furthermore, ring strain of saturated amide **7** (13.7 kcal/mol) is much higher than that of saturated amine **8** (-1.6 kcal/mol), ketone **9** (-1.5 kcal/mol) and hydrocarbon **10** (-1.0 kcal/mol). These values can be compared with the ring strain energy for norbornene **11** (21.8 kcal/mol, cf. norbornane **12**, 15.1 kcal/mol), cyclohexene **13** (2.6 kcal/mol), cyclopentene **14** (6.8 kcal/mol) and cyclobutene **15** (32.0 kcal/mol). *Finally, the difference in ring strain between the unsaturated twisted amide, amine, ketone and hydrocarbon and their saturated analogues is -0.5 kcal/mol, 1.4 kcal/mol, 0.5 kcal/mol, and 1.0 kcal/mol, respectively (not shown).* Taken together, the data demonstrate the key role of the twisted amide bond in increasing ring strain of the [3.3.1] bicyclic ring scaffold.

Thus, the rigidity of the amide bond expressed as the propensity to enforce the planar geometry as a result of energetically favorable $n_N \rightarrow \pi^*_{C=O}$ delocalization translates into the striking ring strain compared to amine, ketone and hydrocarbon counterparts. The ring strain in amide **1** is close to the ring strain observed for the prototypal norbornene, and much higher than that for cyclohexene and cyclopentene. *Overall, (1) the facile access to **1** and its analogues, (2) the high strain while maintaining robust hydrolytic stability, and (3) the high reactivity in ROM bode well for application of twisted amides in ring-opening metathesis in a variety of chemical contexts.*

Additional studies were carried out to gain insight into this novel process: (1) Acyclic, non-bridged analogue of **1** was prepared and subjected to the reaction conditions ($CHCl_3$, 60 °C) (Scheme 2A). The reaction resulted in quantitative recovery of the starting material, supporting the key role of the twisted amide bond in the C–C cleavage. (2) To test reversibility of the reaction, the ring opening-metathesis product was subjected to the reaction conditions (Scheme 2B), resulting in full recovery of the starting material. (3) Intermolecular competition studies between twisted amide **1** and norbornene revealed similar order of reactivity (Scheme 2C). These studies are consistent with the high energy barrier necessary to twist the amide bond from planarity in order to directly close the ring, and highlight the synthetic utility of a peripheral introduction of the twisted amide ring strain by the Heck reaction (Scheme 1).

To further demonstrate the utility of this novel process, we have conducted a sequential ortho-C–H functionalization with methyl acrylate directed by the twisted amide C=O bond, followed by ring-opening metathesis (Scheme 3). This highly efficient sequence of reactions introduces three electronically- and sterically-differentiated olefins, producing a decorated, biologically-relevant tetrahydroisoquinoline scaffold and demonstrates the synthetic versatility of the current process.

In summary, we have reported ring-opening metathesis of twisted amides. This advance represents the third mechanism for selective bond cleavage of non-planar amides reported to date. The reaction is compatible with various olefins to give the corresponding olefin-metathesis products in good yields, while avoiding undesired polymerization. The general approach exploits the propensity of the amide bond to enforce planarity as a result of energetically favorable $n_N \rightarrow \pi^*_{C=O}$ conjugation and leads to the striking ring strain compared to ketone, amine and hydrocarbon counterparts. In a broader context, the development of this reaction demonstrates the untapped potential of non-planar amide bonds in organic synthesis. Future work will focus on expanding the family of twisted amides available for ring opening and applying this method to new amide and reaction types, including ROMP. Studies to better understand the relationship between amide distortion and reactivity and to expand the current process are underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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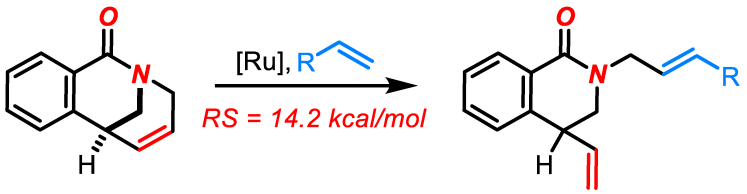
TA-ROM: Twisted amide ring-opening metathesis



- ***mode of activation of amide bonds***
- ***selective ring-opening metathesis***
- ***mild, catalytic conditions***
- ***twisted amide induced ring strain***