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Selective Conversion of Unactivated C−N Amide Bond to C−C bond via Steric and Electronic Resonance Destabilization

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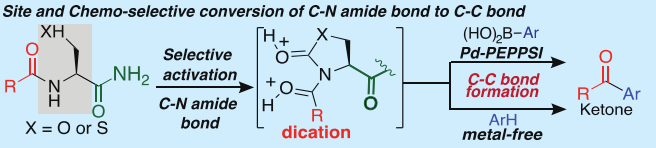
ABSTRACT: The chemo- and site-selective reaction at the particular C−N amide bond among a sea of other amides is a significant and long-standing challenge. Although the use of twisted amides has been demonstrated for modifications of inert C−N amide bonds, none of these methods can selectively activate a particular amide bond for C−C bond formation in the presence of similar amides. Using density functional theory as a guide, we report the first site-selective C−C bond modification of a particular C−N amide bond in polyamides with a low twist angle by combining ground-state steric distortion with electronic activation.



Selective modification of a particular group in the presence of other reactive functional groups is always challenging, but the site-selective modification of an inert C−N amide bond in the presence of other amides of similar reactivity remains an unsolved problem. The inertness of the C−N amide bond is due to the resonance stabilization that leads to a 40% double bond character of the C−N amide bond.[1−3] In the past decade, several methods have been reported for the conversion of both primary and secondary C−N amide bonds to C−heteroatom and C−C bonds using metal-catalyzed[4−11] and metal-free approaches (Figure 1a).[12−21] Despite the elegance and power of these approaches for the modification of C−N amide bonds, none of them are capable of selectively converting a particular C−N amide to a C−C bond in polyamides. In this article, we report the first such method that selectively modifies a particular C−N amide bond to a C−C bond in polyamides (Figure 1b). Most of the previous approaches for the formation of C−C bonds require highly twisted amides (close to the maximum twist angle $\tau \sim 90$), which are achieved by either ground-state steric distortion or electronic activation (Figure 1a).[10,22−27] To our knowledge, the direct metal-free formation of the C−C bond from less twisted amides is unknown. This is notable given that various twisted amides with much higher twist angles (twist angles $\tau = 26−65$) than those utilized in our approach (twists angles $\tau = 21.3−28.6$) did not lead to the formation of a C−C bond in the metal-free Friedel−Crafts acylation conditions (Figure 1a).[22,25] Based on DFT calculations, we developed a novel concept of introducing both steric and electronic factors in one molecule to achieve the significant resonance destabilization of C−N amide bonds to generate C−C bonds (Figure 1b). This is the first approach where C−N amide bonds with small distortions (twist angles $\tau = 21.3−28.6$) can be successfully converted to C−C bonds under exceptionally mild, metal-free Friedel−Crafts acylation conditions (Figure 1b). Here we demonstrate both the metal-catalyzed Suzuki−Miyaura reaction[27] and metal-free Friedel−Crafts acylation reaction[28−32] for the conversion of activated C−N amide bonds to C−C bonds. We also selectively modified a particular C−N amide to C−C bond in polyamides (e.g., peptides) under metal-free conditions.

Selective Activation of Amides

Based on our previous work[33,34] and acylation strategies for amide activation that are limited to C-terminal modification,[35−40] we hypothesized that the amide bond of serine, threonine, and cysteine could be selectively weakened by the formation of oxazolidinone or thiazolidinone cyclic moiety with backbone amide (Figure 2a). In a recent study from our group, DFT calculations on these synthons **1a−1d** confirmed that the addition of carbonyl and thiocarbonyl groups led to the resonance destabilization that weakened the C−N amide bond, thus greatly enhancing its reactivity and availability for further modification (Figure 2a).[41] Using B3LYP/6-311++G(d,p) in our previous study, we also determined their amide bond distortion using Winkler−Dunitz parameters: twist angles (τ), pyramidization at nitrogen (X_N), and N−C(O) and C=O bond lengths.[41,42] We found that the addition of carbonyl or thiocarbonyl group between the side chain of serine and backbone C−N amide bond generated oxazolidinone 1a ($\tau = 21.30$, $X_N = 9.1$) and oxazolidithione **1b** ($\tau = 24.0$, $X_N = 16.1$) and resulted in the twisting of the amide bond relative to the unmodified analog E ($\tau = 3.6$, $X_N = 0.5$) (Figure 2a).[41] Similarly, the addition of carbonyl and thiocarbonyl to cysteine generated twisted thiazolidinone **1c**

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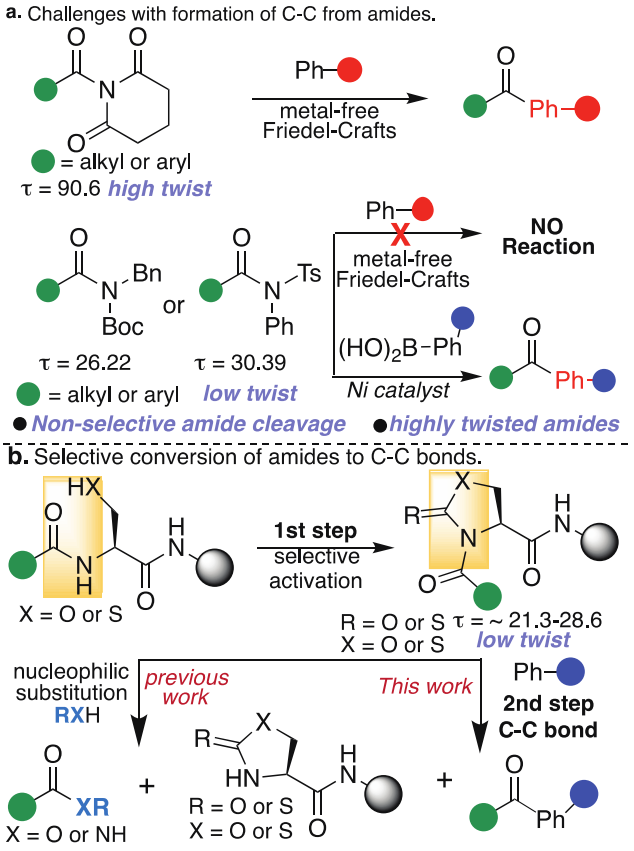


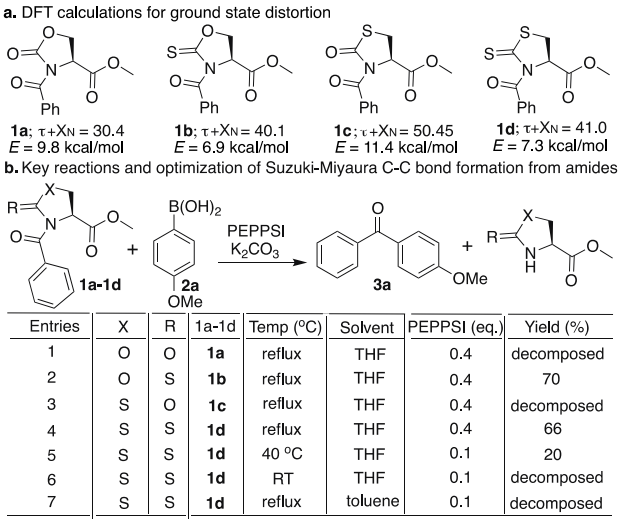
Figure 1. (a) Previous work: Activation of C−N amide bonds via metal-catalyzed and metal-free approaches, not applicable for the selective cleavage of a particular amide bond in polyamides. Requires high twist angle for metal-free C−C bond formation. (b) Our work: The selective activation of an amide in the presence of other amides; previously used for nucleophilic substitution with alcohols and amines to generate esters and amides. This work involves formation of C−C bond from activated amides to generate ketone under metal-free mild conditions.

(τ = 28.65, X_N = 21.8) and thiazolidithione **1d** (τ = 27.3, X_N = 13.7).[41]

Metal-catalyzed C−C Bond Formation from C−N Amide Bonds

Key Experiments and Reaction Optimization. To correlate the twist angle with amide reactivity, in the previous study, activated amides **1a−1d** were converted to esters and amides by nucleophilic substitution reactions with alcohols and amines.[41] In this study, we showed the formation of C−C bond from the activated amides **1a−1d**. This is the first report where oxazolidithione and thiazolidithione have been used for the synthesis of C−C bonds. We initiated our studies by carrying out Suzuki−Miyaura reactions on these activated amides **1a−1d** (for synthesis, see Figure S1) using *p*-methoxy phenylboronic acid **2a** and Pd-PEPPSI catalyst under different reaction conditions (different solvents, equivalents of catalyst, and temperaturetemperature (Figure S2)). The reactions with twisted amides **1b** and **1d** proceeded efficiently under optimized conditions involving PEPPSI, K_2CO_3, and THF[43,44] and generated ketone product **3a** in a good yield (66−70%, entries 2 and 4, Figure 2b).

Twisted amides **1a** and **1c** were unstable and decomposed under the reaction conditions (Figure 2b, entries 1 and 3). We were surprised that twisted amide **1c** with a relatively high



Entries	X	R	1a-1d	Temp (°C)	Solvent	PEPPSI (eq.)	Yield (%)
1	O	O	**1a**	reflux	THF	0.4	decomposed
2	O	S	**1b**	reflux	THF	0.4	70
3	S	O	**1c**	reflux	THF	0.4	decomposed
4	S	S	**1d**	reflux	THF	0.4	66
5	S	S	**1d**	40 °C	THF	0.1	20
6	S	S	**1d**	RT	THF	0.1	decomposed
7	S	S	**1d**	reflux	toluene	0.1	decomposed

Figure 2. (a) DFT calculations to determine the ground-state distortion and activation of modified amides **1a−1d**. (b) Metal-catalyzed C−C bond formation on activated amides **1a−1d**. Reaction conditions: activated amide **1a−1d** (0.07 mm, 1 equiv), *p*-methoxy phenylboronic acid **2a** (2.0 equiv), Pd-PEPPSI (0.1−0.4 equiv), K_2CO_3 (3 equiv) in varying solvents (5 mL) at different temperatures overnight.

twist angle (τ = 28.65) and pyramidization at nitrogen (X_N = 21.8) decomposed and no product was observed as compared to **1b** (τ = 24.0, X_N = 16.1) and **1d** (τ = 27.3, X_N = 13.7) (entries 2−4, Figure 2b). We hypothesized that this anomaly is due to the influence of rotational energy barrier (E) of the molecules **1a−1d** on the reactivity of twisted amides.[16,24] As calculated in our previous studies, compound **1c** has a higher rotational energy barrier (E = 11.4 kcal/mol) as compared to other reactive twisted amides **1b** and **1d** (E = 6.9 and 7.3 kcal/mol);[41] thus, **1c** exhibited lower reactivity for C−C bond formation (entry 3, Figure 2b, Figures S2 and S3).

Scope of the Reaction. Examination of the scope revealed that a remarkably broad range of boronic acids is suitable for this Pd-catalyzed C−C bond formation reaction with twisted amides **1b** and **1d** (Figure 3, Figures S4 and S5). As shown, these conditions are compatible with diverse arylboronic acids, including neutral phenylboronic acid and boronic acids with electron-withdrawing or electron-releasing functional groups **2a−2i**, which is a significant improvement from acylpyrrole and pyrazole amide activation.[45] The methodology was found to be tolerant of pharmaceutically important heterocyclic aryl boronates such as 1,4-benzodioxane-6-boronic acid **2j** and 3-thiopheneboronic acid **2k** and generated corresponding ketones **3j−3k** in good yields (65−76%, Figure 3, Figure S4 and S5). Interestingly, high efficiency was observed with sterically demanding polyaromatic arenes to generate aryl and biaryl ketones **3l−3n** in excellent yields (Figure 3, Figure S5).

Perhaps most notable is the capacity of the reaction to tolerate alkenylboronic acids such as 1-pentenylboronic acid **2o**, 1-octenyl boronic acid **2p**, and styrylboronic acid **2q** which are often problematic in the addition reactions to other secondary amides. We observed an efficient conversion of the starting materials to α,β-unsaturated ketones **3o−3q** with excellent yields (60−80%, intermediate, Figure 3, Figure S5), highlighting the potential impact of this method. Collectively these examples demonstrate the broad scope of this reaction

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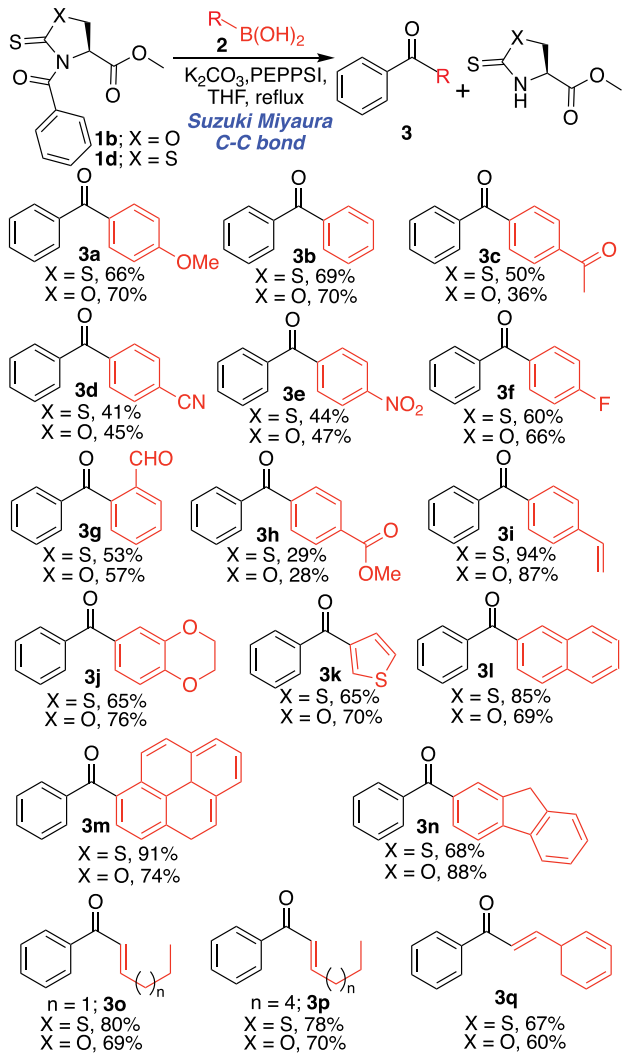


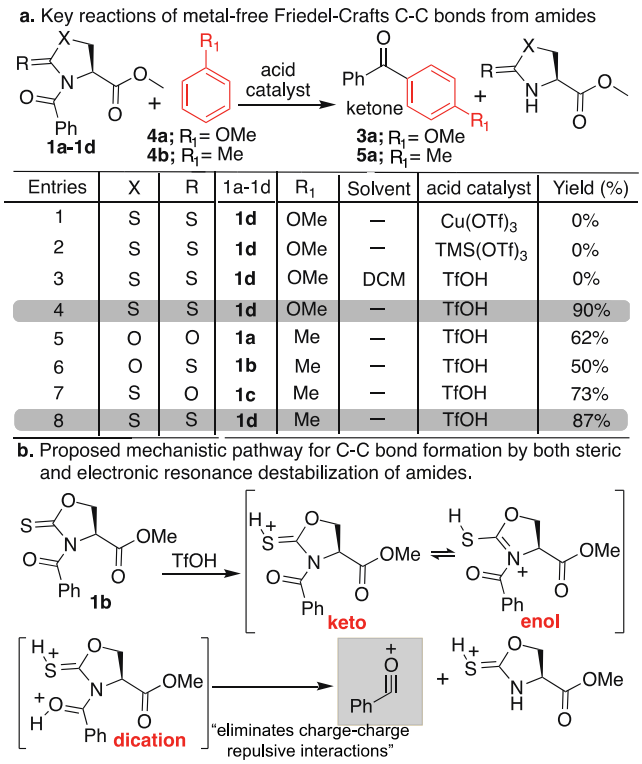
Figure 3. Scope of C−C bond formation was evaluated with both amide substrates **1b** and **1d**, with varying aryl or alkenyl boronic acids. Reaction conditions: activated amide **1b** or **1d** (0.07 mm, 1 equiv), aryl and alkenyl boronic acid (2.0 equiv), PEPPSI (0.4 equiv), K_2CO_3 (3 equiv) in THF (5 mL) under refluxing conditions for overnight.

and provide a conceptually new method for the direct synthesis of ketones from secondary amides.

Metal-Free C−C Bond Formation by Friedel−Crafts Reaction

Current metal-free approaches for making ketones by twist activation and subsequent Friedel−Crafts acylation are mainly limited to highly twisted amides (twist angle ~90.6) such as glutarimides (Figure 1a).[30] Herein, we report for the first time the modification of C−N amide bonds with moderate twist angles (τ = 21.3−28.6) to C−C bonds under mild, metal-free mild conditions.

Key Experiments and Reaction Optimization. We initiated our studies on a model twisted amide **1d** with anisole **4a** using various acid catalysts such as $Cu(OTf)_3$, $TMS(OTf)_3$, and trifluoromethanesulfonic acid (TfOH) (entries 1−4, Figure 4a, Figure S6).[30,46] We were pleased to see a high yield of the ketone product **3a** (90%) from twisted amide **1d** using a stoichiometric amount of TfOH (entry 4, Figure 4a). With optimal conditions in hand, we used toluene **4b** for the formation of a C−C bond with all of the activated amides **1a**−



Entries	X	R	1a-1d	R_1	Solvent	acid catalyst	Yield (%)
1	S	S	**1d**	OMe	—	$Cu(OTf)_3$	0%
2	S	S	**1d**	OMe	—	$TMS(OTf)_3$	0%
3	S	S	**1d**	OMe	DCM	TfOH	0%
4	S	S	**1d**	OMe	—	TfOH	90%
5	O	O	**1a**	Me	—	TfOH	62%
6	O	S	**1b**	Me	—	TfOH	50%
7	S	O	**1c**	Me	—	TfOH	73%
8	S	S	**1d**	Me	—	TfOH	87%

Figure 4. (a) Key reactions and optimization for metal-free C−C bond formation from twisted amides. (b) Proposed pathway for activation of amides for C−C bond formation by both ground-state steric distortion and electronic activation.

1d (entries 5−8, Figure 4a, Figure S6). As expected, **1d** with the Winkler−Dunitz parameters ($\tau + X_N$ = 41.0) and lower rotational energy barrier (E) (7.3 kcal/mol) gave the corresponding ketone product **5a** with the highest yield (87%, entry 8, Figure 4a, Figure S6). All other twisted amides **1a**, **1b**, and **1c** (twist angles τ = 21.3−28.6) also generated the corresponding ketone product **5a** with toluene in moderate yields (50−73%, entries 5−7, Figure 4a) which is in contrast to the electronically activated amides *N*-Bz,-*N*-Boc-amide, and *N*-Ph,-*N*-Ts-amide (twist angles τ = 26.22 and 30.39 and rotational energy barrier (E) = 4.3−7.0 kcal/mol) generating 0% yields under the optimized metal-free conditions.[10,30] From these results, we anticipate that both ground-state steric distortion and electronic destabilization in addition to the twisted amide and rotational energy barrier play an important role in this C−C bond-forming reaction. We hypothesized that in the presence of TfOH the carbonyl and thiocarbonyl of the oxa- and thiazolidinone rings undergo protonation that induces tautomerization between the keto and enol forms with the amidic nitrogen (proposed mechanistic pathway, Figure 4b). This further decreases the tendency of the C−N amide bond to form a resonating structure leading to the weakening of the C−N amide bonds.[31] Moreover, the formation of the "dication" by these activated amides in the presence of TfOH favors the cleavage of the C−N amide bonds as this eliminates charge−charge repulsive interactions in the "dication" (Figure 4b).[31,32,47,48] Such protonation of heteroatoms and formation of dications is not possible with activated amides *N*-Bz,-*N*-Boc-amide and *N*-Ph,-*N*-Ts-amide providing a rationale as to why the C−N bond remains unreactive under metal-free conditions. This study proposed a new concept for the modification of inert C−N amide bonds

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to C−C bonds by combining ground-state steric distortion with electronic destabilization under metal-free mild conditions.

Scope of the Reaction. With optimal conditions in hand, the scope of the reaction was investigated on activated amides **1b** and **1d** with different arenes (Figure 5a, Figure S7). The

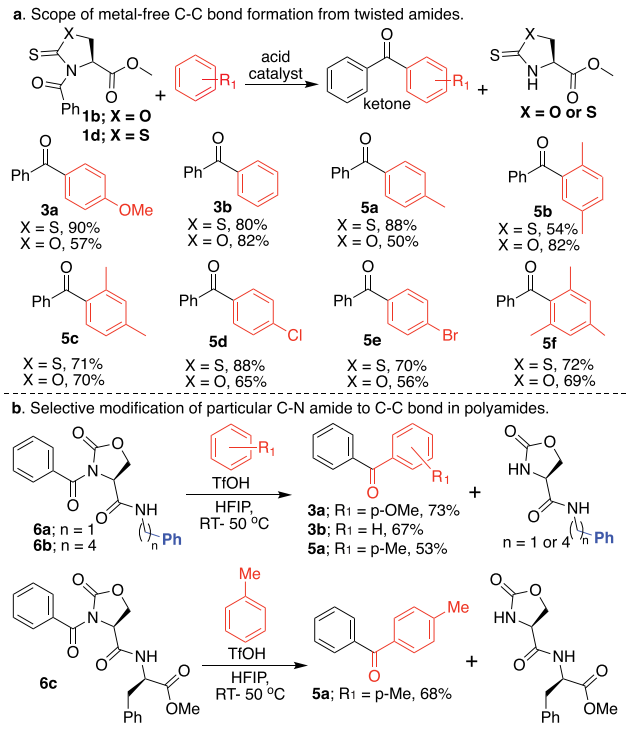

Figure 5. (a) Selective modification of secondary amides **1b** and **1d** with varying arenes (b) Selective activation of a particular secondary amide in polyamides for metal-free C−C formation using varying arenes. Reaction conditions for activated amide (a) **1b or 1d** (**1b**; 0.189 mm; **1d**; 0.178 mm, 1 equiv), acid catalyst (5 equiv), dry arene solvent (5 mL) at room temperature for overnight. Reaction conditions for polyamides (b) **6a**−**6c** (**6a** = **6b**; 0.273 mm, **6c**; 0.0126 mm, 1 equiv), TfOH (10 equiv), in dry arene and HFIP cosolvent (1:3) (6a and 6b; 5 mL, 6c; 600 μL) at 50 °C for 10 h.

reaction readily accommodated varying electron-rich, neutral, sterically hindered and multiple-substituted arenes to generate corresponding ketones **3a**−**3b** and **5a**−**5f** in good yields (70−95% Figure 5a, Figure S7).

Site-Selective Modification of C−N Amide Bond in Polyamides to C−C Bond

For the selective modification of a particular C−N amide bond in polyamides to a C−C bond, we attempted selective insertions of thiocarbonyl at the cysteine amide in tripeptides Boc-FCF-OMe and AcO-RFC by using various thiocarbonylating agents (Figure S8). These reactions failed to generate thiocarbonyl-modified peptides due to the low reactivity of an intermediate obtained by the reaction of the side chain of serine/cysteine in polyamides with thiocarbonylating reagent resulting in its rapid decomposition/hydrolysis before the nucleophilic attack from the backbone amide bond. Since **1a** is also twisted ($\tau + X_N = 30.4$) with low rotational energy barrier (E = 9.8 kcal/mol), we selectively twisted serine amide in a polyamide Ph-Ser-benzamide by reaction with a carbonyl donor (DSC) to generate the corresponding oxazolidinone Ph-Oxa-benzamide **6a** (synthesis in Figures S9 and S11).

We were pleased to see that polyamide **6a** generated benzophenone products **3a** and **3b** in good yields under metal-free conditions with varying arenes (**3a**; 73% with anisole and **3b**; 67% with benzene, Figure 5b, Figure S10). There are no other methods reported in the literature that can selectively activate particular C−N amide bonds of polyamide in the presence of other secondary and primary amides for the formation of C−C bonds under metal-free conditions. To determine the broad scope of this reaction, we selectively generated other twisted polyamides Ph-Oxa-phenylbutylamide **6b** and Ph-Ser-Phe-OMe **6c** (synthesis Figures S9 and S11) and carried out a Friedel−Crafts reaction. The reactions resulted in the selective formation of C−C bonds with toluene to generate benzophenone analog **5a** in high yields irrespective of the nature of polyamides (53% from **6b** and 68% from **6c**, Figure 5b, Figure S10). It is noteworthy that the reaction on peptides for the formation of C−C bonds under mild metal-free reaction conditions overcomes one of the major limitations of nickel-catalyzed C−C bond formation requiring harsh conditions.[4,49]

In conclusion, we developed a conceptually new approach for the activation of unactivated secondary amides for the formation of C−C bonds by combining "ground-state steric distortion" with "electronic activation". We demonstrated that C−N amide bonds of oxazolidinone with small twist angles (twist angles = 21.3−28.6), despite being considered of lower reactivity, can be successfully converted to C−C bonds under exceptionally mild, metal-free Friedel−Crafts acylation conditions, which is in contrast to the previous methods requiring high twist angles. These studies demonstrate for the first time site-selective conversion of the C−N amide bond in polyamides to C−C bond under metal-free conditions using varying arenes.

■ ASSOCIATED CONTENT

Supporting Information

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Supporting figures, experimental procedures, and analytical data for new compounds (PDF)

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Author Contributions

M.R., V.A., and M.S. designed the project. V.A., M.S., and Y.W. performed all the synthetic experiments and characterized the compounds by NMR and LCMS. V.A. performed the DFT

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calculations. All authors analyzed the results. M.R. and V.A. wrote the manuscript.

Notes

The authors declare no competing financial interest.

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