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# Ground-State Distortion in *N*-Acyl-*tert*-butyl-carbamates (Boc) and *N*-Acyl-tosylamides (Ts): Twisted Amides of Relevance to Amide N–C Cross-Coupling

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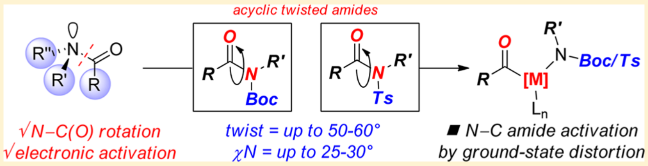
Ⓢ *Supporting Information*

**ABSTRACT:** Amide N–C(O) bonds are generally unreactive in cross-coupling reactions employing low-valent transition metals due to $n_N \rightarrow \pi^*_{C=O}$ resonance. Herein we demonstrate that *N*-acyl-*tert*-butyl-carbamates (Boc) and *N*-acyl-tosylamides (Ts), two classes of acyclic amides that have recently enabled the development of elusive amide bond N–C cross-coupling reactions with organometallic reagents, are intrinsically twisted around the N–C(O) axis. The data have important implications for the design of new amide cross-coupling reactions with the N–C(O) amide bond cleavage as a key step.



Selective activation of amide N–C(O) bonds by transition metals has been a long-standing challenge due to amide bond resonance and the resulting partial double bond character of planar amide linkages.[1,2] Likewise, distortion of amide bonds from planarity has been well-recognized to result in disrupted amide resonance, leading to amino-ketone-like reactivity of amides.[3,4] Such twisted nonplanar amides have captured the attention of chemists for almost a century;[5] however, the vast majority of these studies focused on nonplanarity and theoretical aspects of bridged lactams (Figure 1A).[5−7]

In this context, in 2015, our laboratory introduced a new amide bond activation manifold based on amide ground-state distortion in acyclic amides, whereby amide bond activation by transition metals can proceed only if the amide has been distorted from planarity (Figure 1B).[8] We have further developed this concept to enable a range of previously elusive generic transition-metal catalyzed reactions of amides to form C–C bonds, including Suzuki, Heck, decarbonylative Suzuki, direct C–H arylation and Negishi reactions using Pd, Ni, and Rh catalysis.[8] While various amides predisposed to disfavor amidic resonance were routinely screened in these studies, including *N*-Ts and *N*-Boc amides, we consistently found that the best results were obtained using *N*-acyl-glutarimides as N–C activation substrates. These glutarimide amides contain up to perpendicular amide bonds as a result of amide bond twist.[5] Independently, others demonstrated that acyclic amides participate in Suzuki reactions by N–C cleavage under Ni and Pd catalysis using *N*-acyl-*tert*-butyl-carbamates (Boc) and *N*-acyl-tosylamides (Ts) as substrates (Figure 1C).[9] Intriguingly, a study on the effect of amide bond ground-state distortion on the structural and energetic properties of these amides has not been published. The activation of N–C amide bonds by transition metals represents a powerful disconnection in organic synthesis to forge C–C bonds.[10,11] Nonplanar acyclic amides are of general interest in chemistry and biology to elucidate mechanisms of various chemical and enzymatic processes.[1−6] A better understanding of the structural aspects affecting the amidic resonance and amide bond twist in *N*-Ts and *N*-Boc amides could lead to the design of more efficient amide bond activation reactions[10,11] and provide new insights into the factors affecting amide bond resonance in simple acyclic amides.[1−6]

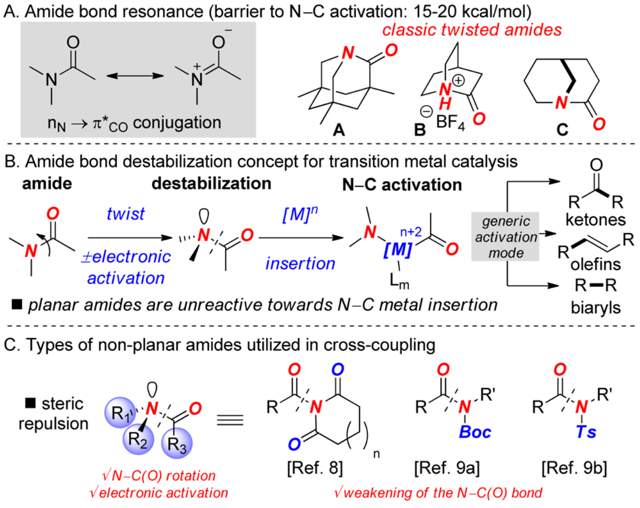


**Figure 1.** Concepts for amide N–C activation.

In this manuscript, by using a combination of computational and crystallographic techniques we report direct evidence that *N*-

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Boc and *N*-Ts amides are intrinsically twisted around the N−C(O) axis in the ground state. Notably, this study provides the first evidence that simple *N*-Ts and *N*-Boc amides that are easily accessible directly from generic secondary amides contain nonplanar amide bonds. Moreover, we demonstrate that, in sharp contrast to conformationally locked bridged lactams and rotationally inverted *N*-glutarimide amides, these amides can adopt a variety of conformations around the amide bond. Considering that all examples of twisted amides reported to date contain either synthetically limited bridged lactam scaffolds[5a,b] or significant steric hindrance around the amide bond,[5c] our study opens the door to consider amide bond distortion as a general reactivity guiding principle in a range of transition-metal catalyzed and transition-metal free acylation reactions by N−C cleavage.[5−11] Importantly, this study demonstrates that significant amide bond distortion[12] can be achieved in simple acyclic amides. The combined steric and electronic activation of the amide bond contributes to the increased reactivity of amides in N−C bond activation.[3f,8,9] Amides with systematic structural variation on the carbon side and on the *N*-substituent show significant changes in amide bond twist and nitrogen pyramidalization. Barriers to rotation, resonance energies, and proton affinities demonstrate the extent of amide bond twist during geometric changes along the N−C(O) axis. The data have important implications for a better understanding of amide bond distortion and the design of new amide cross-coupling reactions with N−C(O) cleavage as a key step.

Figure 2 depicts general structures of *N*-Boc and *N*-Ts amides selected for the present study. Extensive studies showed that *N*-Boc and *N*-Ts amides are less reactive in the transition-metal catalyzed N−C activation than glutarimide amides;[8] importantly, these amides can be prepared directly from secondary amides by standard methods.[1] Amides have been selected on the basis of their importance in amide N−C cross-coupling, structural variation, and predicted distortion range.

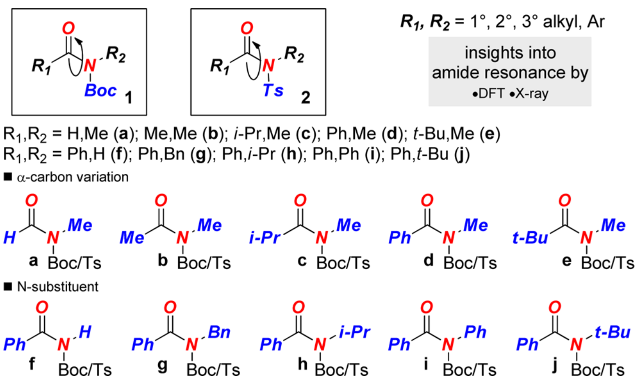

**Figure 2.** Structures of amides employed in the present study.

Selected structural parameters of *N*-Boc and *N*-Ts amides **1−2** are listed in Table 1.[12] The results indicate that with the exception of the first two amides in series **1** (*N* = Boc) and the first three amides in series **2** (*N* = Ts) all amides selected for the study contain nonplanar geometry (vide infra). Note that the additive amide bond Winkler−Dunitz distortion parameter ($\tau + \chi_N$) provides a more accurate representation of amide distortion.[13] In series **1**, the twist angle changes from planar to significantly twisted ($\tau = 0.00°−63.61°$), while the pyramidalization at nitrogen remains between $sp^2$ and $sp^3$ in all amides ($\chi_N = 0.00°−24.41°$). In series **2**, similar changes in the twist angle ($\tau = 0.00°−53.06°$) and the pyramidalization at nitrogen ($\chi_N = 0.00°−30.05°$) are observed. The most distorted amides are compounds **1j** and **2j** ($R_1$, $R_2$ = Ph, *t*-Bu). These amides feature more than half-maximum amide bond distortion ($\tau + \chi_N = 150°$) in both series (**1j**: $\tau = 63.61°$; $\chi_N = 19.76°$; **2j**: $\tau = 53.06°$; $\chi_N = 30.05°$). Remarkably, amides **1d** ($R_1$, $R_2$ = Ph, Me) and **2i** ($R_1$, $R_2$ = Ph, Ph) that have been shown to be particularly effective in N−C cross-coupling[9] contain decidedly nonplanar amide bonds approaching one-third maximum amide distortion (**1d**: $\tau = 32.06°$; $\chi_N = 17.36°$; **2i**: $\tau = 30.39°$; $\chi_N = 22.28°$) (Figure 3a−b).

**Table 1. Energies and Selected Geometric Parameters of Amides 1−2 Calculated Using B3LYP/6-311++G(d,p)[a]**

| entry | amide | $R_1$, $R_2$ | N−C(O) [Å] | C=O [Å] | $\tau$ [deg] | $\chi_N$ [deg] |
|---|---|---|---|---|---|---|
| 1 | **1a** | H, Me | 1.394 | 1.209 | 0.00 | 0.00 |
| 2 | **1b** | Me, Me | 1.420 | 1.215 | 0.00 | 0.00 |
| 3 | **1c** | *i*-Pr, Me | 1.425 | 1.215 | 23.52 | 12.07 |
| 4 | **1d** | Ph, Me | 1.413 | 1.216 | 32.06 | 17.36 |
| 5 | **1e** | *t*-Bu, Me | 1.433 | 1.212 | 33.68 | 18.50 |
| 6 | **1f** | Ph, H | 1.409 | 1.216 | 21.87 | 24.41 |
| 7 | **1g** | Ph, Bn | 1.407 | 1.218 | 28.41 | 9.27 |
| 8 | **1h** | Ph, *i*-Pr | 1.416 | 1.215 | 38.72 | 14.28 |
| 9 | **1i** | Ph, Ph | 1.427 | 1.211 | 30.97 | 15.03 |
| 10 | **1j** | Ph, *t*-Bu | 1.448 | 1.209 | 63.61 | 19.76 |
| 11 | **2a** | H, Me | 1.390 | 1.209 | 1.79 | 3.84 |
| 12 | **2b** | Me, Me | 1.411 | 1.215 | 1.10 | 5.14 |
| 13 | **2c** | *i*-Pr, Me | 1.411 | 1.215 | 1.99 | 4.35 |
| 14 | **2d** | Ph, Me | 1.402 | 1.215 | 25.52 | 12.21 |
| 15 | **2e** | *t*-Bu, Me | 1.398 | 1.217 | 0.16 | 12.82 |
| 16 | **2f** | Ph, H | 1.390 | 1.214 | 9.82 | 2.68 |
| 17 | **2g** | Ph, Bn | 1.401 | 1.216 | 26.22 | 6.93 |
| 18 | **2h** | Ph, *i*-Pr | 1.417 | 1.217 | 31.89 | 7.55 |
| 19 | **2i** | Ph, Ph | 1.416 | 1.214 | 30.39 | 22.28 |
| 20 | **2j** | Ph, *t*-Bu | 1.447 | 1.209 | 53.06 | 30.05 |

[a] For representative data on bridged lactams, see ref 13a−d.

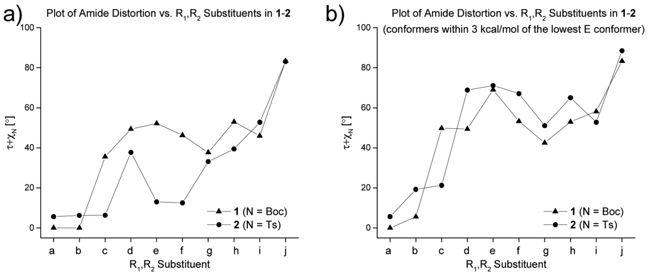

**Figure 3.** Plot of the sum of twist angle ($\tau$) and pyramidalization at nitrogen ($\chi_N$) to $R_1$ and $R_2$ substituents in **1−2**: (a) lowest energy conformations; (b) conformers within 3 kcal/mol of the lowest energy conformer.

Amide bond distortion in **1** and **2** generally follows steric demands of the substituents.[14] A plot of N−C(O) bond length versus twist angle gives a good linear correlation in *N*-substituted series (**1**, $R^2 = 0.80$; **2**, $R^2 = 0.95$; see SI). Moreover, a plot of N−C(O) bond length versus C=O bond length gives an inverse linear correlation in **1** ($R^2 = 0.88$), in agreement with the classic amide resonance. A plot of twist angle versus Charton steric parameter gives an excellent linear correlation in both series (**1**, $R^2 = 0.91$; **2**, $R^2 = 0.98$, Figure 4a−b), indicating that distortion in these amides is steric in origin.[15] Interestingly, correlations involving the $\alpha$-carbon substituent ($R_1$) give scattered results.

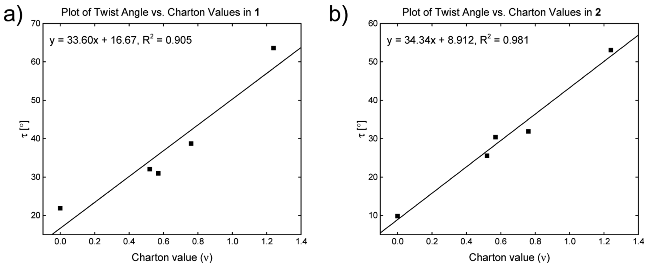

**Figure 4.** Correlation of twist angle ($\tau$) to Charton values ($R_2$ substituent): (a) amides **1**; (b) amides **2**.

A subtle feature of the geometries of acyclic *N*-acyl amides is that several conformations close to the lowest energy conformer can be thermodynamically accessible under the reaction conditions. This is in sharp contrast to bridged lactams, which feature locked amide conformations in bicyclic scaffolds.[13] A plot of the amide bond distortion in **1**−**2** as a function of geometry using the most distorted geometry within the 3 kcal/mol cutoff point[13] is presented in Figure 3b. It is evident that these geometries may be accessible under the thermodynamic conditions of C−N activation reactions.

Detailed rotational profile studies were performed to determine the relationship between energy and C−N(O) bond geometry by systematic rotation along the O−C−N−C dihedral angle in representative amides in series **1** and **2** (**d**, **i**) of relevance to N−C amide cross-coupling (Figure 5a−b). The rotational profiles confirm ground state distortion of **1** and **2**. The rotational profiles of amides **1** are close to symmetrical, with the energy minimum at ca. 20° O−C−N−C dihedral angle, which corresponds to $\tau = 31.99°$; $\chi_N = 17.40°$ for **1d** and $\tau = 30.16°$; $\chi_N = 15.40°$ for **1i**. Interestingly, there is a second energy minimum at ca. 130° dihedral angle (**1d**, $\tau = 39.38°$; $\chi_N = 21.44°$; **1i**, $\tau = 41.45°$; $\chi_N = 17.02°$). The rotational barrier was determined to be 4.26 kcal/mol (**1d**, $R_2$ = Me) and 3.62 kcal/mol (**1i**, $R_2$ = Ph). *Note that, in the present case, the rotational barrier indicates a preference to remain in the twisted conformation.* Interestingly, the geometry at ca. 60° dihedral angle for **1d** ($\Delta E$ = 3.01 kcal/mol) corresponds to $\tau = 64.28°$; $\chi_N = 5.60°$ and for **1i** ($\Delta E$ = 2.50 kcal/mol) to $\tau = 64.05°$; $\chi_N = 6.54°$. Thus, amides **1d** and **1i** are able to adopt a variety of conformations around the N−C(O) axis. The rotational profiles of amides **2** are more complex, likely a result of free rotation around the $N-SO_2$ bond. Classic studies by Paquette established the lack of Nlp to $SO_2$ conjugation in sulfonamides.[16] The rotational barrier was determined as 8.01 kcal/mol (**2d**, $R_2$ = Me) and 7.01 kcal/mol (**2i**, $R_2$ = Ph). In synthetically relevant **2i**, there are three other energy minima (20°, −20°, −150°) corresponding to $\tau = 35.55°$; $\chi_N = 25.79°$, $\tau = 32.77°$; $\chi_N = 19.34°$, $\tau = 22.73°$; $\chi_N = 16.57°$. The barrier to reach the local minimum is 2.10 kcal/mol. Collectively, the ground-state distortion, electronic activation, and ability to adopt a variety of conformations of *N*-Boc and *N*-Ts amides contribute to the high reactivity of these amides observed experimentally.

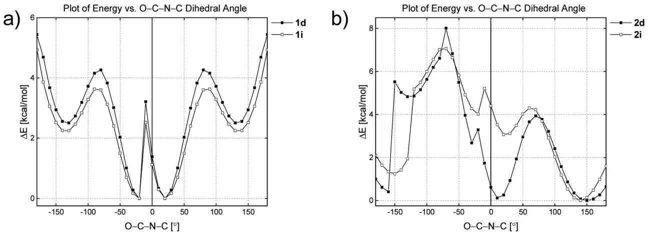

**Figure 5.** Rotational profiles of amides (a) **1**; (b) **2** ($\Delta E$, kcal/mol, vs O−C−N−C [deg]).

Resonance energies of representative amides **1** and **2** determined by carbonyl substitution nitrogen atom replacement method[13b] confirm that the resonance energy of the amide bond is very low (**1d**, 6.2 kcal/mol; **1i**, 7.2 kcal/mol; **2d**, 8.0 kcal/mol; **2i**, 9.7 kcal/mol). These values can be compared with the resonance energy of planar amides (e.g., acetamide, 19.1 kcal/mol) and that of *N*-acetylaziridine (7.1 kcal/mol).[3d] The severely diminished $n_N \rightarrow \pi^*_{C=O}$ delocalization in *N*-Boc and *N*-Ts amides provides the basis for the high reactivity in N−C bond cleavage reactions. Unsurprisingly, these amides should react as highly reactive acylating reagents.[14]

Proton affinities (PA) and differences between N- and O-protonation affinities ($\Delta$PA)[13] of representative amides **1** and **2** indicate that these amides favor protonation at oxygen (**1d**: $\Delta$PA = 8.3 kcal/mol; **1i**: $\Delta$PA = 12.1 kcal/mol; **2d**: $\Delta$PA = 7.5 kcal/mol; **2i**: $\Delta$PA = 9.3 kcal/mol). Protonation of the amide oxygen is favored over carbamate (**1d**: $\Delta$PA = 6.1 kcal/mol; **1i**: $\Delta$PA = 6.2 kcal/mol) and sulfonamide oxygens (**2d**: $\Delta$PA = 17.0 kcal/mol; **1i**: $\Delta$PA = 15.5 kcal/mol). Thus, activation of the acyl group in **1** and **2** by N-protonation is unlikely.[13]

Structures of the representative amides in series **1** and **2** were determined by X-ray diffraction (Figure 6, Table 2). Importantly, structure determination was performed from the same samples as used for the synthetic N−C activation experiments; it is well-known that the crystallization method can influence structural parameters in the solid state. X-ray structures of **1i** and **2i** show that in agreement with calculations both amides contain significantly distorted amide bonds in the solid state (**1i**, $\tau = 29.1°$, $\chi_N = 8.4°$, $\chi_C = 5.9°$; **2i**, $\tau = 18.8°$, $\chi_N = 19.9°$, $\chi_C = 1.0°$).

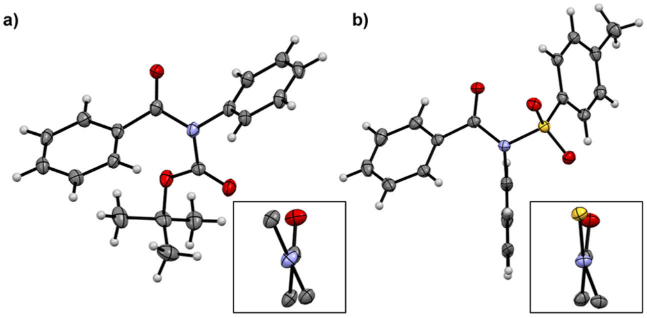

**Figure 6.** Crystal structures of (a) **1i** and (b) **2i** (50% ellipsoids). Insets show Newman projections along N−C(O) bonds. For selected bond lengths (Å) and angles (deg), see Supporting Information.

**Table 2. Selected Crystallographic Structural Parameters of Twisted Acyclic Amides 1−2 and Representative Amides**[a]

| entry | amide | N−C(O) [Å] | C=O [Å] | $\tau$ [deg] | $\chi_N$ [deg] | $\chi_C$ [deg] |
|---|---|---|---|---|---|---|
| 1[a] | **1i** | 1.406 | 1.208 | 29.1 | 8.4 | 5.9 |
| 2[a] | **2i** | 1.410 | 1.215 | 18.8 | 19.9 | 1.0 |
| 3[b] | **A** | 1.473 | 1.196 | 85.8 | 61.7 | 5.5 |
| 4[b] | **B** | 1.526 | 1.192 | 89.1 | 59.5 | 0.2 |
| 5[b] | **C** | 1.374 | 1.201 | 20.8 | 48.8 | 5.9 |
| 6[c] | **formamide** | 1.349 | 1.193 | 0.0 | 0.0 | 0.0 |

[a]This study. X-ray structures. [b]Reference 5a. For structures **A**−**C**, see Figure 1A. [c]Calculated values. Reference 13a.

The N−C(O) and C═O bond lengths are 1.406 and 1.208 Å in **1i** and 1.410 and 1.215 Å in **2i**. These values can be compared with a model twisted bridged lactam containing a fully perpendicular (Table 2, entries 3−4), approximately half-distorted amide bond (Table 2, entry 5),[5a] and planar formamide (Table 2, entry 6).[13a] *N*-Boc and *N*-Ts amides can freely rotate around the N−C(O) axis, which is not available in the fixed conformation of bridged lactams.

In conclusion, we have investigated the effect of structure on the amide bond geometry in a series of *N*-acyl-*tert*-butyl-carbamates (Boc) and *N*-acyl-tosylamides (Ts) of relevance to amide N−C cleavage. These amides have recently emerged as prototypes for the development of elusive amide bond N−C cross-coupling reactions. Our findings provide clear evidence that the *N*-acyl amide bonds in these amides are significantly distorted in the ground state. The results support the amide bond twist as a blueprint for activation of amides toward N−C bond cleavage. The use of simple acyclic twisted amides holds significant potential in transition-metal-catalyzed amide N−C cross-coupling. We expect that this study will enable the design of more efficient reactions by N−C cleavage.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01560.

Cartesian coordinates and energies; detailed description of computational methods used; full citation for Gaussian 09 (PDF)

Crystallographic data for amide **1i** (CIF)

Crystallographic data for amide **2i** (CIF)

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### Author Contributions

§S.S. and G.M. contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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