Acyclic Twisted Amides

Guangrong Meng,[†,§] Jin Zhang,[‡,†,§] and Michal Szostak[*,†]*

[†]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

[‡]College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, Xi'an 710021, China

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Corresponding author

michal.szostak@rutgers.edu

[§]These authors contributed equally to this work.

Abstract: In this contribution, we provide a comprehensive overview of acyclic twisted amides, covering the literature since 1993 (the year of the first recognized report on acyclic twisted amides) through June 2020. The review focuses on classes of acyclic twisted amides and their key structural properties, such as amide bond twist and nitrogen pyramidalization, which are primarily responsible for disrupting n_N to $\pi^*_{C=O}$ conjugation. Through discussing acyclic twisted amides in comparison with the classic bridged lactams and conformationally-restricted cyclic fused amides, the Reader is provided with an overview of amidic distortion that results in novel conformational features of acyclic amides that can be exploited in various fields of chemistry ranging from organic synthesis and polymers to biochemistry and structural chemistry and the current position of acyclic twisted amides in modern chemistry.

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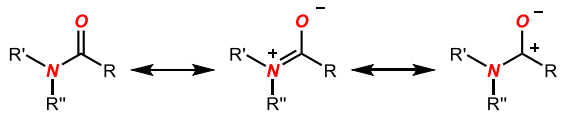
1. Introduction

The amide bond is a fundamental and arguably the most important functional group in chemistry and biology.[1] It is well-accepted that the vast majority of amides are planar as a consequence of amidic resonance as vividly demonstrated by Pauling almost a century ago (n_N to $\pi^*_{C=O}$ conjugation; amidic resonance of 15-20 kcal/mol in planar amides) (Scheme 1).[2–5] However, distortions of the amide bond from planarity[6–24] have profound consequences on all major chemical properties of amides, which include (i) barrier to cis–trans rotation; (ii) planarity of the six atoms comprising the amide bond; (iii) geometric changes, such as shortening of the N–C(O) bond and elongation of the C=O bond; (iv) change of the thermodynamic protonation site from oxygen to nitrogen; (v) increased propensity to hydrolysis and nucleophilic acyl substitution; (vi) cleavage of σ N–C bonds; and more recently, (vii) oxidative addition of the N–C(O) bond to transition metals, among others.

Scheme 1. Amide Bond Resonance



The concept of amide bond distortion was first recognized in the 1930s.[25] Following the studies by Pauling on amide bond planarity and the conclusion that typical amides are approximately 40% double bond in character,[2–5] Lukeš proposed that restriction of the amide bond in a rigid bicyclic structure would have major implications on the properties of such twisted amides.[26] The studies by Woodward and Robinson on the structure prediction of β-lactam antibiotics in the 1940s represented another early example that amide bond strain could produce the key driving force for the reactivity of amides.[27] In the following years, many research groups reported significant studies on the structure and properties of non-planar amides enclosed in rigid bridged scaffolds.[28–35] One of the most elegant of those is the now classic synthesis of a perfectly perpendicular 2-quinuclidonium tetrafluoroborate (**2.32**, Figure 4) accomplished by the Stoltz group in 2006,[36–38] while the studies by Kirby[39–43] and Greenberg[44–48] on 1-aza-2-adamantanone (**2.14**, Figure 1) and 1-azabicyclo[3.3.1]nonan-2-one (such as **4.9**, Figure 13),

respectively, have enabled a greatly improved understanding of the properties of geometrically non-planar amide bonds.

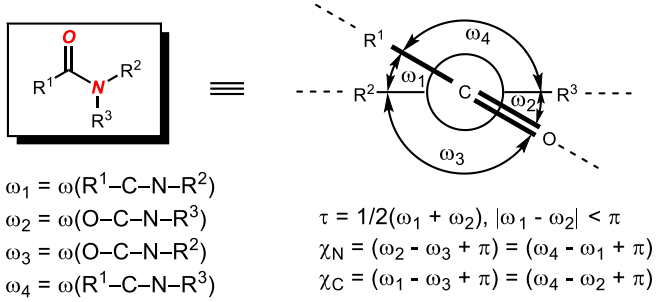
In contrast to the conformationally-restricted bridged lactams,[28–48] recent years have witnessed an explosion of interest in acyclic twisted amides. Amide bond distortion in acyclic amides leads to conformational and electronic modifications of the properties of acyclic amides that are commonly encountered in organic chemistry.[49–56] Recognized as early as in 1993 by Yamada,[57–62] this ground-state-destabilization has recently resulted in the development of amide bond cross-coupling reactions, wherein the twisted amide N–C(O) bond undergoes oxidative addition to a low valent metal.[63–78] Moreover, studies demonstrate that acyclic twisted amides can be effectively utilized in direct nucleophilic addition reactions, a class of processes that has a major impact on polymer modification, synthesis of pharmaceuticals, and peptide cleavage.[79–82] Furthermore, acyclic amide bond twisting has been exploited in structural chemistry, showing that geometric changes around the amide bond could be applied to effectively control the conformation of molecules.[83–90] Moreover, amide bond distortion of acyclic amides has been studied in the context of peptide cis-trans isomerization and peptide cleavage,[91–102] wherein two mechanisms have been proposed: (i) hydrolysis via ketene intermediates, (ii) steric repulsion of N-substituents, both exploiting ground-state-destabilization and amide bond twist.[103–105] Perhaps most importantly, numerous examples in synthetic chemistry demonstrate that acyclic twisted amides behave as carboxylic acid derivatives characterized by properties vastly different from classical amides.[106–115] Thus, taken together with the fact that selective activation of planar amides to achieve distortion in acyclic amides is feasible,[49,50] twisting of acyclic amide bonds results in a broadly applicable amide bond activation concept in small molecule synthesis.

Despite the fact that acyclic twisted amides represent a major class of amides in organic synthesis, structural chemistry and biochemistry and significant advances have been reported, a comprehensive review on acyclic twisted amides has not been published. In this manuscript, we provide a comprehensive overview of acyclic twisted amides, focusing on (i) classes of acyclic twisted amides, and (ii) their key structural properties, such as amide bond twist and nitrogen pyramidalization, which are primarily responsible for disrupting n_N to $\pi^*_{C=O}$ conjugation. By discussing acyclic twisted amides

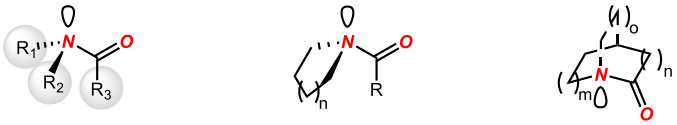
in comparison with the classic bridged lactams and conformationally-restricted cyclic fused amides, such as β-lactams, the reader will be provided with an overview of the area and the current position of acyclic twisted amides in modern chemistry. Twisted amides cover a broad range of amidic distortion that results in novel conformational features that can be exploited in various fields of chemistry ranging from organic synthesis and polymers to biochemistry and structural chemistry.

Amide bond distortion is typically defined by the Winkler-Dunitz distortion parameters (Scheme 2).[116] Twist angle (τ) describes the magnitude of rotation around the N–C(O) bond, while pyramidalization parameters (χ_N) and (χ_C) describe pyramidalization at nitrogen and pyramidalization at carbon, respectively. Twist is 0° for planar amide bonds and 90° for fully orthogonal bonds, while χ parameters are 0° for planar bonds, and 60° for fully pyramidalized bonds. Since (χ_C) parameter is typically 0° or close to 0° irrespective of the geometry of the amide bond, twist angle (τ) and pyramidalization at nitrogen (χ_N) are used as the primary descriptors of non-planar amide bond geometry. In addition to Winkler-Dunitz distortion parameters, the additive distortion parameter ($\tau+\chi_N$) has been defined and it is particularly useful in comparing amide bond distortion within the same classes of non-planar amides.[117,118] Furthermore, N–C(O) and C=O bond lengths, in particular, and to a lesser extent C–C(O) and C–NC(O) bond lengths typically give a very useful information about the structures and properties of acyclic non-planar amide bonds and should be considered when reporting new acyclic twisted amides and discussing their reactive properties.[28–35] In terms of amidic resonance, resonance energies and barriers to rotation provide insight into the strength of the amide N–C(O) bond, and these values measured by spectroscopic or computational methods are available for numerous non-planar amides for comparison purposes.[12,45,46,119–121]

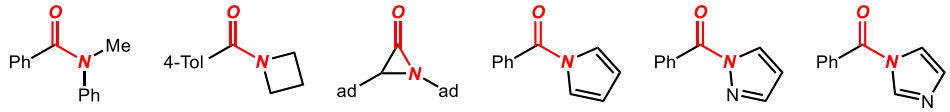
Scheme 2. Winkler-Dunitz Distortion Parameters (τ, χ_N, χ_C) of Amide Bonds



Scheme 3. Types of Amide Bond Distortion. Note that Steric Restriction Applies to Both Bridged and Fused Ring Systems.



Scheme 4. Structures of Additional Amides Discussed in the Manuscript.



Steric distortion by non-bonding interactions that is feasible in several classes of tertiary amides represents by far the most effective strategy for distortion of the amide bond planarity in acyclic amides (Scheme 3). While similar geometric alteration is not easily achievable in primary and secondary amides, from a synthetic standpoint, in many cases common primary and secondary amides can be readily and reversibly converted into sterically twisted tertiary amides,[49,50] thus enabling the acyclic twisting concept to be applicable to all classes of amides.

An additional point that should be discussed is the fact that in many cases steric distortion of the acyclic amide bond is associated with electronic activation through N_{lp} delocalization (lp = lone pair) on the substituents outside of the twisted N–C(O) bond. Depending on the class of amides, these effects may have a cooperative effect or be a consequence of one another. As such, in many instances acyclic twisted amides can also be considered as N-acyl, N-sulfonyl, N-carbamoyl or related derivatives. According to IUPAC (IUPAC = International Union of Pure and Applied Chemistry), amides are defined as carboxylic acid derivatives in which "acidic hydroxy group has been replaced by an amino or

substituted amino group." Thus, it is important to correctly assign the twisted N–C(O) amide bond when referring to non-planar amides and their derivatives. In this context, it is likely that more amides that have been synthesized over the years could be classified as twisted, but their twist remains unknown. In general, although DFT methods can be used to correctly predict amide bond distortion in bridged and related lactams,[45,46,117,118] the accurate determination of the geometry of acyclic twisted amides is feasible only by x-ray crystallography, while DFT predictions in the absence of x-ray crystallographic analysis should be treated with caution.[12,126,232] In general, DFT predictions of acyclic amides overestimate one or both distortion parameters (τ, χ_N) depending on the level used. In addition, it should be noted that DFT is unable to accurately predict the carbonyl bending angle of bridged lactams.[38]

With the aim of providing a comprehensive overview of acyclic twisted amides, we have conducted a comprehensive CCDC (Cambridge Structural Database) search of non-planar amides covering all years up to 2020. The analysis indicated >63,000 distinct tertiary amide and amide derivatives with reported structural parameters (63,071). For the purpose of the review, only amides without coordinated metal are included as it is well-established that metal-coordination to polar bonds changes their geometrical properties.[122] These amides will be considered separately in the future studies. Similarly, polar derivatives of amides, such as ureas, carbamates and thiocarbamates as well as hydrazides and related compounds are not included.[123–125] The polar derivatives will be the topic of our future studies. A summary of structurally-characterized amides as determined from the CCDC database is presented in Table 1.

For comparison purposes, the total number of tertiary amides includes amides without coordinated metal (48,024) and amides with coordinated metal (15,047). Furthermore, the total number of structurally characterized tertiary amides includes ureas (8,953), carbamates (6,507) and thiocarbamates (266). It is further interesting to note that anilides (N–Ar) represent a major class of structurally-characterized tertiary amides to date (11,419). These amides are well-known to be electronically-activated due to $n_N \rightarrow$ Ar conjugation with significantly reduced amidic resonance (RE, resonance energy, 13.5 kcal/mol of PhC(O)NPhMe, **1.1**, Scheme 4).[126] Furthermore, the total number includes

hydrazides (3,988), N-acyl-hydroxylamines (803), and N-acyl-thiohydroxylamines (1,298). It should be noted that there is some overlap between the classes of amides in Table 1, entires 3-16.

The total number of structurally-characterized tertiary amides (63,071) should be compared with the total number of structurally-characterized tertiary acyclic amides (16,505) with representative subclasses presented for comparison (anilides, 3,455; hydrazides, 1,749; N-acyl-hydroxylamines, 408; N-acyl-thiohydroxylamines, 585). It is worthwhile to note that there are only few structurally-characterized acyclic amides in which the nitrogen atom is contained in a small ring, such as N-azetidinyl amides (108), N-aziridinyl amides (53). These amides are well-established to contain pyramidalized nitrogen atom (e.g. χ_N = 32.5°, 4-Tol-C(O)-azetidine, **1.2**, Scheme 4; χ_N = 54.9°, aziridinyl, 1,3-diadamantylaziridin-2-one, **1.3**, Scheme 4). In this context, an important study on surveying crystallographically characterized amides by Chakrbarti and Dunitz should be noted.[127] While the study by Dunitz focused on conformational preferences of planar amides with respect to bond lengths, C(O)–N–C–C(H) torsion and C(O)–N–C angles, the main conclusion of our study is that non-planarity of amide bond is commonly found in N-activated tertiary amides achieved by several methods of activation (Sections 2-5).

Table 1. Structurally Characterized Tertiary Amides[a]

entry	type	no. of amides and derivatives
1	All amides	63,071
2	Amides w/o metal	48,024
3	Ureas	8,953
4	Carbamates	6,507
5	Thiocarbamates	266
6	Anilides	11,419
7	Hydrazides	3,988
8	N-Acyl-hydroxylamines	803
9	N-Acyl-thiohydroxylamines	1,298
10	Acyclic amides	16,505

11	Acyclic anilides	3,455
12	Acyclic hydrazides	1,749
13	Acyclic N-acyl-hydroxylamines	408
14	Acyclic N-acyl-thiohydroxylamines	585
15	Acyclic N-acyl-azetidines	108
16	Acyclic N-acyl-aziridines	53

[a]CCDC ConQuest analysis, 05/05/2020. Note that for compounds in which two or more structures have been characterized in a single unit cell, the number of amides is one.

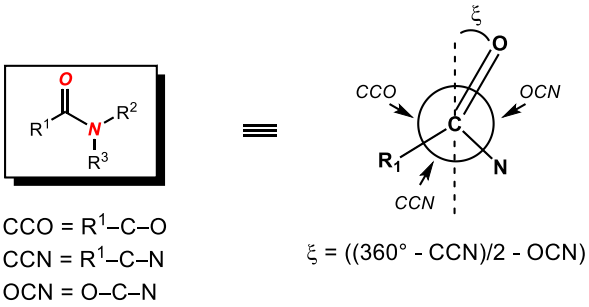
The evaluation of amide bond distortion distribution of structurally-characterized tertiary acyclic amides indicates a significant number of >200 amides with twist >40º, and >500 with pyramidalization >40º (Winkler-Dunitz distortion). Based on the experimental studies on twisted amides,[28–35] the values of $\tau = 40º$ and $\chi_N = 40º$ are considered as threshold values that allow for unique reactivity of the amide bond that is distinct from typical planar amides. In many cases, these amides should be considered as "amino-ketones" or "activated amides" rather than classic amides, while the increasing continuum of changes in reactivity is enabled by steric and electronic activation.[63–78,115] The Winkler-Dunitz parameters (τ, χ_N, χ_C) were calculated on the basis of the equation in Scheme 2.[116] For classification purposes in the review, these values are given with the accuracy to two decimal places. In general, amide bond distortion parameters are given with the accuracy to three decimal places with respect to the bond lengths of the amide bond, while Winkler-Dunitz parameters are given with the accuracy to one or two decimal places. It should be noted that changes in the properties of the amide bond represent a continuum of change.

It is also worth noting that the additive Winkler-Dunitz parameter ($\tau+\chi_N$) represents a very accurate predictor of the twisted amide bond properties in conformationally-locked bridged lactams;[117,118] however, in contrast to bridged systems, in which correlation between twist and pyramidalization is typically linear within the same scaffold, geometric distortions of acyclic amide bonds can be separately achieved by twist, pyramidalization and/or combination of twist and pyramidalization (i.e. twisted, pyramidalized and twisted pyramidalized amides by Yamada's classification).[30,57] As a result, twist

angle (τ) and pyramidalization at nitrogen (χ_N) parameters are considered separately for acyclic geometrically distorted amide bonds, while the effects of the second parameter are discussed where relevant.

An additional parameter that should be discussed is the carbonyl bending angle (ξ).[33,128] It has been noted by Bürgi and co-workers that strained lactones and lactams exhibit a compression of the amide NCO bond angle.[128] Subsequently, Stoltz and co-workers made the same observation in their synthesis of 7-hypoquinuclidonium systems.[38] The carbonyl bending angle has been mathematically defined as (ξ) = ((360° – CCN)/2 – OCN) (Scheme 5).[38] This value has been proposed to correlate with the relative activation of amides as a trapped intermediate of the intramolecular elimination of the amine to form an acylium ion. For the most twisted bridged lactam, 7-hypoquinuclidone BF_3 complex (**2.33**, Figure 4), ξ is 5.8°, which indicates early stage of acylium formation.[38] For comparison, for the most twisted acyclic amides, such as N-benzoyl-glutarimide (**3.100**, Figure 9), ξ is 3.5°; for Yamada's amide (**3.56**, Figure 8), ξ is 3.3°; for 4-Me_2N-C_6H_4-C(O)N-Boc_2 (**3.88**, Figure 9), ξ is 4.4°; for the fully twisted Ph-C(O)-N-Ts/Boc (**3.139**, Figure 11), ξ is 4.4°; and for benzoyl-2,5-dimethyl-pyrrole (**3.107**, Figure 10), ξ is 1.5°. Future studies on twisted amides should routinely report the carbonyl bending angle parameter (ξ).

Scheme 5. Carbonyl Bending Angle (ξ) of Amide Bonds



CCO = R^1–C–O
CCN = R^1–C–N
OCN = O–C–N

ξ = ((360° - CCN)/2 - OCN)

The reader should note that in order to allow for a broad overview and comparison of acyclic twisted amides with their more established bridged and cyclic counterparts, bridged lactams and cyclic amides

are included in the review. As outlined in the section above, since it is well-established that twist and pyramidalization in acyclic twisted amides are typically independent of each other, these values are considered separately. As such, the review is arranged into the following sections: (i) cyclic amides with twist of 40° to 90°; (ii) acyclic amides with twist of 40° to 90°; (iii) cyclic amides with N-pyramidalization of 40° to 90°; (iv) acyclic amides with N-pyramidalization of 40° to 90°. Relevant examples of amide bond properties, computational characterization and amide bond reactivity are included along with the discussion of the structural properties of structurally-distorted amides. We hope that this review will stimulate the additional use of amide bond distortion by a range of interested chemists and lead to further progress in this highly important area of amide bond chemistry.

Note that detailed summary tables including Winkler-Dunitz distortion parameters are included in the Supporting Information (SI).

2. Cyclic Amides: Twist 40-90°

In this section, we present a comprehensive overview of structurally-characterized cyclic amides with twist values of 40° to 90°. In general, these amides can be divided into the following classes: (1) classic bridged lactams; (2) N-acyl-activated cyclic amides; (3) N-sulfonyl-activated cyclic amides; (4) N-quaternized cyclic amides; (5) N-aziridinyl cyclic amides; and (6) miscellaneous examples.

2.1. Bridged Cyclic Amides

Conformational-restriction of the amide bond geometry in a bicyclic ring with the nitrogen atom at the bridgehead position represents the most classic and historically relevant method for freezing out non-planar amide bond conformation (Figure 1). After the seminal proposal by Lukeš in 1938,[26] many researchers became intrigued by the prospect of synthesizing these elusive amides, including very elegant studies by Yakhontov,[129–132] Pracejus,[133–135] Brown,[136–138] and others,[28–35] which after a clear misassignment by Yakhontov,[129] culminated in the unambiguous synthesis of fully perpendicular 2-quinuclidonium tetrafluoroborate and 1-aza-2-adamantanone by Stoltz[36–38] and Kirby,[39–43] as well as the

establishment of 1-azabicyclo[3.3.1]nonan-2-one as a model medium bridged twisted lactam characterized by the N-/O-protonation switch cross-over geometry by Greenberg.[44–47]

The most twisted of these bridged lactams show the reactive properties of "amino-ketones", while additional unique reactivity can be achieved by differentiating distortion of planarity of the C–N–C–O bonds, such as σ N–C bond cleavage, which served as the basis the discovery of novel reactivity of acyclic twisted amides.[49–78]

In general, very few bridged lactams with twist values close to 90° have been reported. After early studies on increased rate of hydrolysis of bridged lactams by Pracejus and Brown,[28–35] studies by Greenberg first quantified that the cross-over of the "amino-ketone" type reactivity can be expected with the τ values close to 40°.[45,46] Studies by Aubé demonstrated the increased reactivity of the unactivated σ N–C bond to hydrogenolysis conditions, which represented one of the first examples of N–C bond scission of unactivated amide bonds.[32,139] The amide bond geometry required for this type of reactions has been demonstrated to be close to 40°. These studies culminated in the demonstration of an instantaneous hydrolysis of N–C(O) bond in the perpendicular 2-quinuclidonium tetrafluoroborate (**2.32**, Figure 4) and 1-aza-2-adamantanone (**2.14**, Figure 1) systems by Stoltz[36] and Kirby.[39] Since several reviews on the properties of the bridged lactams have been published,[28–35] this section briefly summarizes the geometry of bicyclic scaffolds.

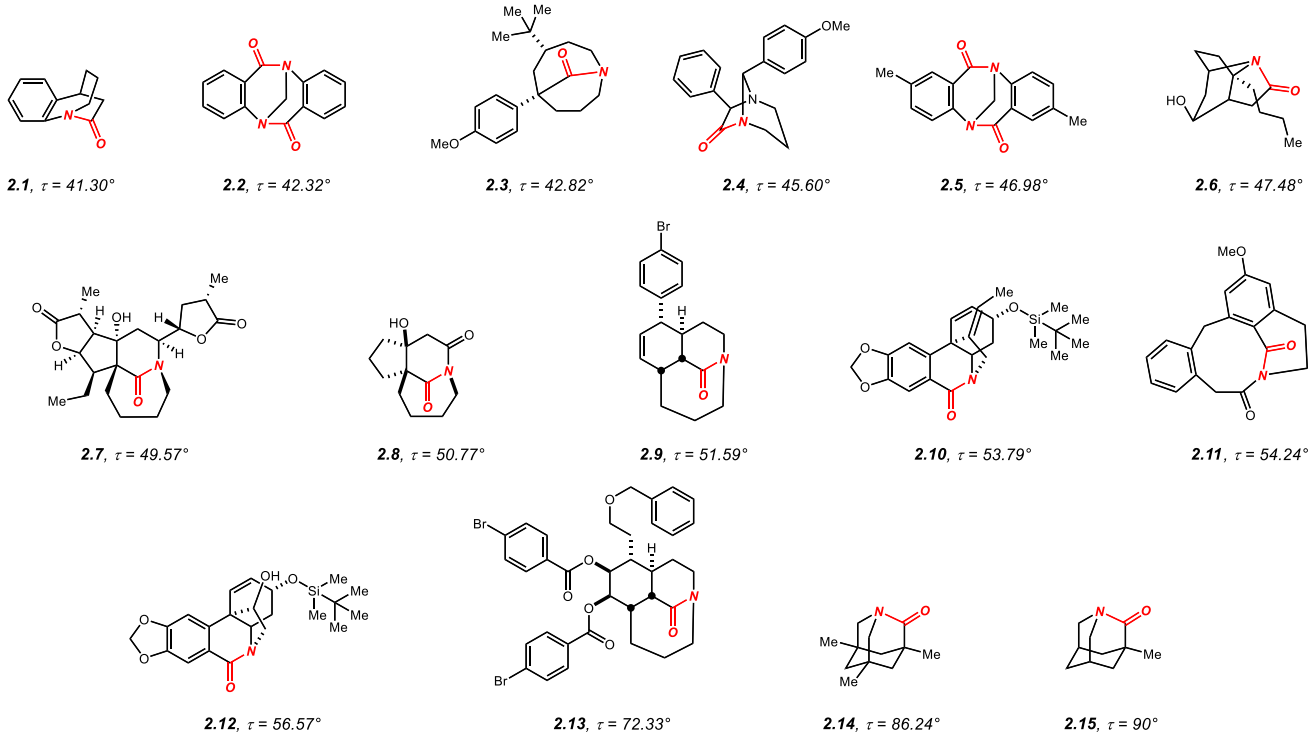


Figure 1. Bicyclic Bridged Amides with Twist Values of 40° to 90°. (See SI for details and expanded tables).

Examination of amides in Figure 1[140–152] reveals that highly rigid adamantanone (**2.14-2.15**),[39,43] haemanthidine (**2.10**, **2.12**)[151] and tricyclic bridged stemona (**2.7-2.9**, **2.13**)[147,148] bicyclic frameworks are most effective for achieving high twist in bridged lactams. Note that the nomenclature that underlines the bridge with the C=O bond in bicyclic structures containing the lactam linkage is used. It is important to note that the position of the bridge determines the properties of amides in this class of lactams. It is interesting to note that related one-carbon bridged [6.3.1] (**2.11**)[152] and [4.3.1] (**2.3**)[142] systems result in a comparably high twist of the amide bond. Other ring systems that lead to $\tau > 40°$ include a [2.3.2] benzo-fused system (**2.1**),[140] unique Tröger's base bis-twisted amides (**2.2**, **2.5**),[144,145] a related [2.1.3] 1,5-diazabicyclo[3.2.1]octane system (**2.4**)[143] and stemofoline alkaloid framework (**2.6**).[146] Overall, it is rather surprising that more than 80 years after the original proposal by Lukeš only very few bridged lactams with appreciable twist have been structurally characterized.

2.2. N-Acyl-Activated Cyclic Twisted Amides

Activation of cyclic amides with N-acyl group represents another effective approach to achieve geometric distortion of the amide bond (Figure 2).[153–162] Note that in contrast to acyclic amides and amide derivatives (Section 3), the twisted amide bond in examples in Figure 2 refers to the cyclic amide bond in lactams (cf. exo-cyclic amide bond). These examples also include related imidoyl-type activation as represented by **2.16**.[153] As shown in Figure 2, the activating group can be within the ring (endocyclic), such as amides **2.16**,[153] **2.17**,[154] **2.23**,[160] **2.25**[162] or more commonly outside the lactam ring (exocyclic), such as **2.18**,[155] **2.19**,[156] **2.20**,[157] **2.21**,[158] **2.22**.[159] The twisted lactams feature 7-membered rings (**2.16**, **2.17**, **2.19**, **2.22**, **2.23**, **2.25**), 8-membered rings (**2.18**, **2.20**, **2.21**) or macrocyclic rings (**2.24**).[161] The latter compound is related to imide macrocycles (*vide infra*, Section 2.6.) The most recognized in this series is the eight-membered lactam **2.20**, featuring a transoid amide bond, wherein the amide bond distortion arises from steric and electronic factors.[157] The main distortion has been ascribed to the avoidance of allylic strain between the lactam N–C(O) bond and the N–acyl bond. Overall, N-acyl-activation appears as a highly effective way of distorting cyclic amide bonds, while the $n_N \rightarrow \pi^*_{C=O}$ conjugation is accomplished through the presence of another carbonyl group (exo- or endocyclic).

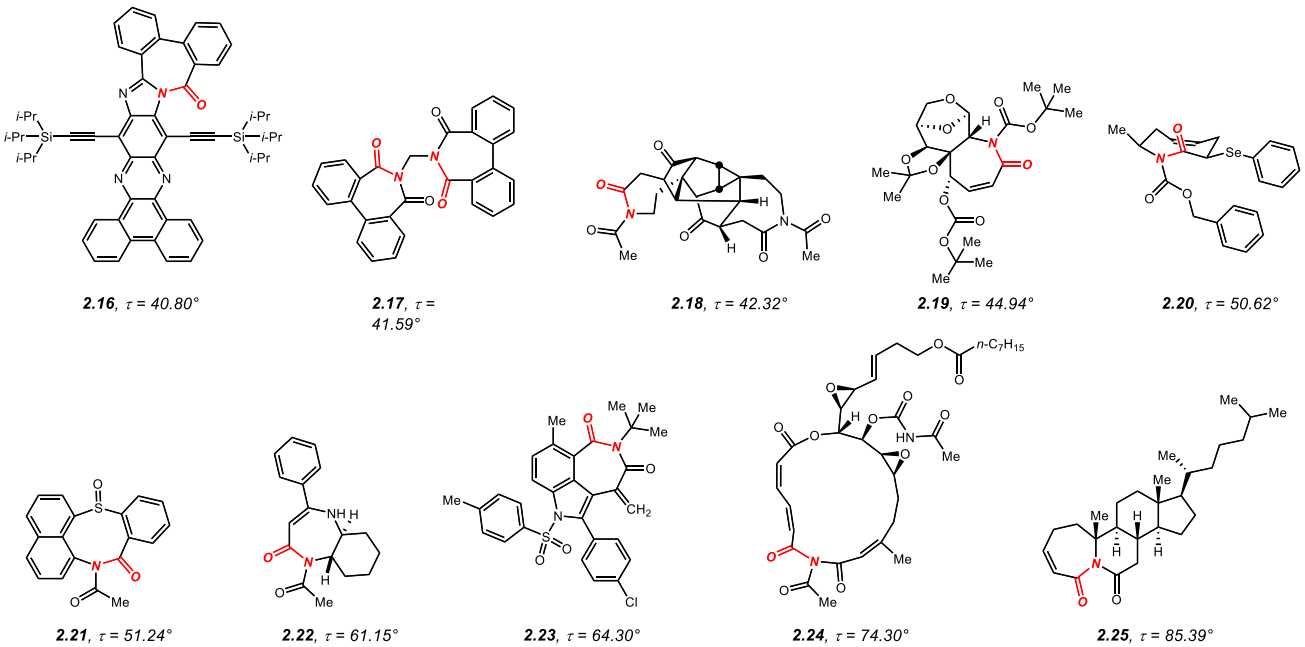
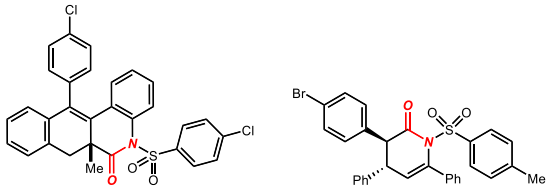


Figure 2. N-Acyl-Activated Cyclic Amides with Twist Values of 40° to 90°.

2.3. N-Sulfonyl-Activated Cyclic Twisted Amides

N-sulfonyl activation represents a related method to N-acyl activation to twist cyclic amides bonds (Figure 3).[163] The twist in the two lactams reported (**2.26-2.27**)[164,165] results from a significant non-bonding interaction between the N-sulfonyl group and the adjacent C-substituents on both sides on the amide bond. It is interesting to note that both types of lactams are readily available by 1,7-enyne bicyclizations[164] and enolate cyclizations.[165]



2.26, τ = 43.78° ***2.27***, τ = 49.59°

Figure 3. N-Sulfonyl-Activated Cyclic Amides with Twist Values of 40° to 90°.

2.4. N-Quaternized Cyclic Twisted Amides

Two classes of N-quaternized cyclic amides containing highly twisted amide bonds have been reported: (i) bridged lactams (Figure 4A); and (ii) cyclic non-bridged amides (Figure 4B).

It is particularly interesting from the standpoint of novel reactivity of N–C(O) bonds that amides **2.28-2.33** in Figure 4A have been prepared by the direct N-protonation of the corresponding bridged lactams.[142,43,36,38] Note that this class also includes the incredibly strained bridged lactam **2.33** embedded in a one-carbon bridged [2.2.1] ring system with N-coordinated BF_3 complex.[38] The nitrogen atom in this particular lactam as well as in the archetypal 2-quinuclidonium tetrafluoroborate **2.32** featuring unsubstituted [2.2.2] system are protected in situ as quaternary salts after the ring forming intramolecular Schmidt reaction, which enables their facile isolation.[36] In contrast, tricyclic lactam precursors to **2.28-2.30** are stable to the aqueous isolation conditions and undergo facile N-protonation by mild acids, such as *p*-TsOH.[142] This class is also represented by the parent 1-aza-adamantanone **2.31** crystallized as HBF_4 salt.[43] In general, quaternization of the nitrogen atom in bridged lactams results in a significant increase of amide bond twist.[166]

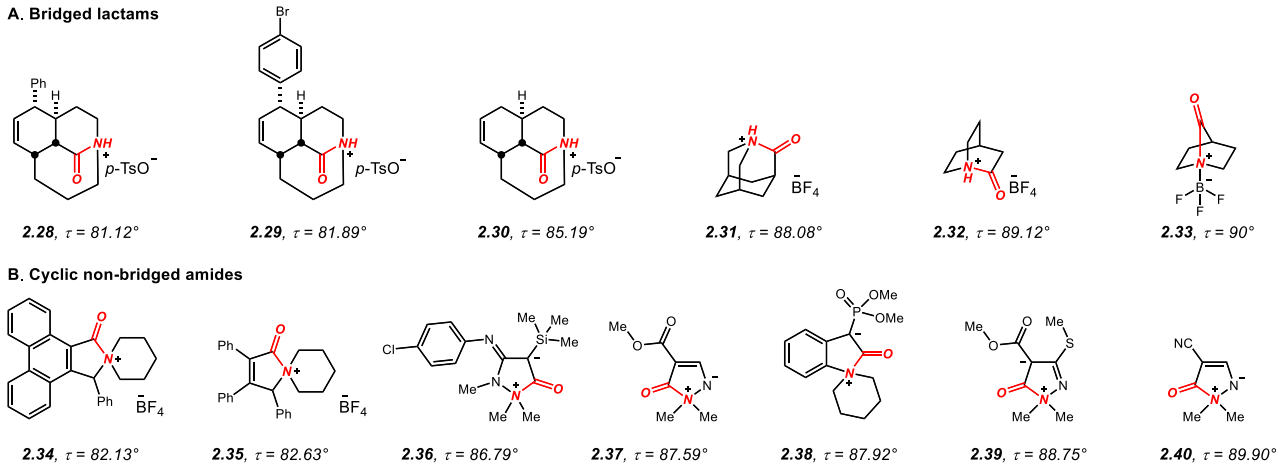


Figure 4. N-Quaternized Cyclic Amides with Twist Values of 40° to 90°.

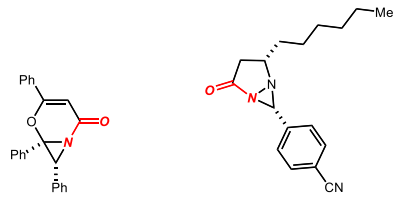
N-Quaternized amides **2.34-2.35** feature close to perpendicular twist of the amide bond (Figure 4B).[167–171] These amides have been prepared by the reaction of aminocarbene complexes of chromium with alkynes and demetallation. Of interest is the facile N–C(O) ring opening upon exposure to Et_3N, consistent with the high reactivity of N-alkylated non-planar amides.[167]

Five-membered betaines, such as **2.36** has been isolated from the reaction of aryl isocyanate with an yne-hydrazines.[168] Related compounds include pyrazolinium ylides **2.37** and **2.40** prepared from β-enaminoesters[169] as well as 2-oxoindolinium enolate **2.38** from Wolff rearrangement/intramolecular nitrogen addition[170] and pyrazolium betaines, such as **2.39** from the reaction of ketene ethylene acetals with N,N-dialkylhydrazines.[171] Overall, these zwitterionic N-alkyl amides represent an attractive indirect way of accessing fully twisted ($\tau > 82°$) cyclic amide bonds.

2.5. N-Aziridinyl-Fused Cyclic Twisted Amides

Amides **2.41-2.42** featuring fused [4.1.0] and [3.1.0] ring systems with the bridgehead nitrogen in a 3-membered ring contain significantly twisted amide bonds ($\tau > 50°$) (Figure 5).[172,173] It should be noted that in these examples, amide bond twist is accompanied by full pyramidalization of the nitrogen atom geometrically enforced by the 3-membered ring (χ_N = 68.1° and 61.9° for **2.40** and **2.41**, respectively).[17]

Amide **2.40** undergoes facile aziridine ring opening with MeOH to give the seven-membered lactam; the reaction is likely initiated by N-protonation of the amide bond nitrogen.[172]



2.41, $\tau = 51.14°$ ***2.42***, $\tau = 68.53°$

Figure 5. N-Aziridinyl Cyclic Amides with Twist Values of 40° to 90°.

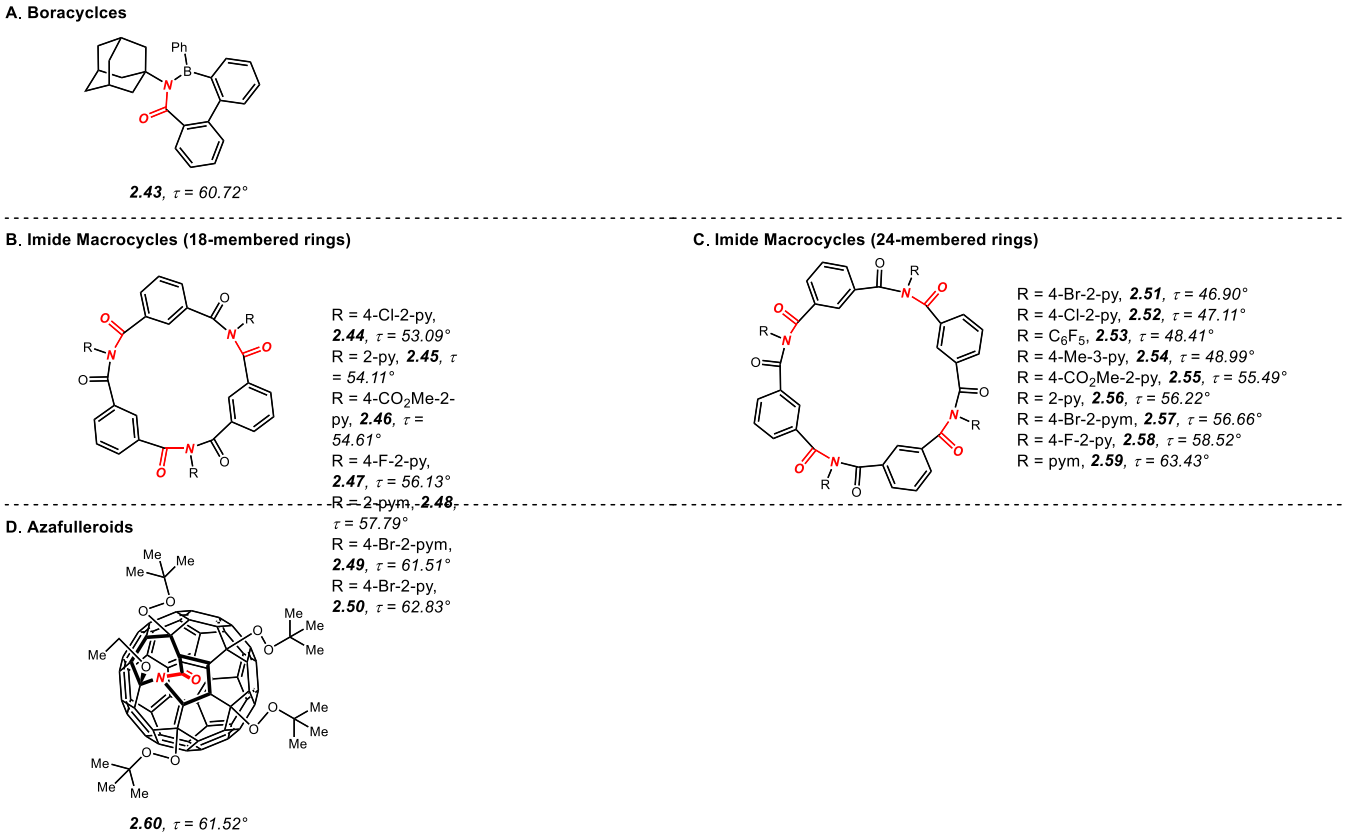


Figure 6. Miscellaneous Cyclic Amides with Twist Values of 40° to 90°.

2.6. Miscellaneous Cyclic Twisted Amides

Miscellaneous examples of cyclic amides with considerable twist of the amide bond include an intriguing BNC_5 boracycle **2.43** reported by Martin (Figure 6A),[174] imide macrocycles with 18-membered (**2.44-2.50**) and 24-membered (**2.51-2.59**) ring systems (Figure 6B-C)[175–179] and

azafulleroids, such as **2.60** (Figure 6D).[180] In particular, the x-ray structure of boracycle **2.43** indicates N_{lp} delocalization into the boron atom (short B–N bond of 1.417 Å and short C=O bond of 1.209 Å).[174] Resonance energies have not been reported. These intriguing compounds might find applications as boron Lewis acids in organic chemistry. Imide macrocycles **2.44-2.50** and **2.51-2.59** feature 3 and 4 sets of non-planar amide bonds, respectively, restricted by the imide-conformation.[175–179] Azafulleroid **2.60** contains one-carbon bridged [4.3.1] ring system (*vide supra*, Section 2.1.) and readily reacts with basic alumina or $BnNH_2$ to give the corresponding azafullerenes.[180]

3. Acyclic Amides: Twist 40-90°

Activation of acyclic tertiary amides by intramolecular steric repulsion between amide bond substituents results in disruption of amidic resonance, N–C(O) bond rotation and overall deformation of the amide bond geometry.[163] The first to recognize that such geometric repulsion can be used to effectively twist acyclic amide bonds was Yamada in 1993,[57–62] which resulted in an elegant investigation of 3-pivaloyl-1,3-thiazolidine-2-thiones (such as **3.56**, Figure 8) benefiting from the large radius of the thiocarbonyl group in a compact 1,3-thiazolidine scaffold with a very significant τ of 74.3°.[57] It was also noted that since in these acyclic systems, twist is generally disconnected from amide bond pyramidalization. As such, these amides depict the most accurate representation of twisted amides.

In general, acyclic twisted amides can be categorized into the following classes depending on the type of N-activating moiety: (1) N-mono-acyl-activated twisted amides; (2) N-di-acyl-activated twisted amides; (3) N-sulfonyl-activated twisted amides; (4) N-heterocycle-activated twisted amides; and (5) miscellaneous examples.

3.1. N-Acyl-Activated Acyclic Twisted Amides

At present, N-acyl-activation represents by far the most common method to achieve distortion of acyclic twisted amides with numerous examples of various amides, scaffolds and N-acyl activating

groups approaching τ values of 80-90°. For clarity, N-acyl-activated amides have been divided into N-mono-acyl and N,N-di-acyl-activated twisted amides (sections 3.1.1. and 3.1.2.).

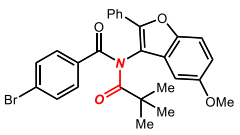
It should be noted that depending on the bond or substitution that are discussed, these amides can also be referred to as imides or derivatives. In these systems, steric distortion is closely related to the electronic activation of the amide bond owing to the presence of another carbonyl group that can participate in $n_N \rightarrow \pi^*_{C=O}$ conjugation.[49–78] In many cases, these amides represent extremely reactive twisted amides with "resonance-disconnected" N–C(O) bond conjugation. Importantly, these acyclic twisted are significantly more stable to storage and hydrolysis conditions than most of the highly twisted bridged lactams,[28–35] which enables their application as acyl transfer reagents or, more recently, as resonance and geometry-tunable electrophilic cross-coupling reagents by N–C(O) oxidative addition to low valent metals.

3.1.1. N-Mono-Acyl-Activated Acyclic Twisted Amides

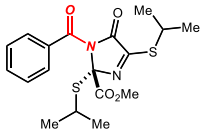
N-Mono-acyl-activated twisted amides with τ values of 40-90° are presented in Figures 7-8.[57,60,181-230] Three points of amide bond geometry should be considered when discussing structures of acyclic twisted amides: (1) N-acyl-activating substituent; (2) the other N-substituent; (3) substitution at the α-carbon. It is important to note that when both of the N–C(O) groups are acyclic, geometric distortion of the more twisted bond represents a balance between the optimum geometry for the two acyl bonds, which often leads to the flattening of the other N-acyl bond.[196]

Examination of the examples in Figures 7-8[57,60,181-230] shows that N-acyl-substituents that result in a substantial twist of the amide bond include acyclic C(O)R, such as aromatic (aryl: **3.1**, **3.21**; anthracenyl: **3.6**, **3.13**), vinyl (**3.9**, **3.39**, **3.59**), heterocyclic (**3.5**, **3.15**), 1° aliphatic (**3.14**, **3.17**, **3.23**, **3.44**, **3.55**, **3.60-3.61**, **3.64**), 2° aliphatic (**3.34**, **3.41-3.42**, **3.45**) and CF_3 (**3.51-3.52**). Furthermore, the activating acyclic acyl group can be C(S)R (such as **3.7**, **3.11**, **3.16**, **3.24**, **3.38**), CO_2R (such as **3.10**, **3.35**, **3.48**, **3.50**, **3.54**, **3.57-3.58**, **3.62**), C(S)OR (such as **3.25**) or $CONR_2$ (such as **3.29**). Cyclic acyl groups include acyl heterocycles, such as imidazolidin-4-ones (**3.2**), 1,3-oxazinan-4-ones (**3.3-3.4**, **3.18**,

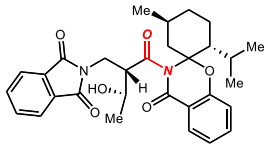
3.27, **3.37**), indolin-2-ones (**3.8**), thiazolidin-2-imines (**3.12**), imidazolidine-2-thiones (**3.19-3.20**, **3.36**, **3.43**, **3.47**), 3,4-dihydroquinazolin-2(1*H*)-ones (**3.22**, **3.26**, **3.28**, **3.31**, **3.33**, **3.40**), tetrahydropyrimidine-



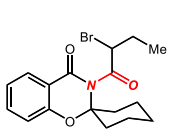
3.1, τ = 40.20°



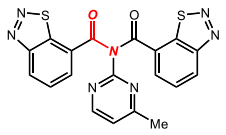
3.2, τ = 40.41°



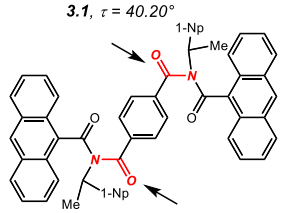
3.3, τ = 40.58°



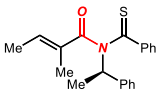
3.4, τ = 40.75°



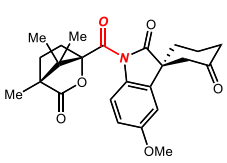
3.5, τ = 40.80°



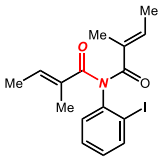
3.6, τ = 40.82°



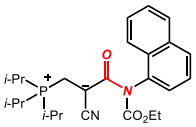
3.7, τ = 41.02°



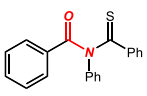
3.8, τ = 41.05°



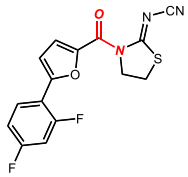
3.9, τ = 41.11°



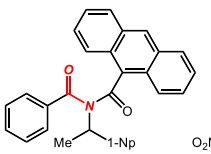
3.10, τ = 41.64°



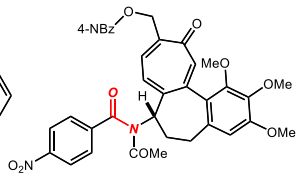
3.11, τ = 41.79°



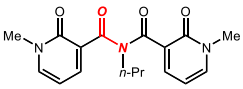
3.12, τ = 41.85°



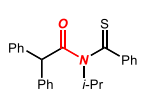
3.13, τ = 41.99°



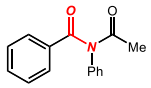
3.14, τ = 42.27°



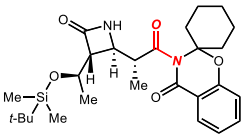
3.15, τ = 42.52°



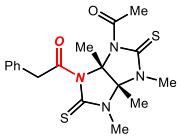
3.16, τ = 42.52°



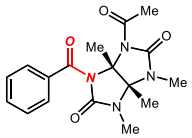
3.17, τ = 42.93°



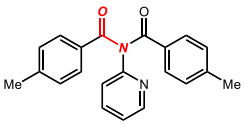
3.18, τ = 44.12°



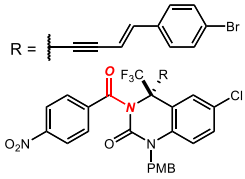
3.19, τ = 44.30°



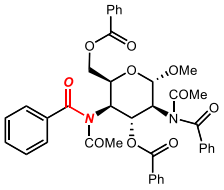
3.20, τ = 44.83°



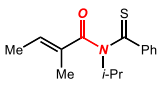
3.21, τ = 46.39°



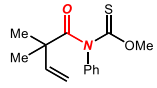
3.22, τ = 46.61°



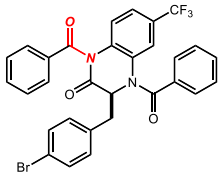
3.23, τ = 46.71°



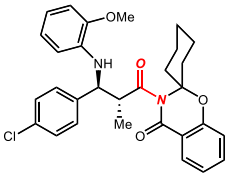
3.24, τ = 47.31°



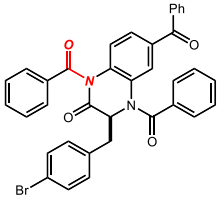
3.25, τ = 47.36°



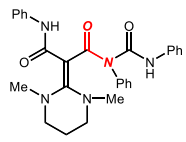
3.26, τ = 48.42°



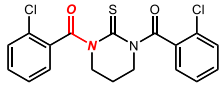
3.27, τ = 50.03°



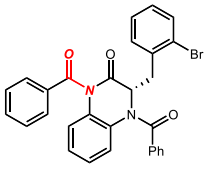
3.28, τ = 50.71°



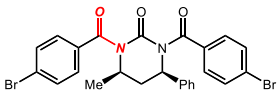
3.29, τ = 51.05°



3.30, τ = 51.52°



3.31, τ = 52.13°



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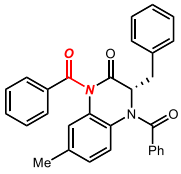
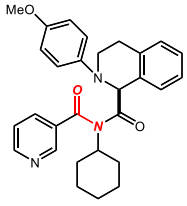
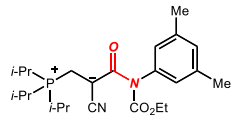


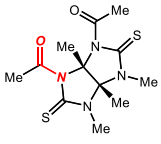
3.33, τ = 53.61°



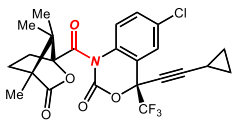
3.34, τ = 54.67°



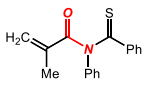
3.35, τ = 55.00°



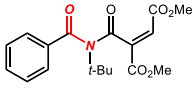
3.36, τ = 55.04°



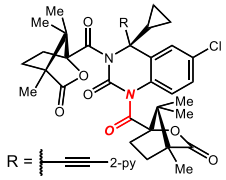
3.37, τ = 55.41°



3.38, τ = 55.93°



3.39, τ = 56.21°



3.40, τ = 57.80°

3.41, τ = 58.47°

3.42, τ = 60.36°

3.43, τ = 60.50°

3.44, τ = 61.15°

3.45, τ = 61.44°

Figure 7. N-Mono-Acyl-Activated Acyclic Amides with Twist Values of 40° to 65°.

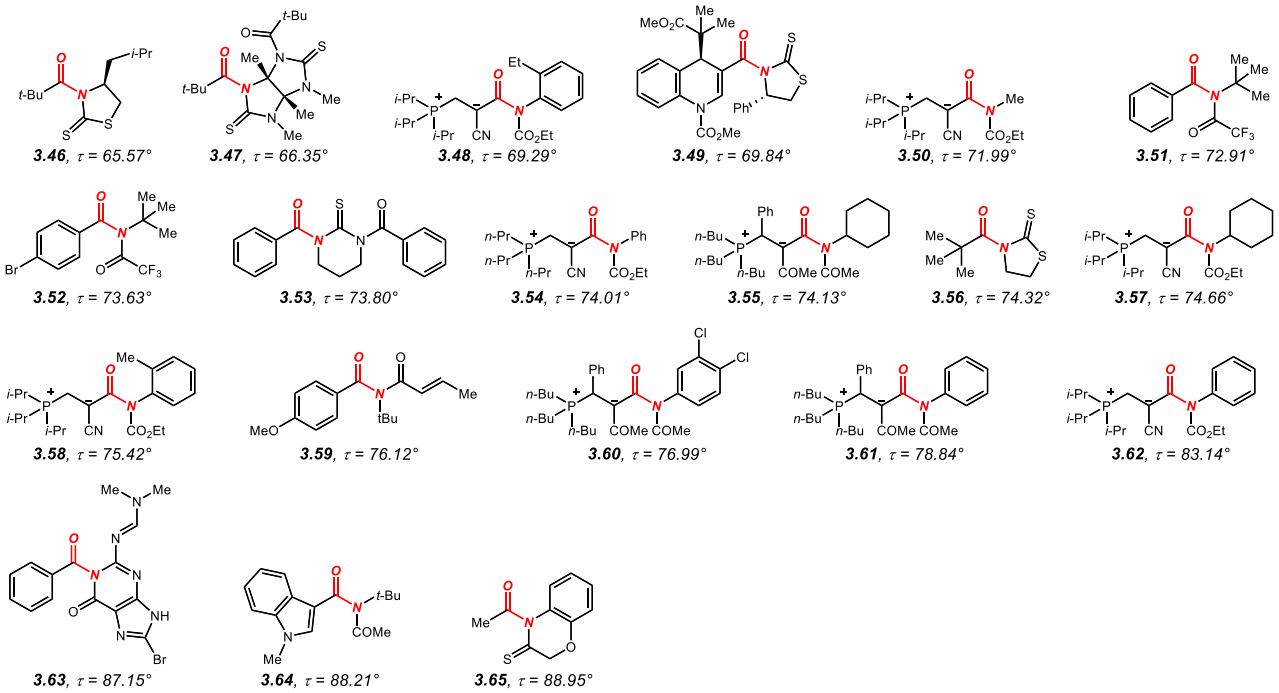


Figure 8. N-Mono-Acyl-Activated Acyclic Amides with Twist Values of 65° to 90°.

2(1*H*)-thiones (**3.30**, **3.53**), tetrahydropyrimidin-2(1*H*)-ones (**3.32**), thiazolidine-2-thiones (**3.46**, **3.49**, **3.56**), 1,9-dihydro-6*H*-purin-6-ones (**3.63**), and 2*H*-benzo[*b*][1,4]oxazine-3(4*H*)-thiones (**3.65**).

There is also a significant variation in terms of the other N-substituent, which includes N-aryl (**3.9-3.11**, **3.17**, **3.25**, **3.29**, **3.35**, **3.38**, **3.48**, **3.54**, **3.58**, **3.60-3.62**), N-heteroaryl (**3.1**, **3.5**, **3.21**), 1° alkyl (**3.15**, **3.50**), 2° alkyl (**3.6-3.7**, **3.13**, **3.14**, **3.16**, **3.23-3.24**, **3.34**, **3.41-3.42**, **3.45**, **3.55**, **3.57**) and 3° alkyl (**3.39**, **3.44**, **3.51-3.52**, **3.59**, **3.64**).

Similarly, the α-carbon substitution can be 1° alkyl (**3.19**, **3.36**, **3.65**), 2° alkyl (**3.3-3.4**, **3.10**, **3.16**, **3.18**, **3.27**, **3.35**, **3.48-3.50**, **3.54-3.55**, **3.57-3.58**, **3.60-3.62**), aryl (**3.2**, **3.6**, **3.11**, **3.13-3.14**, **3.17**, **3.20-3.23**, **3.26**, **3.28**, **3.30-3.33**, **3.39**, **3.41-3.42**, **3.45**, **3.51-3.53**, **3.63**), heteroaryl (**3.5**, **3.12**, **3.15**, **3.34**, **3.44**, **3.59**, **3.64**), vinyl (**3.7**, **3.24**, **3.29**, **3.38**), and 3° alkyl (**3.1**, **3.8**, **3.25**, **3.37**, **3.40**, **3.43**, **3.46-3.47**, **3.56**).

It has been recognized quite early on that increased steric substitution at the α-position leads to an increase in steric repulsion with the N-activating substituents, resulting in a general order of twist correlating with the increase of steric Charton and Taft parameters.[57,60] In contrast, the substitution at the nitrogen atom typically represents a balance between the steric demand of the N-moieties, with the highest twist obtained with a large difference in steric hindrance between the substituents.

Several examples summarized in Figures 7-8 deserve additional discussion. Mono-twisted N-acetyl amides, such as **3.17**, undergo selective N–C(O) scission of the more twisted ArC(O)–N amide bond (τ = 43.0° cf. N–Ac, τ = 5.1°) under Pd and Ni catalysis to give ketones and biaryls.[196] These "mono-twisted" acyclic amides are readily synthesized from the corresponding 2° benzamides. Twisted amides embedded in 2,5-dithioglyucoluril scaffold, such as **3.19-3.20**, **3.36** and **3.47** have been studied by Harrison and co-workers.[198,199,213,219] These amides feature one of the exocyclic amide bonds significantly more twisted than the other exocyclic bond for small α-carbon substituents (e.g., R = Me, **3.36**, τ = 55.0° vs. τ = 2.6°), and undergo further twisting with the increase of steric hindrance at the α-carbon (e.g., R = *t*-Bu, **3.47**, τ = 66.4° vs. τ = 54.3°).[213,219] N-Acyl-1,3-thiazolidine-2-thiones, such as **3.46**, **3.49** and **3.56** have been pioneered by Yamada as the first models of the acyclic twisted amides.[57,60] The most twisted in the series is N-pivaloyl derivative **3.56** (τ = 74.3°). These amides undergo selective hydrolysis with the rate correlated to the amide bond twist.[59] Recent studies by Weng introduced N-trifluoroacetyl amides, such as **3.51-3.52**.[223] Facile synthesis from the corresponding nitrones and very high twist (τ = 72.9-73.6°) in the presence of electronically-activating trifluoroacetyl group are noteworthy. These amides are formally analogous to N-triflyl amides.[231] Finally, amide **3.65** featuring a benzofused morpholine-3-thione system reported by Yamada represents one of the rare examples of exceptionally twisted amides (τ = 89.0°) with sterically unbiased 1° alkyl substituent at the α-carbon.[230] The authors proposed that the steric interactions between the thiocarbonyl group and the alkyl substituent contribute to the high twist of the amide bond.

3.1.2. N,N-Di-Acyl-Activated Acyclic Twisted Amides

N,N-Di-acyl activation represents one of the most effective methods for twisting amide bonds (Figure 9).[232–266] In this class of amides, n_N to $\pi^*_{C=O}$ conjugation is satisfied by delocalization onto two exo-cyclic carbonyl groups (cf. single C=O, section 3.1.1.), which leads to enhanced geometric distortion dependent primarily on steric and to a lesser extent on electronic properties of the activating group (cf. balanced effect of steric hindrance of all substituents comprising the amide bond, section 3.1.1.).

In particular, N,N-di-acyl-activation is notable for providing amide-based electrophilic reagents with reactivity exceeding acyl halides that have been exploited both in transition-metal-catalyzed cross-coupling chemistry and as acyl transfer reagents in transition-metal-free reactions.[49–78] Computational studies on N,N-di-acyl-activated amides have been published, demonstrating that in many cases amidic resonance of the twisted amide bond is very low or virtually non-existent (e.g., N-acyl-glutarimides, RE < 2.4 kcal/mol depending on the R substituent at the α-position of the amide bond, **3.100**, Figure 9).[232,240,244] Furthermore, it is worth noting that in contrast to the typically less twisted N-mono-acylated amides which are generally synthesized from the corresponding acyl halides or other activated carboxylic acid derivatives, the direct N,N-di-acylation of fully planar 1° amide bonds is possible,[49,50] which enables for twisting of otherwise planar bonds.

In general, N,N-di-acyl activation can be accomplished using N-acyclic activating groups,[232–266] such as C(O)R where R is an aromatic or heteroaromatic ring (**3.67**, **3.70**) or CO_2R where R is *t*-Bu group (**3.78**, **3.80**); however, more common is the use of cyclic N-activating groups, including heterocycles such as succinimide (**3.66**, **3.69**, **3.77**), hydantoin (**3.68**, **3.71-3.72**, **3.74**, **3.76**), 2,4-thiazolidinedione (**3.73**), phthalimide (**3.75**, **3.91**), 1,3,5-triazinane-2,4-dione (**3.79**), uracil (**3.81-3.83**, **3.85-3.87**, **3.89-3.90**, **3.94-3.96**, **3.99**, **3.101-3.103**), 1,8-naphthalimide (**3.84**), thioquinazoline-2,4-dione (**3.92**), 1,3,5-triazinane-2,4,6-trione (**3.93**), 3-azabicyclo[3.2.1]octane-2,4-dione (**3.97**), 1,2,4-triazine-3,5-dione (**3.98**), glutarimide (**3.100**) and isoquinoline-1,3-dione (**3.104**).

The α-carbon substitution can be 1° alkyl (**3.79**, **3.103**), 3° alkyl (**3.91**, **3.93**), alkenyl (**3.66**, **3.84**, **3.97**) or most commonly aryl (**3.67-3.70**, **3.72-3.78**, **3.80-3.83**, **3.86-3.90**, **3.92**, **3.94-3.96**, **3.98-3.102**, **3.104**) or heteroaryl (**3.71**, **3.85**). In general, an increase of amide bond twist is observed with more

sterically-demanding α-carbon substituents. Furthermore, six-membered N-acyl-activating groups result in a higher twist than their five-membered counterparts. A study of the series of glutarimides, succinimides and phthalimides demonstrated the following order of amide bond distortion (3° alkyl >

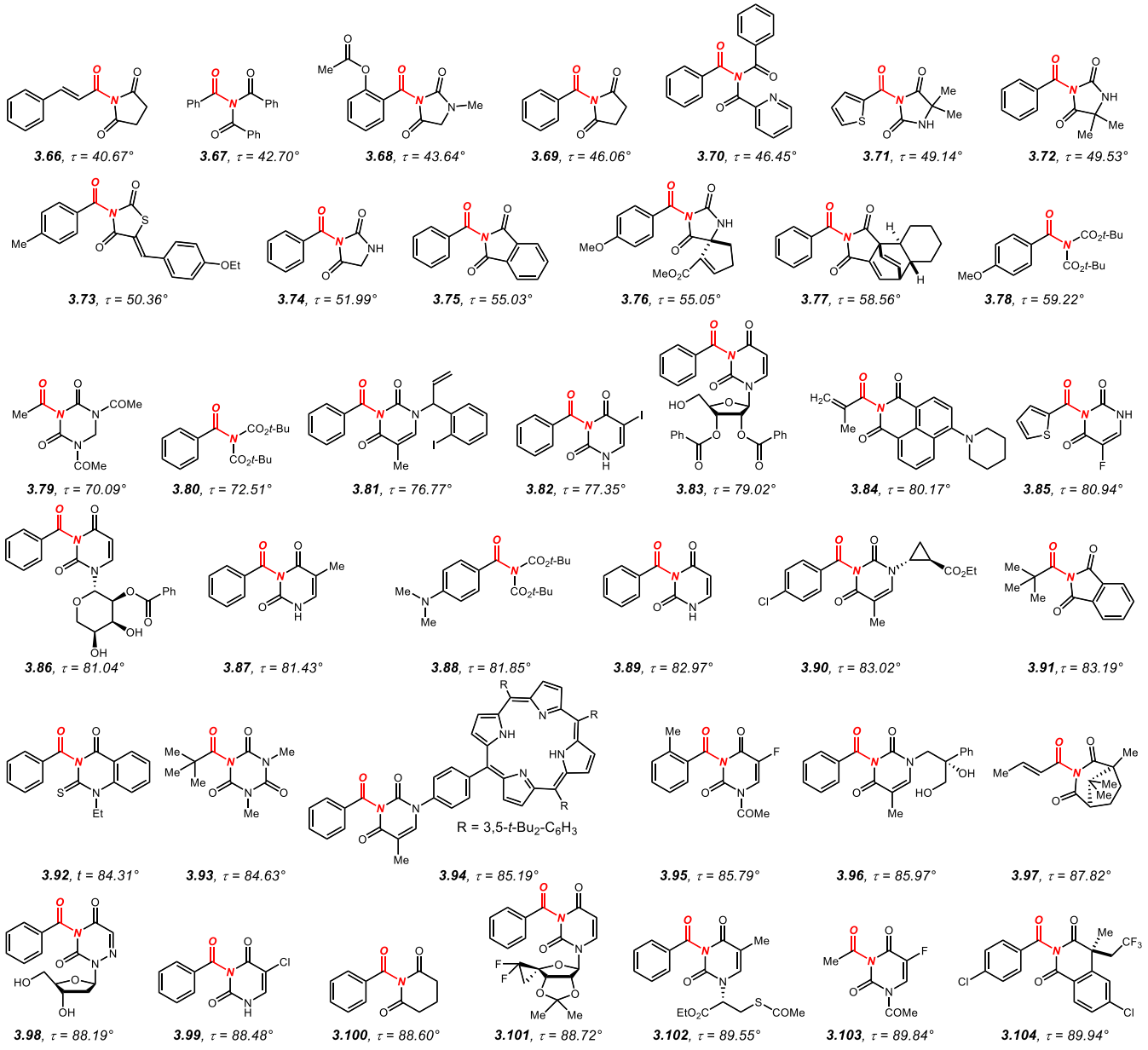


Figure 9. N,N-Diacyl-Activated Acyclic Amides with Twist Values of 40° to 90°.

aryl > 2° alkyl > 1° alkyl; glutarimide > succinimide > phthalimide).[237] It is further interesting to note that heteroatom substitution of the activating ring has a noticeable but not a significant difference in amide bond twist (e.g., succinimides, **3.69** vs. hydantoins, **3.74**).[239,240]

Several amides in this series deserve an additional comment. First, N-acyl-glutarimides and N-acyl-succinimides, such as **3.69** and **3.100**, have emerged as highly reactive yet stable acyl- and aryl-electrophiles by metal-catalyzed N–C(O) bond oxidative addition.[237] In many cases, the more twisted N-acyl-glutarimides are significantly more reactive than N-acyl-succinimides (**3.100**, $\tau = 88.6°$ vs. **3.69**, $\tau = 46.1°$); however, it should be noted that the use of both classes of these acyclic twisted amides is highly advantageous in metal-catalysis due to higher stability than that of the corresponding acyl halides and anhydrides.[49–78] Second, twisted amides activated by exo-cyclic Boc groups, such as **3.88** ($\tau = 82.9°$) permit for rapid synthesis from 1° benzamides.[244] These amides have also been utilized in cross-coupling chemistry by acyl and decarbonylative mechanisms. Interestingly, while the amidic resonance is significantly reduced (RE = 6.3 kcal), steric distortion closely depends on the *t*-Bu groups.[244] Third, many of the amides in this class based on the uracil and thymine frameworks have been synthesized with the goal of medicinal chemistry applications (e.g., **3.98**, **3.101-3.103**),[261,263–265] and it is likely that amide bond twist plays a role in the biological activity of these compounds. Finally, the N-pivaloyl phthalimide derivative **3.91** synthesized by Yamada represents one of the classic examples of acyclic twisted amides, wherein the amide bond is almost fully perpendicular by the virtue of N-activating group and α-carbon substituent ($\tau = 83.2°$ vs. **3.75**, $\tau = 55.0°$).[254]

3.2. N-Heterocycle-Activated Acyclic Twisted Amides

N-Heterocyclic activation (i.e., activation by connecting the amide nitrogen atom to a heterocyclic system) represents another highly effective method of twisting amide bonds (Figure 10).[267–288] In this method, heterocycles are either aromatic resulting in N_{lp} delocalization onto the aromatic ring system with a subsequent twisting of the amide bond, or non-aromatic, which leads to amide bond twisting due to steric repulsion in the absence of additional N_{lp} delocalization.

The most recognized amides in this class are N-benzoylpyrroles, such as **3.107**, studied by Brown and co-workers.[269] More recently, Miller and co-workers reported the synthesis and structural characterization of related imidazole analogues, such as **3.118**, **3.126** and **3.133**.[278] In general, these N-

acyl-azolides are well-established to undergo hydrolysis with the enhanced rate depending on the heterocycle and twist of the amide bond.[289–292]

The heterocyclic N-acyl twisted amides are of interest in medicinal chemistry as heterocyclic building blocks and target active compounds.[293,294] Furthermore, cross-coupling of N-acyl-azolides by N–C(O) oxidative insertion has been reported.[289,290] It should be noted that twisting in this class of amides is closely dependent on the steric impact of the heterocyclic ring system, which in all cases requires at least a single substitution at the adjacent C2-position to the amide nitrogen atom to achieve appreciable amide bond twist (Figure 10).[267–288] As a consequence, the synthesis of these twisted amides is often is more challenging than N,N-di-acyl or N-mono-acyl-derivatives discussed in sections 3.1.1. and 3.1.2. Moreover, N-heterocyclic activated twisted amides are typically less hydrolytically stable than N-acyl or N,N-di-acyl counterparts since they cannot benefit from the n_N to $\pi^*_{C=O}$ delocalization on the adjacent carbonyl group.[289–292]

In general, twisting of the amide bond in this class of amides (Figure 10) [267–288] can be achieved by using aromatic N-heterocycles, such as pyrroles (**3.105**, **3.107**, **3.111**, **3.117**), pyrazoles (**3.108**, **3.125**), indoles (**3.112**, **3.114**, **3.122**, **3.124**, **3.129-3.132**), imidazoles (**3.113**, **3.118**, **3.126**, **3.133**), benzimidazoles (**3.115**, **3.120**), pyridazin-4(1*H*)-ones (**3.119**) and pyrrolo[3,2-*d*]pyrimidines (**3.121**, **3.128**) or saturated N-heterocycles, such as oxazolidin-5-ones (**3.106**, **3.110**, **3.116**), 1,2-dihydropyridines (**3.109**), octahydrocyclopenta[*b*]pyrroles (**3.123**) and 1,2,3,6-tetrahydropyridazines (**3.127**). An important difference is that in N-aromatic heterocycles the amide bond twisting has its origin in electronic delocalization of the lone pair at nitrogen on the aromatic ring[269,289] in conjunction with steric hindrance at the ortho positions to the amide nitrogen. These N-acyl-azolides have been shown to have significantly reduced amidic resonance (e.g., N-benzoyl-pyrrole: RE = 9.3 kcal/mol, **1.4**, Scheme 1; N-benzoyl-pyrazole: RE = 7.8 kcal/mol, **1.5**, Scheme 1; N-benzoyl-imidazole: RE = 7.8 kcal/mol, **1.6**, Scheme 1).[289] As expected, the resonance is further decreased with steric substitution and the subsequent N–C(O) twisting (e.g., benzoyl-2,5-dimethyl-pyrrole, RE = 2.8 kcal/mol, such as **3.107**, Figure 10).

In contrast, in non-aromatic N-heterocycles (Figure 10),[267–288] the amide bond is twisted primarily due to steric repulsion with the adjacent substituents in the absence of additional N_{lp} delocalization. The α-carbon substitution can be 1° alkyl (**3.105**, **3.111**, **3.113**, **3.117**), 2° alkyl (**3.115**, **3.123**), 3° alkyl (**3.114**, **3.122**, **3.129**, **3.131-3.132**), aryl (**3.106-3.110**, **3.112**, **3.116**, **3.118-3.121**, **3.126-3.128**, **3.133**), heteroaryl (**3.125**) or carbaboranyl (**3.124**, **3.130**). As expected, there is a good correlation between the

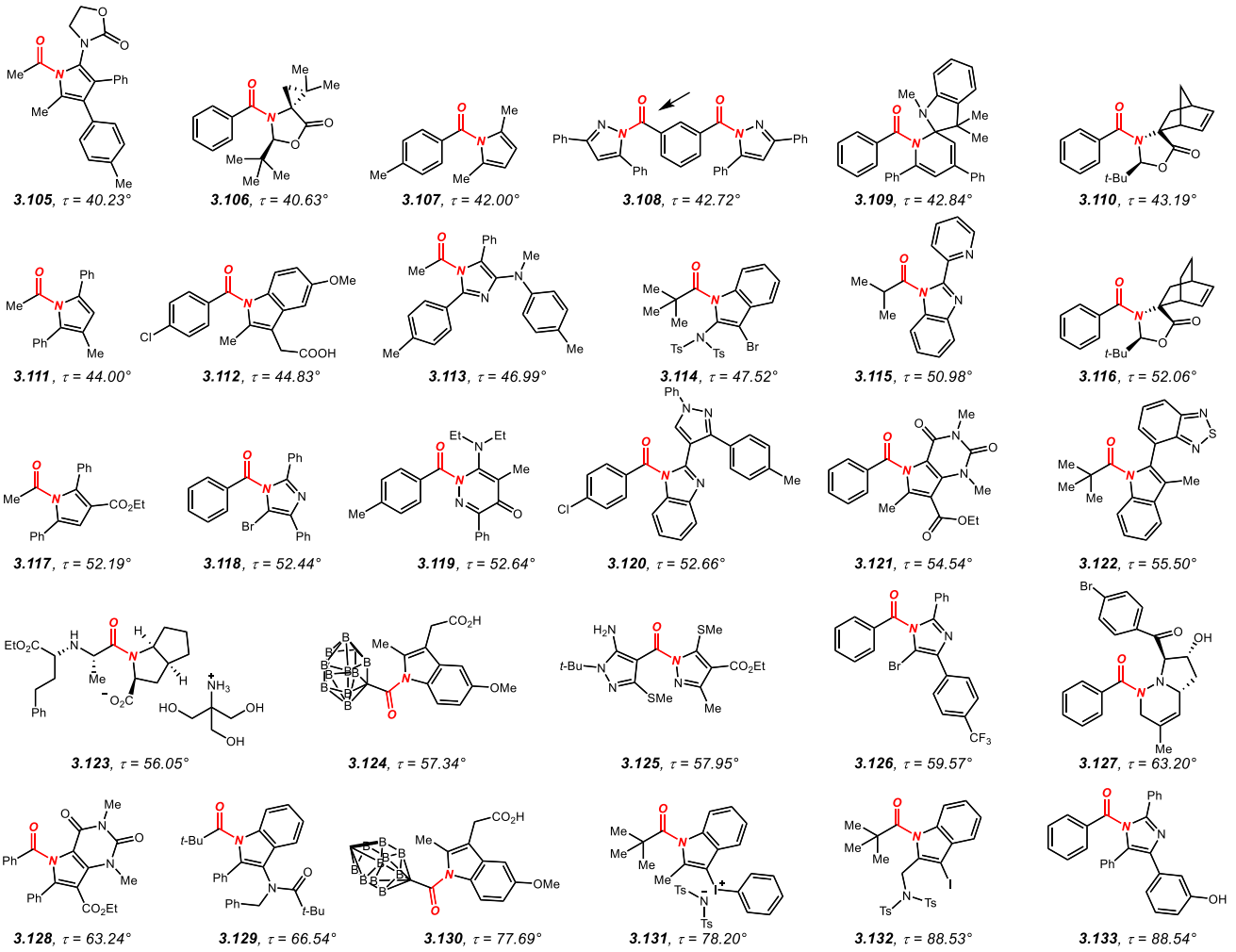


Figure 10. N-Heterocycle-Activated Acyclic Amides with Twist Values of 40° to 90°.

amide bond twist and α-carbon substitution in the following order: 1° < 2° < aryl < 3°. Furthermore, there is the following order of N-heterocycles in amide bond twisting: pyrrole < pyrazole < indole < imidazole; however, specific ring substitution can often alter this trend.

There are several notable amides in this series that deserve additional discussion. Amide **3.107** was prepared by Brown and co-workers in a study of altered amidic resonance in acyclic and cyclic

amides.[269] The authors found that while the twist considerably increased in **3.107** in comparison with N-benzoyl-pyrrole (τ = 7.9° to 42.0°), the N–C(O) and C=O bond lengths have remained practically unchanged (1.409Å to 1.416 Å and 1.211 Å to 1.208 Å), indicative of significant N_{lp} to Ar delocalization. Twisted amides such as **3.111** and **3.117** are readily accessible by Pd(II)-catalyzed C–H annulation of enamides with alkynes, which in principle enables to activate otherwise unsubstituted 1° amides.[273] Amide bonds in N-acyl-indoles undergo twisting due to steric repulsion with a C2-substituents (e.g., **3.112**).[274] In this respect, the direct oxidative C2-imidation of unsubstituted indoles such as **3.114** leads to moderate twist (τ = 47.5°),[276] while the benzylic imidation, such as in **3.132**, affords practically perpendicular amide bonds (τ = 88.5°).[288] N-Acyl-imidazoles, such as **3.118** and **3.133** have been studied by Miller and co-workers.[278] In this case, a significant increase of twist is observed by introducing 2,5-diphenyl substitution on the imidazole ring (τ = 52.4° to τ = 88.5°). Finally, N-acyl-imidazoles, such as **3.120** are potent bacterial FabH inhibitors,[280] while **3.123** is a hydroxymethyl aminomethane salt of ramipril, an antihypertensive drug.[283] Of medicinal interest are also twisted amide carbaboranes derivatives (**3.124**, **3.130**) of indomethacin, a nonsteroidal anti-inflammatory drug.[284] The use of large carbaboranyl substituents instead of 4-chlorophenyl contributes to the high amide bond twist in these compounds. In this case, both the steric and the electronic effect of the carbaboranyl substituent should be considered; electronically, such an electropositive group on the amide bond would be expected to enhance amidic resonance.

3.3. N-Sulfonyl-Activated and N,N-Di-Sulfonyl-Activated Twisted Amides

Several examples of N-sulfonyl-activated twisted amides have been reported (Figure 11).[295–298] With the exception of the moderately twisted α-diazo-substituted amide **3.134** (τ = 43.5°),[295] which is derived from Oppolzer's sultam, amides in this class feature two activating substituents at the nitrogen atom. There are two types of activation: (1) bis-sulfonyl, such as in **3.135-3.136** and **3.138**;[296,297] and (2) combination of N-sulfonyl with N-acyl, such as in **3.137** and **3.139**.[298] The use of more sterically-hindered N-Ts substitution leads to a larger geometrical distortion than with N-Ms (Ms: **3.135**, τ =

63.2°; Ts: **3.138**, τ = 81.0°).[296] Furthermore, it is noteworthy that N-Ts activation is more effective than the related N-Boc activation (Figure 9, **3.80**, τ = 72.5°),[244] which leads to practically perpendicular amide bonds (**3.139**, τ = 87.2°). These N-bis-sulfonyl-amides, such as N-Ms_2 (**3.135**) and N-Ts_2 (**3.138**) as well as N-Ts/Ac (**3.137**) and N-Ts/Boc amides (**3.139**) undergo Pd-catalyzed cross-coupling by oxidative addition of the N–C(O) bond.[296,298]

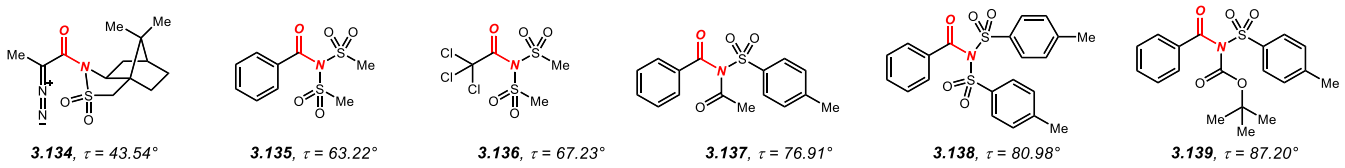


Figure 11. N-Sulfonyl-Activated Acyclic Amides with Twist Values of 40° to 90°.

3.4. Miscellaneous Acyclic Twisted Amides

Amide **3.140** features N-Ph/N-1,3,5-triazin-2-yl substitution, which leads to moderate twist (τ = 44.4°) (Figure 12).[299] It is interesting to note that this amide is significantly more twisted than the related N,N-diphenylbenzamide ($PhCONPh_2$, τ = 11.2°). In contrast, amide **3.141** is a quaternary acyclic N-acyl ammonium salt (τ = 85.1°)[300] that is related to the cyclic counterparts (section 2.4., **2.34**);[167] however, the lack of cyclic structure leads to low hydrolytic stability of this class of N-acyl quaternary ammonium salts.

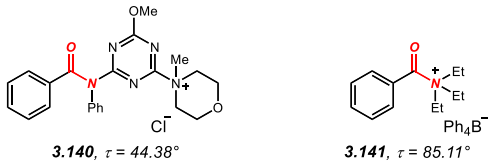


Figure 12. Miscellaneous Acyclic Amides with Twist Values of 40° to 90°.

4. Cyclic Amides: N-Pyramidalization 40-60°

In addition to twisting, amide bond geometric distortion can be achieved by pyramidalization of the nitrogen atom.[28–35] In the extreme cases, these pyramidalized amides feature sp^3 hybridization that is

more characteristic to amines rather than amides.[12,17] The most well-known examples of such pyramidalized amides include confining the amide bond nitrogen in a cyclic ring system, such as azetidine or aziridine, however in these moieties the inherent ring strain of the small-ring heterocycle contributes to the reactivity of these amides.[301] Recent elegant studies by Ohwada and co-workers identified 7-azabicyclo[2.2.1]heptane amides (such as **5.7**, Figure 21) as another class of fully pyramidalized amides.[302-314]

It should be noted that with the exception of these inherently restricted ring systems,[302-314] at present, it is not clear if N-pyramidalization alone is sufficient to engender new reactivity of amide bonds.[28–35] In this respect, the case of bridged lactams is instructive; it has been shown in several studies that properties of twisted bridged lactams can be correlated with both twist and nitrogen pyramidalization when (1) comparing amide distortion within the same classes of N-alkyl non-planar bridged amides, and (2) the amide bond is sufficiently geometrically altered to promote N-amino-ketone type reactivity.[45,46,117,118,315] By contrast, electronic activation by N-acyl or related substitution leads to redistribution of the nitrogen lone pair into the activating substituent,[49–78] which in turn disconnects the amide bond conjugation within the N–C(O) moiety and results in N_{lp} being engaged in another n_N to $\pi^*_{X=O}$ delocalization.

Although thus far, with the exceptions noted above, clear correlations between N-pyramidalization and amide bond reactivity have not been found, these pyramidalized amides are fundamentally important as geometric probes for amide bond resonance,[12] amide pyramidalization[302] and cis/trans amide bond rotation.[305] Applications of pyramidalized amides as peptidomimetics have been reported.[308,310–314] Furthermore, N-pyramidalization is the key feature in the mechanism of action of β-lactam antibiotics.[316–318]

4.1. Bridged and Related Amides

Due to the geometric confinement of the amide bond in a rigid bicyclic ring structure, bridged amides are unique in the class of distorted amides in that typically twist and nitrogen pyramidalization are correlated with each other, [45,46,117,118,315] while one effect follows the other depending on the ring size,

type of the ring and peripheral substitution.[28–35] This correlation is expressed by the additive distortion parameter ($\tau+\chi_N$) introduced recently using one-carbon bridged lactams,[117,118] while earlier studies, in particular, by Greenberg and co-workers,[45,46,48] demonstrated similar correlations in larger ring systems.

Since in this class of amides twist (τ) and nitrogen pyramidalization (χ_N) are connected to each other, the reader is encouraged to consider this section together with section 2.1.[140–152, 36,38,43] Representative examples of bridged amides together with related amides featuring significant χ_N values of >40° are presented in Figure 13.[319–336] Detailed summary of distortion parameters is presented in the Supporting Information. This section focuses on highlighting examples of bridged lactams that feature high χ_N in the absence of considerable twist, a property that is closely related to the specific ring system and can be potentially utilized to separate χ_N from twist in studying the properties of non-planar amide bonds.[47,166]

In this respect, amides **4.1** (χ_N = 41.4°, τ = 5.4°),[319] **4.2** (χ_N = 43.4°, τ = 1.2°),[320] **4.7** (χ_N = 46.6°, τ = 7.5°),[325] **4.8** (χ_N = 47.7°, τ = 16.7°),[326] **4.9** (χ_N = 48.8°, τ = 20.7°),[327] **4.10** (χ_N = 49.0°, τ = 21.9°),[328] **4.11** (χ_N = 49.2°, τ = 16.3°),[329] **4.13** (χ_N = 50.5°, τ = 23.5°),[330] **4.14** (χ_N = 51.4°, τ = 28.1°),[331] **4.16** (χ_N = 52.7°, τ = 30.8°),[332] **4.17** (χ_N = 52.8°, τ = 23.4°),[328] **4.18** (χ_N = 54.9°, τ = 30.2°),[331] **4.19** (χ_N = 54.9°, τ = 16.7°),[333] **4.20** (χ_N = 55.9°, τ = 29.8°),[331] **4.22** (χ_N = 57.1°, τ = 35.3°),[334] **4.23** (χ_N = 57.2°, τ = 35.6°),[335] **4.24** (χ_N = 57.5°, τ = 34.4°)[336] and **4.26** (χ_N = 58.6°, τ = 39.1°)[144,315] feature significantly larger χ_N values than τ and may be considered as bridged amide models for probing the effect of nitrogen pyramidalization on the properties of these amides under the proviso that in these systems both properties are still connected with each other.

In general, these amides include (1) constrained amides with additional bridging, such as **4.1**, **4.2**; (2) amides in [4.3.1] bridged systems, such as **4.7**, and [3.3.1] bridged systems, such as **4.8-4.11**, **4.13**, **4.16-4.17**, **4.19**; (3) Tröger's base twisted amides, such as **4.14**, **4.18**, **4.20**, **4.24**, **4.26**; (4) azetidinyl bridged amide **4.22** in a [4.1.1] system; (5) amide **4.23** in a [2.2.3] ring system. In addition, amides **4.3** (χ_N = 43.5°, τ = 9.7°)[321] and **4.4** (χ_N = 43.7°, τ = 10.2°)[322] feature tetracyclic spirolactam scaffold that is structurally related to bridged lactams by an additional C–C bond connectivity.

In contrast, bridged lactams, such as tricyclic bridged **4.12** (χ_N = 49.8°, τ = 72.3°) and their N-protonated analogues, such as **4.15** (χ_N = 52.0°, τ = 81.9°),[142,149] 1-aza-2-adamantanone derivatives, such as **4.27** (χ_N = 61.7°, τ = 90.0°)[39,43] and 2-quinuclidone derivatives, such as **4.29** (χ_N = 69.8°, τ = 90.0°)[36,38] feature high pyramidalization and high twist. In particular, the reactivity of N-pyramidalized bridged amides in a [3.3.1] ring system has been studied, showing increased rates of hydrolysis,[327,329] It is worth noting that the high rigidity of structures **4.25** and **4.29** means that little change in distortion is observed in going from the unprotonated lactam structure to the N-protonated salts.

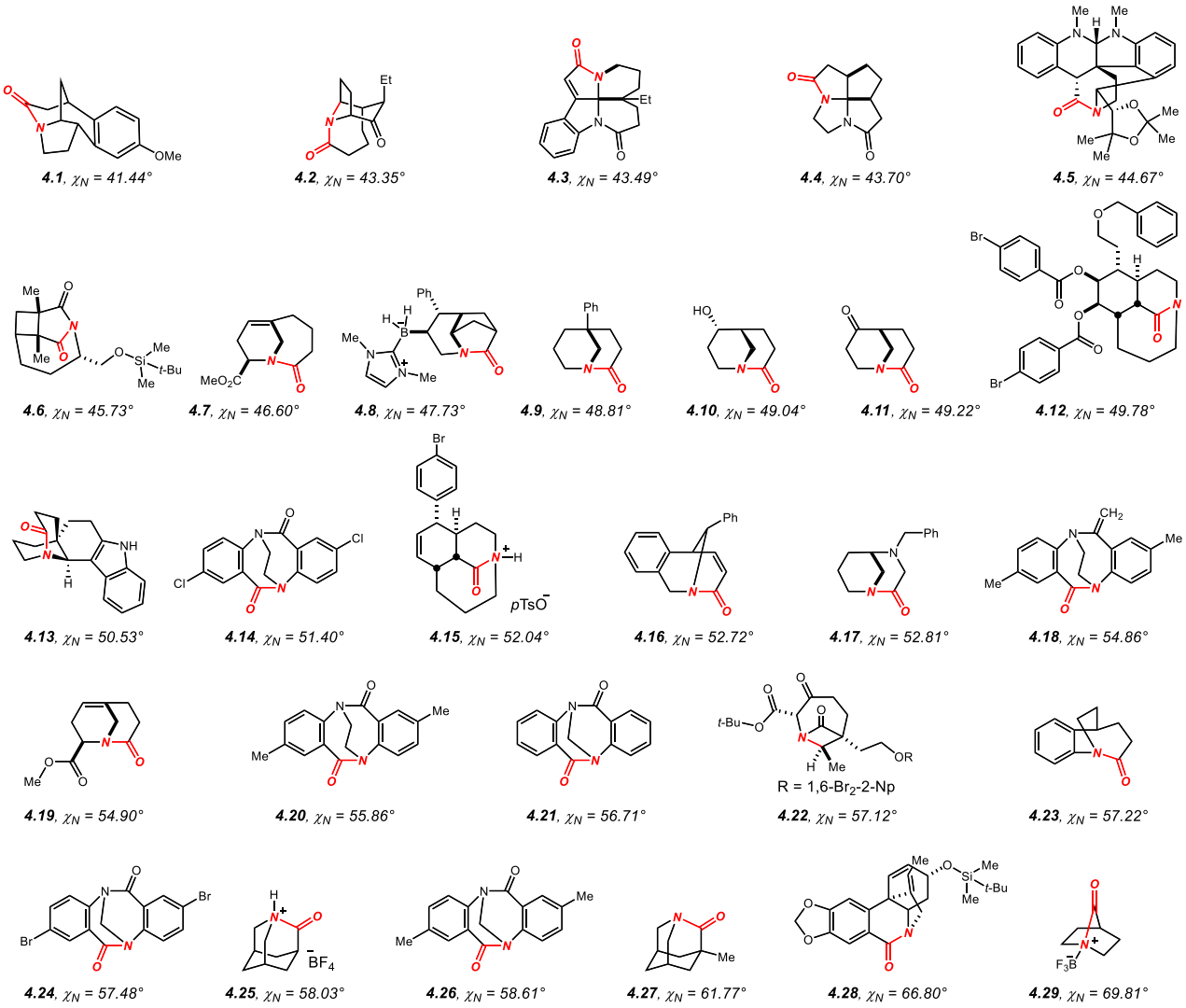


Figure 13. Bridged and Related Amides with Nitrogen Pyramidalization Values of 40° to 70°.

protonation at the nitrogen atom[47] and σ N–C bond cleavage.[166] While it may be assumed that nitrogen pyramidalization is the predominant amide bond distortion mechanism in these cases, further studies are needed to separate the effect of pyramidalization from twist in bridged bicyclic amides.

4.2. Fused Amides

In addition to bridged amides, significant nitrogen pyramidalization can also be achieved in fused ring systems. In general, these structurally-characterized amides can be categorized based on the ring system featuring the amide bond into the following classes: (1) four-membered ring twisted/pyramidalized amides; (2) five-membered ring twisted/pyramidalized amides; (3) six-membered ring twisted/pyramidalized amides; and (4) miscellaneous examples.

4.2.1. Four-Membered Ring N-Pyramidalized Amides

Constraining the amide bond in a β-lactam ring represents a classic example of enhancing the reactivity of the amide bond by ring strain.[27] This increased amide bond distortion is critical for the mechanism of action of β-lactam antibiotics. Since comprehensive monographs on β-lactams[337–339] and β-lactams[316–318] antibiotics have been published, this section presents a summary of structurally-characterized pyramidalized amides embedded in a four-membered ring (Figures 14-15).

In general, the amide bond geometry of structurally-characterized β-lactams presented in Figures 14-15[340–416] can be characterized as N-pyramidalized (average χ_N of 54.4°), while twist is less significant (average τ of 19.2°), as expected from the geometry of the fused four-membered ring system. There is only a very scattered correlation between N-pyramidalization and twist of the amide bond, with the general trend of higher twist with increased nitrogen pyramidalization ($R^2 = 0.30$).

The most common are [2.4.0] and [2.3.0] ring systems with the six-membered ring such as 1,3-oxazinane (e.g., **4.30**),[340] and more common five-membered ring, such as thiazolidine 1,1-dioxide (e.g., **4.32**),[342] thiazolidine 1-oxide (e.g., **4.33**),[343] thiazolidine (e.g., **4.34**),[344] 1,3-selenazolidine (e.g., **4.36**),[346] pyrrolidine (e.g., **4.81**),[383] imidazolidine (e.g., **4.94**),[395] or oxazolidine (e.g., **4.101**).[401] In general, more

dense substitution of the fused ring, in particular at the α-positions to the nitrogen atom and the carbonyl group and ring unsaturation result in higher N-pyramidalization.[340–416] These N-pyramidalized amides are well known to be highly reactive as acylating reagents and are important pharmacophores in medicinal chemistry research.

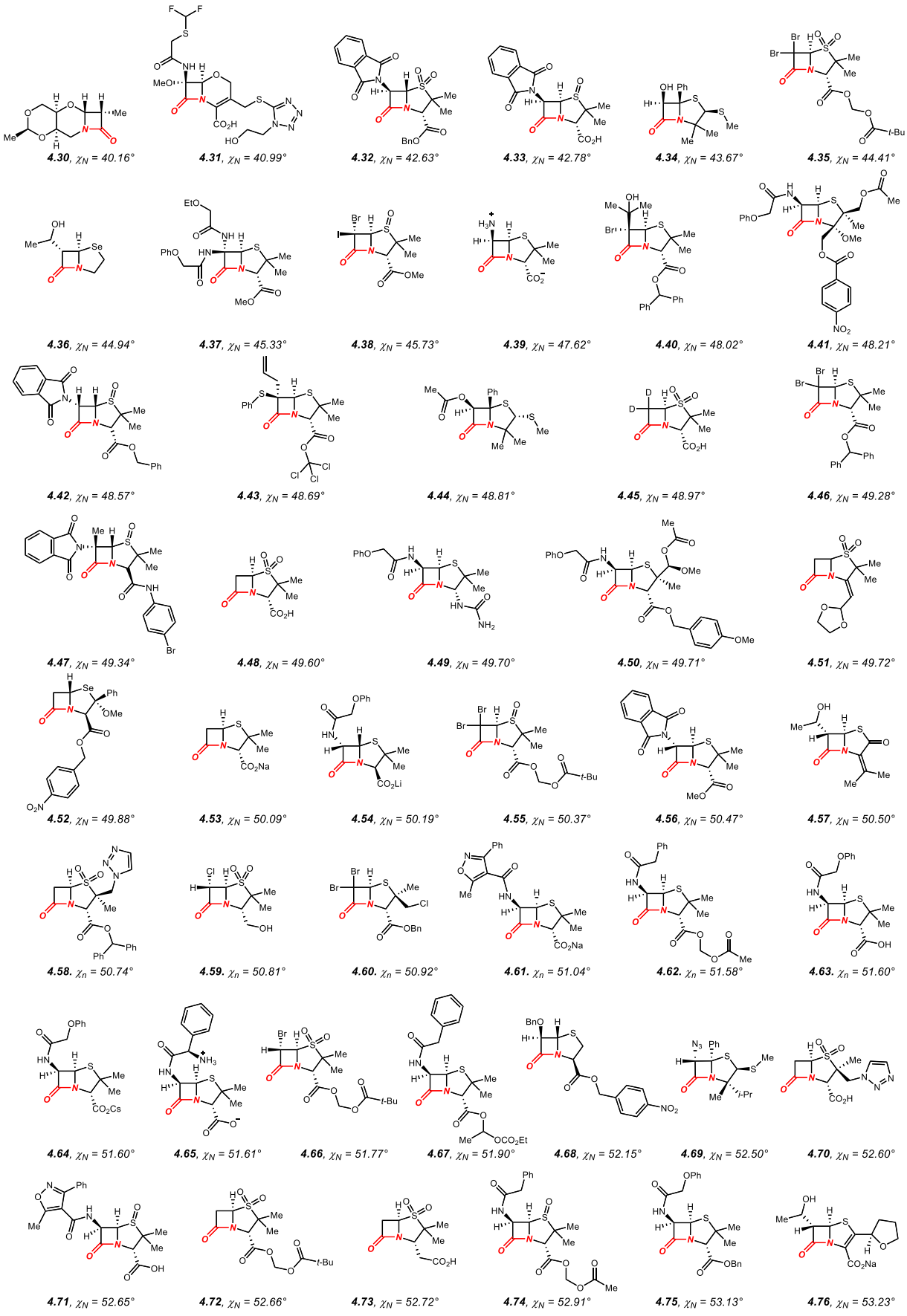


Figure 14. Amides in Four-Membered Rings with Nitrogen Pyramidalization Values of 40° to 53°.

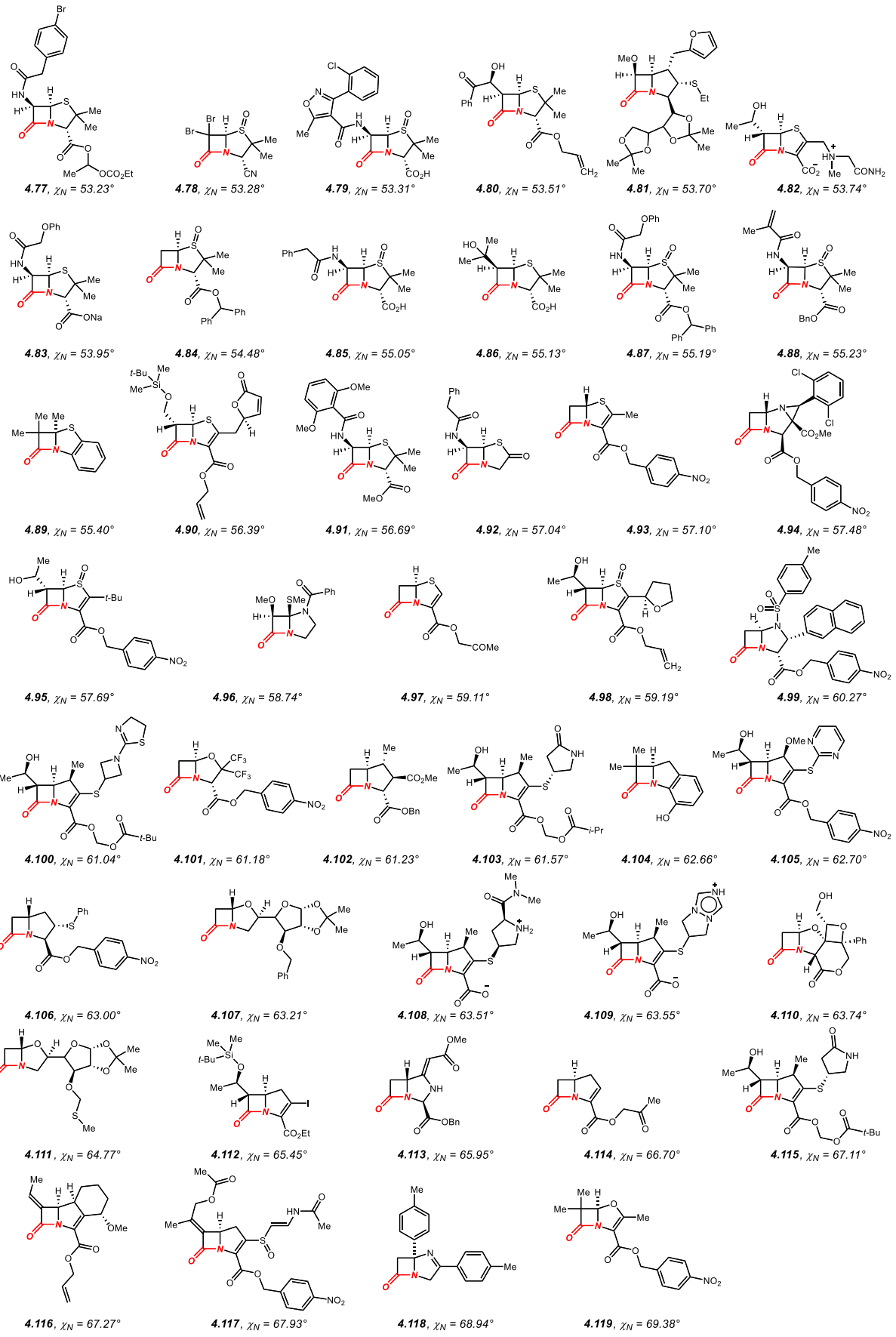


Figure 15. Amides in Four-Membered Rings with Nitrogen Pyramidalization Values of 53° to 69°.

4.2.2. Five-Membered Ring N-Pyramidalized Amides

In contrast to the well-known β-lactams, it is much less recognized that constraining the amide bond in a five-membered fused ring system also leads to significant pyramidalization of the amide bond. This class of five-membered ring fused lactams plays a prominent role in heterocyclic chemistry[293] and natural product synthesis[417] en route to indolizidine, pyrrolizidine and related alkaloids.[418–421] In these systems, it has been acknowledged that the reduction of lactam carbonyl groups often proceeds under mild reaction conditions, clearly a consequence of amide bond pyramidalization that weakens $n_N \rightarrow \pi^*_{C=O}$ resonance.[417–421]

Similar to β-lactams, the amide bond geometry of structurally-characterized amides embedded in a fused five-membered ring system (Figures 16-18)[422–522] can be characterized as N-pyramidalized (average χ_N of 45.9°) with minimal twist (average τ of 11.7°). As expected, the average values of N-pyramidalization and twist are slightly lower as compared to β-lactams by χ_N: 8.5° and τ: 7.5°, respectively,[340–416] which is a consequence of less strained five-membered fused ring system. Similarly, the highest reported χ_N value for a five-membered fused lactam is lower than that of the most N-pyramidalized β-lactam (**4.248**: 55.6°;[522] **4.119**: 69.4°,[416] respectively); however, it clearly indicates a predominant sp^3 character of the amide bond nitrogen atom in this ring system. Finally, there is no correlation between N-pyramidalization and amide bond twist in structurally-characterized amides constrained in fused five-membered ring systems.

Most common in this class (Figures 16-18)[422–522] is ring fusion to six-membered rings in [3.4.0] scaffold, including piperazine, such as **4.120**,[422] and hexahydropyrimidine, such as **4.121**,[423] and much more common [3.3.0] ring system with the ring fusion to five-membered rings, including pyrrolidine, such as **4.122**,[424] thiazolidine, such as **4.123**,[425] imidazolidine, such as **4.124**,[426] and oxazolidine, such as **4.125**,[427] as the most common ring scaffolds. This class also includes benzo-fused lactams, such as **4.140**,[442] **4.146**[434] and **4.173**,[470] and tricyclic fused ring systems, such as **4.138**,[440] **4.171**,[468] **4.172**[469] and **4.181**.[474] In general, increased substitution at the α-position to the nitrogen atom and additional constraints of the five-membered ring, such as unsaturation, conformationally rigid ring systems and

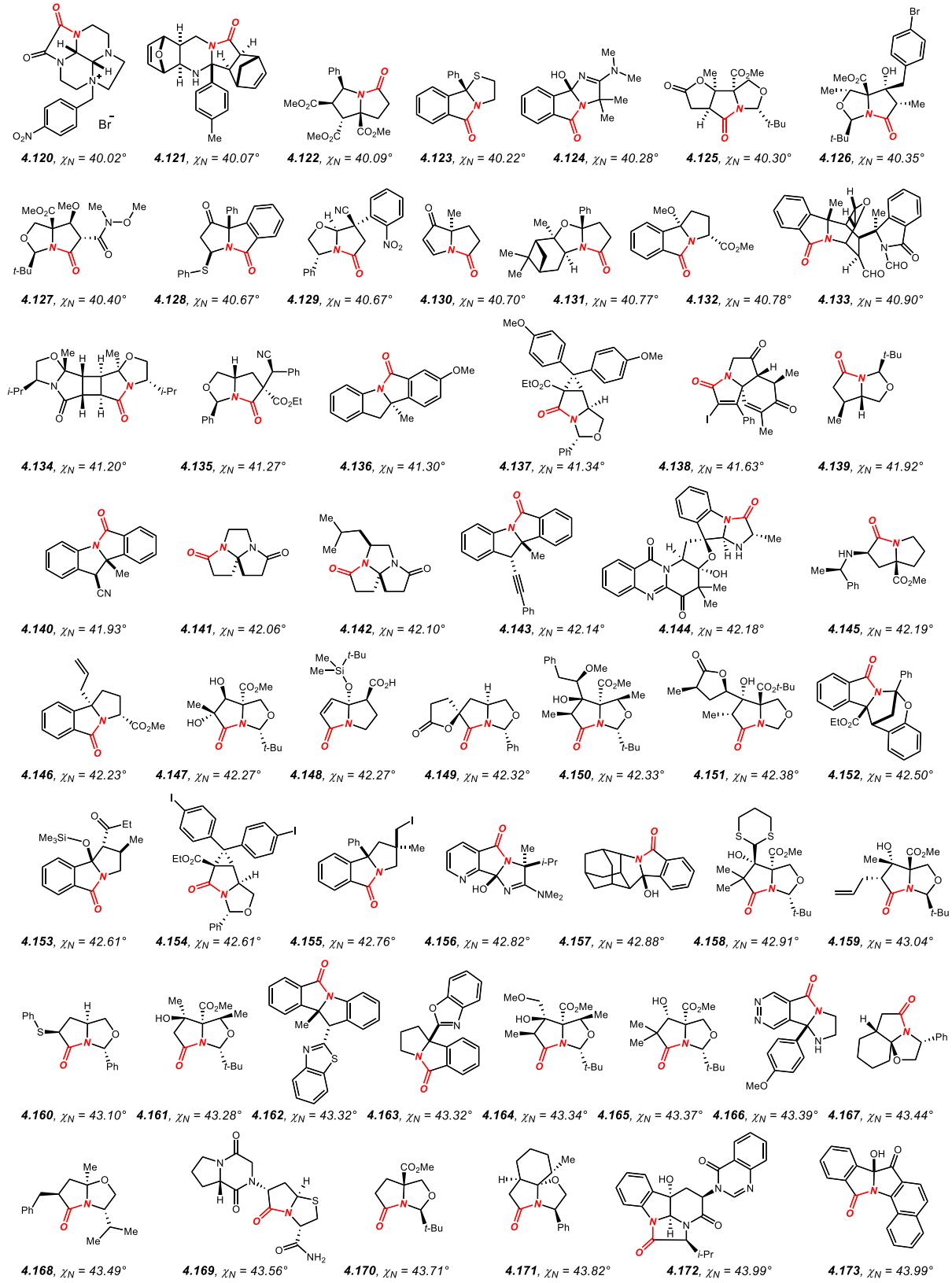


Figure 16. Amides in Five-Membered Rings with Nitrogen Pyramidalization Values of 40° to 44°.

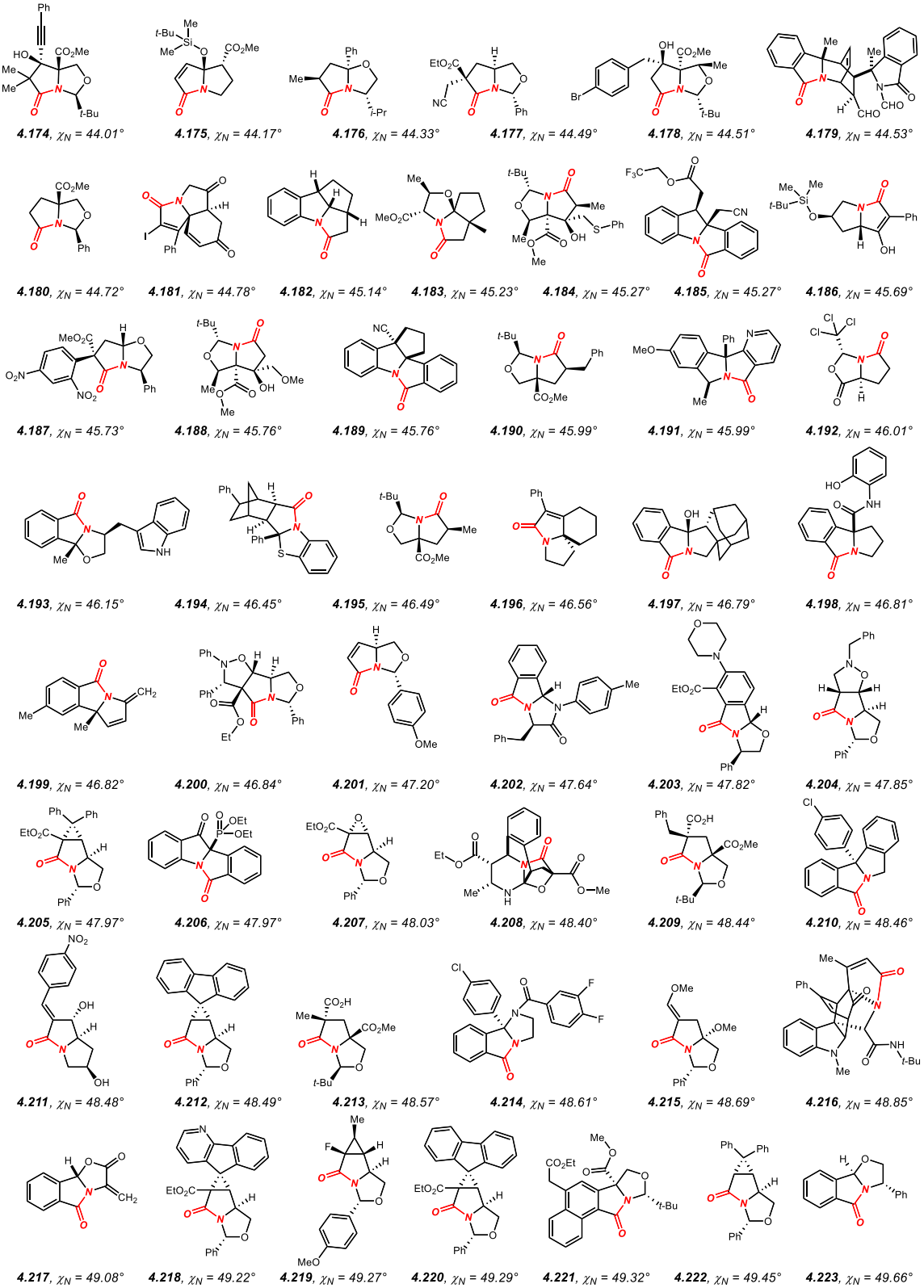


Figure 17. Amides in Five-Membered Rings with Nitrogen Pyramidalization Values of 44° to 50°.

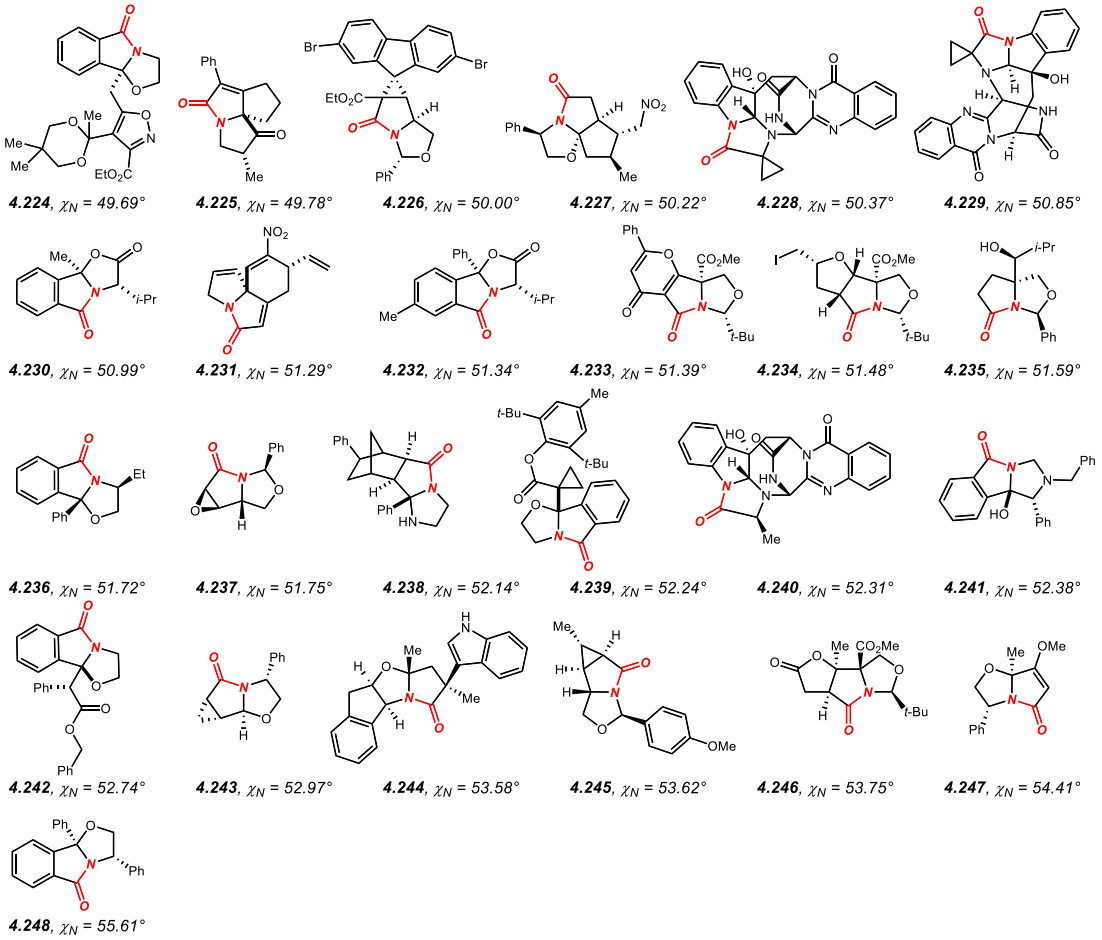


Figure 18. Amides in Five-Membered Rings with Nitrogen Pyramidalization Values of 50° to 60°.

steric effects lead to higher N-pyramidalization.[422–522] The high N-pyramidalization in five-membered fused lactams should be taken into account when studying the carbonyl addition reactions to amide bonds in this class of amides.

4.2.3. Six-Membered Ring N-Pyramidalized Amides

In addition to β-lactams and five-membered rings (sections 4.2.1. and 4.2.2.), amide bond pyramidalization can also be achieved in fused six-membered rings (Figure 19).[422,523–531] As expected, comparatively fewer examples of structurally-characterized N-pyramidalized amides embedded in six-membered rings have been reported; however, these amides feature significant N-pyramidalization (average χ_N of 46.1°), while twist is much lower (average τ of 11.2°). These values compare well with the five-membered fused ring lactams (χ_N: 45.9° and τ: 11.7°),[422–522] suggesting similar geometrical

effects on the amide bond in these systems. Likewise, there is no correlation between N-pyramidalization and amide bond twist in six-membered fused amides.

In general, structurally-characterized six-membered fused amides that show significant pyramidalization of the amide bond[422,523–531] feature [3.3.0] or [3.2.0] ring systems, wherein the six-membered ring is typically fused to piperidine, such as **4.249**,[523] pyrrolidine, such as **4.250**,[524] or imidazolidine, such as **4.257**.[422] Six-membered fused amides are important precursors in the syntheses of quinolizidine, indolizidine and 2,5-diketopiperazine alkaloids.[532–534] Similar to the fused five-membered lactams, N-pyramidalization disrupts amidic resonance, which results in more facile electrophilic addition to the amide carbonyl group in these systems.[418–421,532–534]

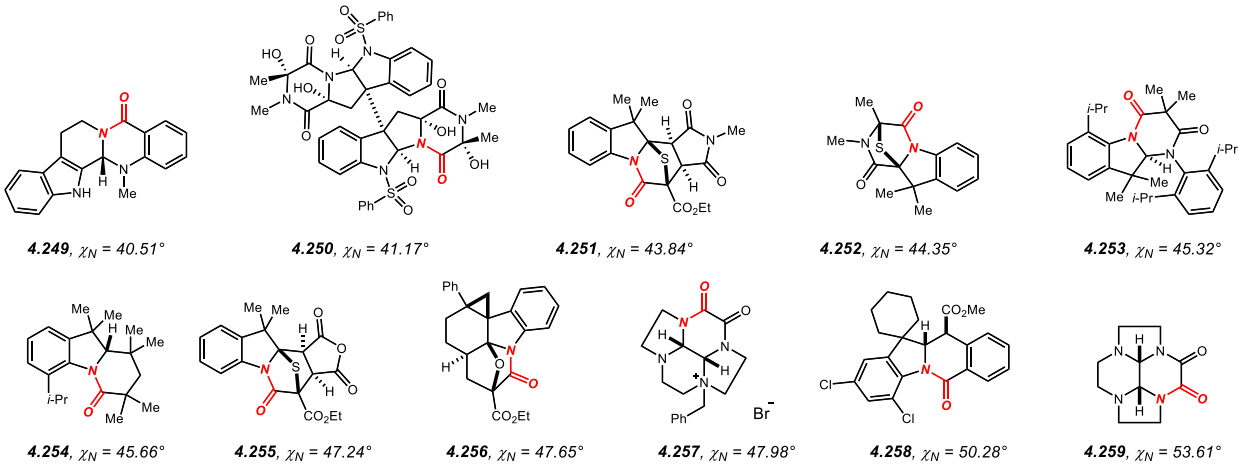


Figure 19. Amides in Six-Membered Rings with Nitrogen Pyramidalization Values of 40° to 60°.

4.3. Miscellaneous

Significant N-pyramidalization has been observed in saccharin-based imidoiodane **4.260** (χ_N = 40.1°) (Figure 20).[535] This compound is synthesized from the direct reaction between saccharin and iodine acetate and serves as an aminating reagent using silyl enol ethers as nucleophiles.

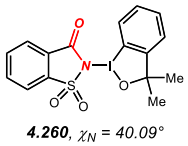


Figure 20. Miscellaneous Amides with Nitrogen Pyramidalization Values of 40° to 60°.

5. Acyclic Amides: N-Pyramidalization 40-60°

Nitrogen pyramidalization in acyclic amides leads to reduction of rotational barriers of the amide bond.[12,28–35] The major methods to generate N-pyramidalization in acyclic amides are as follows: (1) N-heterocycle-activation; (2) N-sulfonyl-activation; (3) N-pyramidalization in aliphatic amides.

5.1. N-Heterocycle-Activated N-Pyramidalized Amides

Structurally-characterized N-pyramidalized N-heterocycle-activated amides with χ_N values >40° are summarized in Figure 21.[268,302,305,306,536–547] In general, these amides can be divided into the following classes of amides: (1) conformationally-constricted N-acyl-7-azabicyclo[2.2.1]heptanes (**5.4**, **5.5**, **5.7**, **5.9-5.20**)[302,305,306] and related derivatives, such as N-acyl-8-azabicyclo[3.2.1]octanes (**5.2**)[537] and N-acyl-2-azabicyclo[2.1.1]hexanes (**5.8**);[540] (2) N-acyl-pyrrolidines (**5.1**, **5.3**);[536,538] and (3) N-acyl-oxazolidin-5-ones (**5.6**, **5.21**).[539,268] N-acyl-azetidines and N-acyl-azridines are not included since the ring strain of the small ring significantly contributes to the properties of these amides.[17,301]

It is interesting to note that N-acyl-7-azabicyclo[2.2.1]heptanes (Figure 21) can be classified as pyramidalized amides (average χ_N of 52.0°; average τ of 16.6°). The origin of nitrogen pyramidalization in N-acyl-7-azabicyclo[2.2.1]heptanes has been proposed to be due to small C–N–C angle and allylic strain between the amide substituents and the bridgehead hydrogen atoms.[302–314] In agreement with this hypothesis, increased substitution of 7-azabicyclo[2.2.1]heptane results in an increase in nitrogen pyramidalization (e.g. **5.20**, χ_N of 64.5°).[547] Rotational barriers of 7-azabicyclo[2.2.1]heptane amides have been measured and are comparable to N-acyl-azetidines (**5.12**, 15.0 kcal/mol; N-4-toluoyl-azetidine, 15.7 kcal/mol).[302] The intrinsic nitrogen pyramidalization in N-acyl 7-azabicyclo[2.2.1]heptanes provides an attractive scaffold for controlling cis/trans amide rotation.[305,312]

Similar to 7-azabicyclo[2.2.1]heptane amides, N-acyl-pyrrolidines **5.1** and **5.3** contain predominantly N-pyramidalized amide bonds cf. twist (**5.1**: χ_N = 40.2°, τ = 13.2°; **5.3**: χ_N = 43.7°, τ = 13.2°),[536,538] which originates from the steric interactions between amide bond substituents and pyrrolidine ring. The

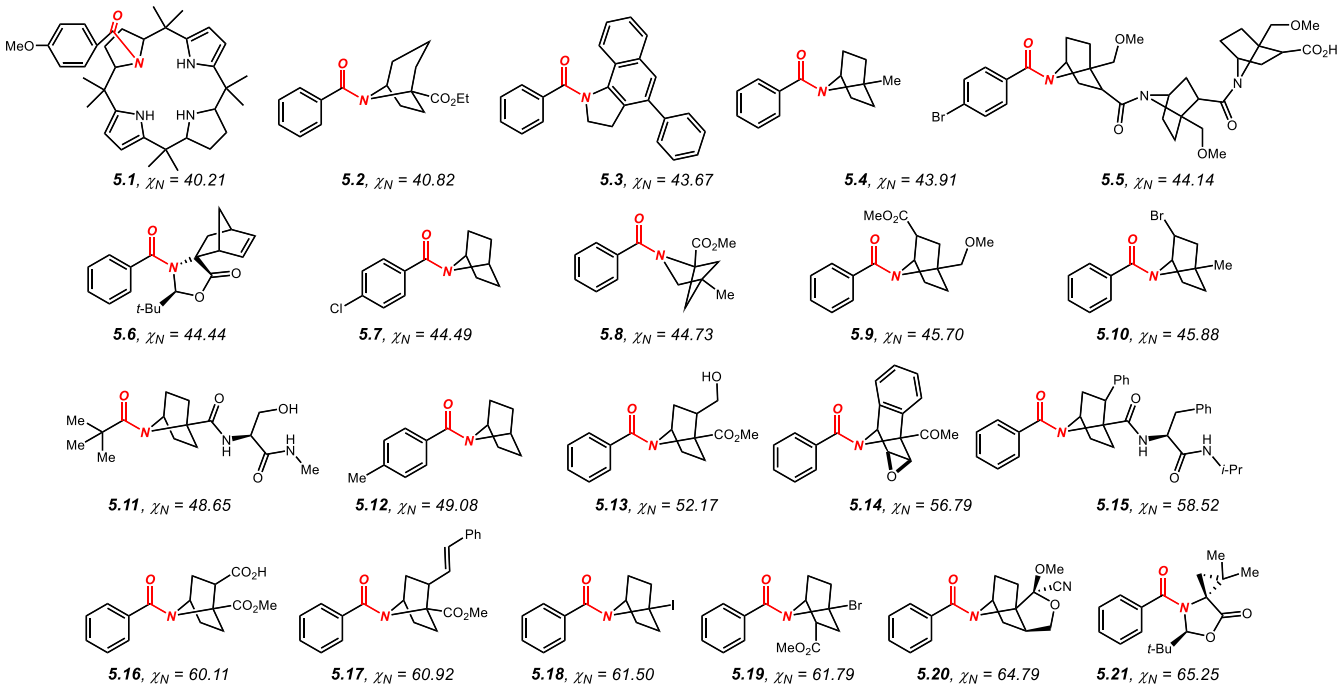


Figure 21. N-Heterocycle-Activated Acyclic Twisted Amides with Nitrogen Pyramidalization Values of 40° to 65°.

nitrogen pyramidalization leads to an increased electron density at the nitrogen and more electrophilic carbonyl groups in these amides.

In contrast, N-acyl-oxazolidin-5-ones **5.6** and **5.21** feature both N-pyramidalized and twisted amide bonds (**5.6**: χ_N = 44.4°, τ = 43.2°; **5.21**: χ_N = 65.3°, τ = 40.6°).[539,268] These amides represent very rare examples of twisted pyramidalized N-acyclic amides that do not require additional electronic activation to achieve high geometric distortion (cf. section 3.2.).

5.2. N-Sulfonyl-Activated N-Pyramidalized Amides

In addition to using heterocyclic ring systems (section 5.1.), N-pyramidalization of the amide bond can be achieved using N-sulfonyl activation (Figure 22).[242,295,548–562] These N-acyl sulfonamides are derived from camphorsultam (Oppolzer's sultam) and feature predominantly pyramidalized amide bonds cf. twist (average χ_N of 45.3°; average τ of 24.4°). Substitution at the α-carbon can be aliphatic (e.g., **5.23**),[549] alkenyl (e.g., **5.22**),[548] aromatic (e.g., **5.29**)[554] or heterocyclic (e.g., **5.24**).[550] In general,

increased N-pyramidalization is observed with higher substitution at the α-carbon (e.g., **5.37**: χ_N = 49.0°, τ = 22.4°),[560] while the last three compounds in the series **5.38-5.40** feature both high pyramidalization and higher twist (**5.38**: χ_N = 49.3°, τ = 35.2°; **5.39**: χ_N = 50.2°, τ = 43.5°; **5.40**: χ_N = 51.6°, τ = 39.1°).[561,295,562] These N-sulfonyl-activated N-pyramidalized amides are expected to undergo N–C(O) bond cleavage under mild conditions owing to the higher electron density at the nitrogen atom and n_N to $\pi^*_{S=O}$ conjugation with the sulfonyl group (cf. section 3.3.).

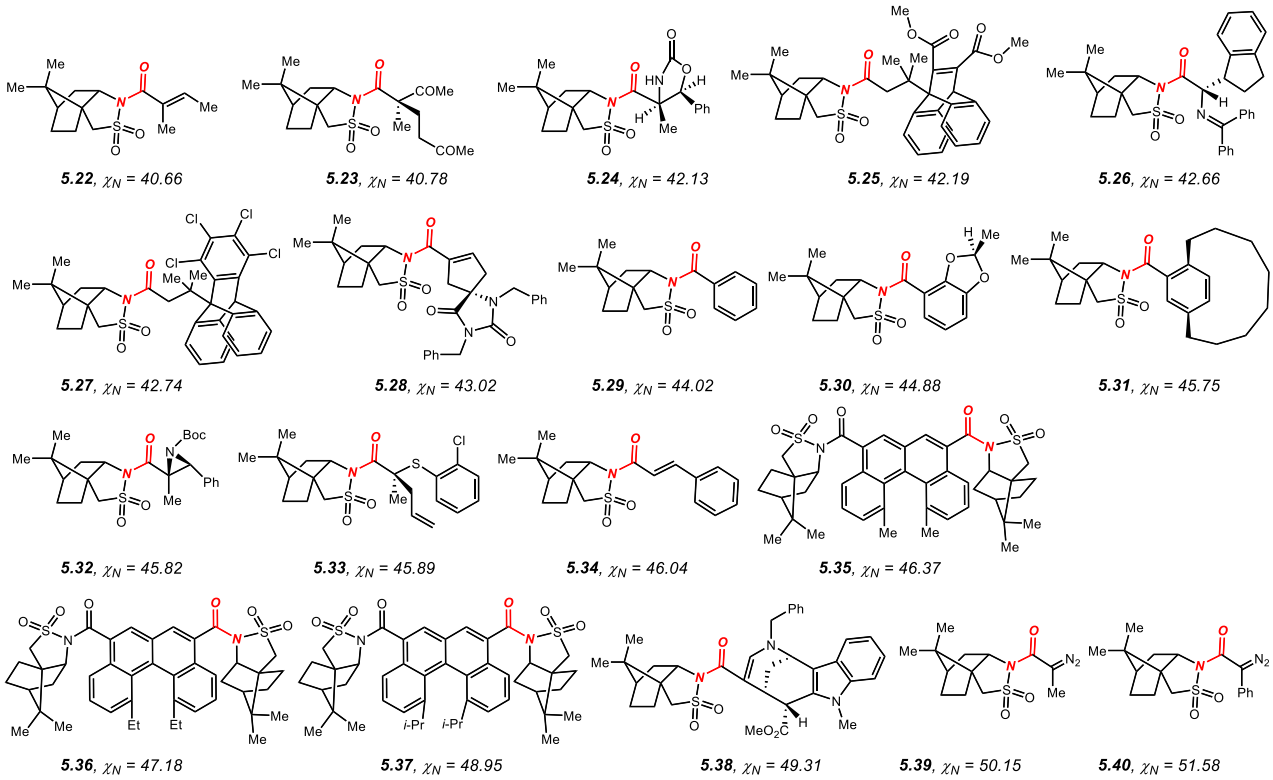
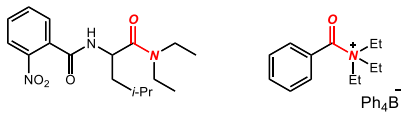


Figure 22. N-Sulfonyl-Activated Acyclic Twisted Amides with Nitrogen Pyramidalization Values of 40° to 60°.

5.3. N-Aliphatic N-Pyramidalized Amides

Amide **5.41** features pyramidalized amide bond (χ_N = 46.7°, τ = 16.7°) (Figure 23).[563] The pyramidalization originates from steric syn-pentane-type interactions between N-ethyl group and iso-butyl substituent at the α-carbon. Furthermore, acyclic quaternary N-acyl ammonium salts, such as **5.42**, contain fully pyramidalized amide bonds (χ_N = 63.5°, τ = 85.1°) (cf. section 3.4.).[300]



5.41, χ_N = 46.71 ***5.42***, χ_N = 63.47

Figure 23. N-Aliphatic Acyclic Twisted Amides with Nitrogen Pyramidalization Values of 40° to 65°.

6. Application of Acyclic Twisted Amides in Bond Cleavage Reactions

An important point that should be addressed is synthetic application of acyclic twisted amides.[63–82] In principle, N-activation of tertiary amides leads to geometric and electronic alteration of the amide bond, which disrupts amidic resonance through (1) twisting and N-pyramidalization; (2) channeling of the n_N to $\pi^*_{C=O}$ conjugation onto the external N-substituent of the amide bond. This permits for utilization of acyclic amides through selective bond cleavage processes that are beyond the scope of reactivity of classical amides. To date, the following classes of reactions of twisted amides have been developed: (1) N–C(O) acyl cleavage; (2) C–NCO decarbonylative cleavage; (3) NCO–C cleavage; (4) acyl nucleophilic addition; (5) generation of acyl radicals. These processes have been reviewed.[63–82]

An additional point that should be addressed in this context is the synthesis of acyclic twisted amides. In general, there are two main pathways for the synthesis of non-planar acyclic amides and derivatives, namely (1) amine acylation with carboxylic acids or derivatives; (2) N-acylation of 1° or 2° amides and related processes. For the major classes of acyclic twisted amides discussed, the synthetic pathways have now been well established, and these amides are readily available on preparative scale.[63–82] From the standpoint of medicinal chemistry and late-stage derivatization, N-acylation of 1° or 2° amides has an advantage over amine acylation in that it permits to directly utilize planar amides as precursors to acyclic twisted amides. Since the synthesis of acyclic twisted amides directly affects their application, attention should be given to versatile, high yielding and practical methods of synthesis.

7. Conclusions and Outlook

In conclusion, amide bond planarity manifesting in the placement of all six atoms comprising the amide bond in a single plane is a fundamental and widely accepted property of amide bonds. Amide bond planarity has a major impact on application of amide bonds in chemical fields ranging from organic synthesis to polymers, medicinal chemistry, structural chemistry and biochemistry. Although classical studies on geometric constraint of amide bonds with the resulting decrease of amidic resonance and amino-ketone properties of amides have been focused on cyclic lactams, recent years have seen rapid developments of acyclic twisted amides.

In this review, we have presented a comprehensive overview of amide bond distortion in acyclic amides. Steric distortion in acyclic amides can be achieved by twist, nitrogen pyramidalization or a combination of both. Importantly, there are many different and complementary methods that result in high geometric distortion of acyclic amides. These methods include electronic activation, such as N-acylation, N-sulfonylation, or activation by aromatic N-heterocycles which leads to N_{lp} conjugation onto an exocyclic group as well as steric activation and N-pyramidalization in acyclic scaffolds. Remarkably, as demonstrated in this review, there are many examples of structurally-characterized acyclic amides that feature twist and N-pyramidalization values close to full twist ($\tau = 90°$) and full pyramidalization ($\chi_N = 60°$). Furthermore, comparison with the classic bridged lactams and conformationally-restricted cyclic fused lactams demonstrates many effective methods to achieve geometric alteration of the amide bond in acyclic amides.

Despite the undeniable progress in the last years, there are a number of challenges that need to be addressed, including: (1) development of rational models correlating amide bond distortion with the observed reactivity; (2) development of a better understanding of the properties of non-planar amide bonds, in particular, focused on the different impact of twist and pyramidalization; (3) development of considerably twisted acyclic amides that feature non-electronically-activated amide bonds; (4) development of new activation methods of acyclic amide bonds that cover broad scope and diverse structural variation of acyclic amides, including peripheral activation[564] and mechanical twisting;[565] and (5) expansion of the scope of activating groups used for twisting of acyclic amide bonds. Furthermore,

there is clearly a need for studies merging the properties of classic cyclic twisted amides with their acyclic counterparts, including structure and reactivity.

We believe that the importance of amide bonds in various facets of chemistry and the inspiring journey of non-planar amide bonds since the seminal studies by Pauling will lead to the discovery of new and highly valuable twisted amides.

8. Author Information

Corresponding Author

michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interests.

[§]These authors contributed equally to this work.

Biographies

Guangrong Meng was born in Shandong Province, P.R. of China, and received his B.Sc. degree from Dalian Medical University in 2011. He received his M.Sc. from Fudan University in 2014. He completed his Ph.D. at Rutgers University in 2019 where he worked under the supervision of Professor Michal Szostak. Currently, he is a post-doctoral fellow in the group of Professor Jin-Quan Yu at The Scripps Research Institute. His research interests are focused on transition-metal-catalysis and C–H activation reactions.

Jin Zhang received his B.Sc. in Applied Chemistry in 2007 and Ph.D. in Organic Chemistry in 2012 both from Northwest University. He joined Shaanxi University of Science and Technology in 2012 and then worked as a postdoctoral fellow at SUST with Prof. Yangmin Ma from 2013 to 2016. He worked with Prof. Michal Szostak group at Rutgers as a visiting scholar in 2018-2019. His current research interests are focused on inert bond activation based on transition-metal-catalysis, carbonylation reactions and mechanochemistry.

Michal Szostak received his Ph.D. from the University of Kansas with Professor Jeffrey Aubé in 2009. After postdoctoral stints at Princeton University with Prof. David MacMillan and at the University of

Manchester with Prof. David Procter, in 2014, he joined the faculty at Rutgers University. His research group is focused on the development of new synthetic methodology based on transition-metal-catalysis, amide bonds, C–H, C–O and C–N activation, decarbonylative coupling, and application to the synthesis of biologically active molecules.

9. Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org. Detailed summary tables including Winkler-Dunitz distortion parameters for all amides discussed.

10. Acknowledgements

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GRAPHICAL ABSTRACT