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Thieme Chemistry Journals Awardees – Where Are They Now? Bis(2-pyridyl)amides as Readily Cleavable Amides Under Catalytic, Neutral, and Room-Temperature Conditions

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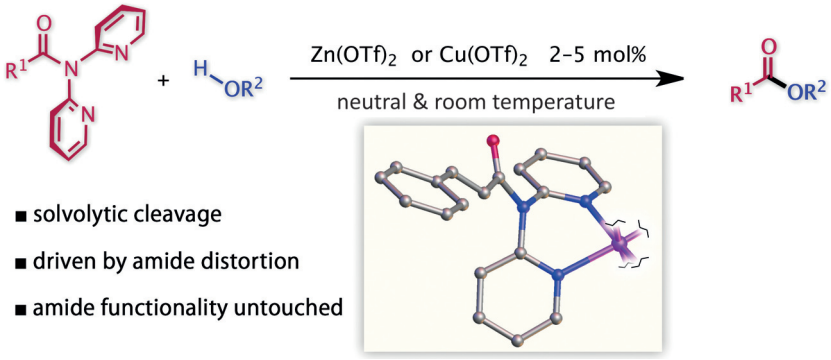

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Abstract Mild solvolytic cleavage of bis(2-pyridyl)amide under neutral and room-temperature conditions is described. The inherently stable amide was readily activated by catalytic amounts of metal cations to react with alcohols. Based on X-ray crystallographic analysis, the primary driving force was considered to be amide distortion induced by the metal coordination of two pyridyl groups in a bidentate fashion without affecting the amide functionality. The compatibility of the acid/base-sensitive functionalities and the absence of racemization during solvolysis highlight the mildness of the present protocol.

Key words amide, deconjugation, amide distortion, amide twisting, solvolysis, metal coordination, mild conditions

The amide group is a vital functionality that determines the primary structure of proteins by interconnecting α-amino acid units, and it is ubiquitously present in various naturally occurring compounds and artificial chemical entities, e.g., therapeutic agents and functional polymers. The amide functionality is characterized by a flat structure that dictates its inherently stable nature due to n_N–$\pi^*_{C=O}$ conjugation, which renders the robust amide-bond linkage least reactive in the class of carbonyl-type functionalities.[1] Modulation of amide planarity to elicit hidden reactivity of the amide functionality has been a sustained topic in organic chemistry[2] since the first appearance of a postulated twisted amide in 1938.[3] Distortion of the flat structure of an amide by twisting (τ) as well as *N*-pyramidalization (χ_N)[4] was established to significantly increase the susceptibility of amide-bond linkages via deconjugation, best represented by highly distorted examples **1**–**3** with rigid bicyclic architectures (Scheme 1, a).[5,6] Recently, *N*-acylglutarimide **4** was disclosed to exhibit a considerable twist angle comparable to bridged derivatives **1**–**3** despite its noncyclic structure;[2e–g,7]

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this substantial distortion is general for other *N*-acylimides and was elegantly exploited in a series of catalytic coupling reactions involving facile oxidative addition of the C–N bond.[7a,8,9]

The innate reactivity of other decorated amides, e.g., electron-deficient *N*-sulfonyl and *N*-Boc amides[10] as well as *N*-acylsaccharins,[10c,11] *N*-pyrazolylamides,[12] azetidine amides,[13] and anilides[14] were also revealed as competent amides

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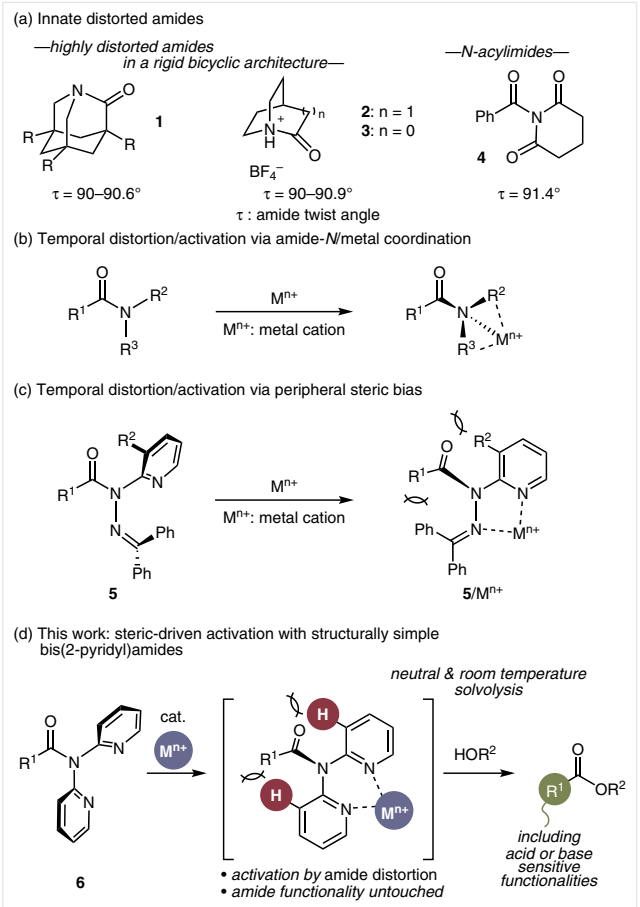
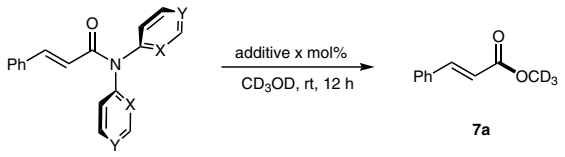


Scheme 1 (a)–(c) Prior art to access distorted amides and (d) this work on the solvolytic cleavage of amides under neutral and room-temperature conditions

in reaction manifolds involving oxidative addition of the amide C–N bond, where a low rotational barrier of the amide C–N bond is proposed for high reactivity.[7] In addition to these inherently activated amides, in situ activation of unreactive amides by structural distortion is another highly investigated topic, demonstrating that deformation indeed occurs by direct metal coordination to the amide nitrogen (Scheme 1, b).[15] On the other hand, in situ distortion and activation while maintaining the amide functionality untouched was recently manifested by our group, with peripheral steric bias induced by metal coordination having a crucial role (Scheme 1, c).[16] Although non-Lewis acidic amide activation was supported by structural evidence (X-ray and NMR) and solvolytic cleavage of the amide occurred at room temperature, the rather uncommon structure of amide **5** severely affected the utility of this sterically driven activation mode. We reasoned that structural distortion for temporary activation might take place even with structurally simpler amides. Herein, we document mild solvolysis of bis(2-pyridyl) amides **6** promoted by catalytic amounts of metal salts under neutral and room-temperature conditions (Scheme 1, d). X-ray crystallographic analysis suggested that amide distortion was the driving force behind the solvolysis.

We began our study with methanolysis of cinnamyl amide **6a** installed with two 2-pyridyl groups on the amide nitrogen (Table 1). Screening of readily available first-row transition-metal salts as an azophilic chelator in CD_3OD quickly identified $Zn(OTf)_2$ and $Cu(OTf)_2$ as promising promoters with catalyst loading of 5 mol%, affording nearly quantitative yield of ester **7a**-d_3 at room temperature (Table 1, entries 1–4). Amide **6a** was sufficiently stable in the absence of metal salts (Table 1, entry 5). While $Zn(NTf_2)_2$ exhibited similar catalytic activity as $Zn(OTf)_2$, $ZnCl_2$ had a slower catalytic profile, presumably due to intimate ion pairing with chlorides retarding the coordination/dissociation kinetics (Table 1, entries 6 and 7). Because amide **6a** was sufficiently stable in acidic conditions and ester **7a**-d_3 was not detected after treatment with 1 equiv of TfOH, metal cations were responsible for the catalysis, and the involvement of any acidic impurities was ruled out (Table 1, entry 8).[17] On the other hand, amide **6a′** bearing isomeric 4-pyridyl groups did not exhibit any reactivity in the presence of 5 mol% or stoichiometric amounts of $Zn(OTf)_2$, which also supports the involvement of chelating activation through two 2-pyridyl groups (Table 1, entries 9 and 10). To shed light on the mechanistic aspect of this room-tempera-

Table 1 Methanolysis (CD_3OD) of Bis(pyridyl)amide Derivatives **6** in the Presence of a Catalytic Amount of Metal Salts[a]



Entry	Amide **6** X =	Y =		Additive	x (mol%)	Yield (%)[b]
1	N	H	**6a**	$Fe(OTf)_2$	5	69
2	N	H	**6a**	$Ni(OTf)_2$	5	20
3	N	H	**6a**	$Zn(OTf)_2$	5	>95
4	N	H	**6a**	$Cu(OTf)_2$	5	>95
5[c]	N	H	**6a**	–	–	0
6	N	H	**6a**	$Zn(NTf_2)_2$	5	>95
7	N	H	**6a**	$ZnCl_2$	5	86
8	N	H	**6a**	TfOH	100	0
9	H	N	**6a′**	$Zn(OTf)_2$	5	0
10	H	N	**6a′**	$Zn(OTf)_2$	100	0

[a] 5.6 mM.
[b] Determined by ^1H NMR analysis of the crude mixture with dibenzyl as an internal standard.
[c] Run for 48 h.

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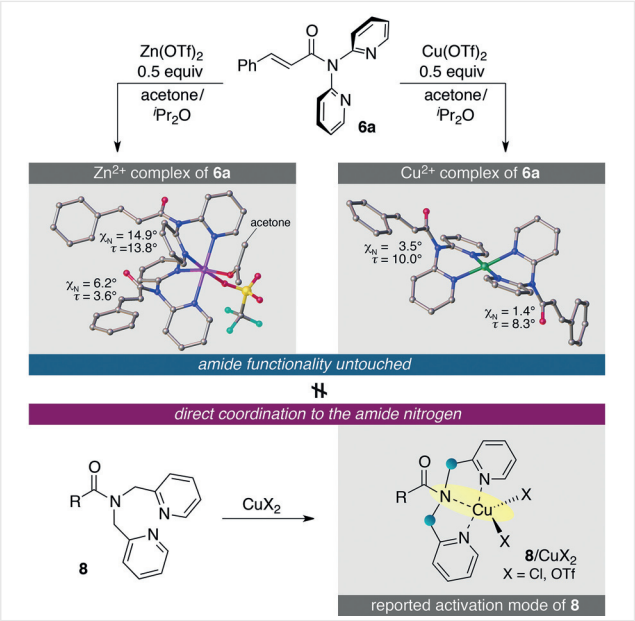
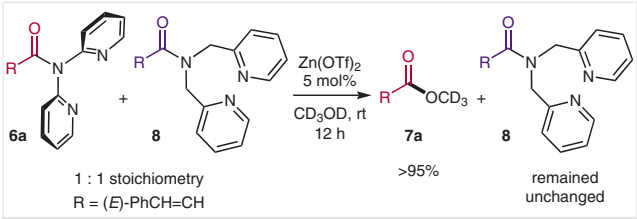
ture solvolytic protocol and dissect the activation mode operative for **6a** in the presence of metal salts, single crystals were grown from a mixture of **6a** and $Zn(OTf)_2$ at a 1:1 ratio in anhydrous acetone/$^iPr_2O$ (Scheme 2). X-ray crystallographic analysis of the crystals revealed a homoleptic $(\mathbf{6a})_2/Zn^{2+}$ complex, in which two pyridyl groups coordinated to two Zn^{2+} in an octahedral coordination mode. Of note, the amide functionality was free from the Zn^{2+} coordination sphere and the involvement of Lewis acidic activation was unlikely.

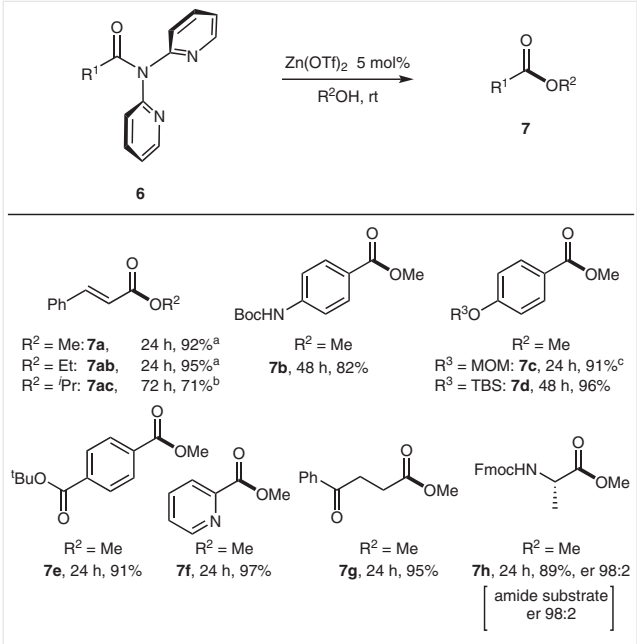


Scheme 2 Crystallographic analysis of **6a**/Zn^{2+} and **6a**/Cu^{2+} and reported activation mode of structurally similar amide **8**. For X-ray structures, hydrogen atoms, one molecule of triflate anion (for **6a**/Zn^{2+}), and two triflate anions (for **6a**/Cu^{2+}) are omitted for clarity. Color code; grey: carbon, blue: nitrogen, red: oxygen, light green: fluorine, yellow: sulfur, dark green: cupper, purple: zinc.

Instead, increasing peripheral steric bias induced by two rigidified Zn^{2+}-coordinated pyridyl groups deformed the amide planarity ($\tau = 13.8°$, $\chi_N = 14.9°$; $\tau = 3.6°$, $\chi_N = 6.2°$), enhancing the susceptibility of the amide carbonyl to nucleophilic attack by methanol for solvolysis. As expected by the catalytic solvolysis, coordination and dissociation of **6a** to Zn^{2+} was rapid and largely averaged spectra were observed in NMR analysis.[18] This activation mode was likely dictated by the peripheral steric bias and distinct from that observed for structurally similar amide **8**; a methylene group was embedded between the amide nitrogen and 2-pyridyl group (Scheme 2). Reported crystallographic analysis of complex **8**/$CuCl_2$ and **8**/$Cu(OTf)_2$ clearly revealed direct coordination of the amide nitrogen to Cu^{2+}, which was responsible for amide pyramidalization and the following solvolysis.[15a,15c–e,15g–j] Moreover, **8** recovered unchanged under the solvolytic conditions with $Zn(OTf)_2$ in CD_3OD and **6a** served as a complimentary amide cleavable by $Zn(OTf)_2$ in a catalytic manner, as shown in the competitive reaction outlined in Scheme 3.[19] Whereas Cu^{2+} ($Cu(OTf)_2$) was also competent to effect the solvolysis of **6a** (Table 1), the crystal structure of **6a**/Cu^{2+} indicated that distortion-driven activation mode was operative for **6a**,[20] and there was no direct contact of the amide nitrogen to Cu^{2+} (Scheme 2).[21]



Scheme 3 Chemoselective catalytic methanolysis (CD_3OD) of **6a** in the presence of structurally similar amide **8**



Scheme 4 Catalytic solvolysis of bis(2-pyridyl)amides **6** promoted by $Zn(OTf)_2$ at room temperature. Reactions were run on 0.2 mmol scale, and isolated yields are presented. Reactions were run on 0.1 M except for the synthesis of **7ac** (0.02 M); er: enantiomeric ratio. [a] 2 mol% of $Zn(OTf)_2$ were used. [b] 10 mol% of $Cu(OTf)_2$ were used instead of $Zn(OTf)_2$. [c] 5 mol% of $Cu(OTf)_2$ were used instead of $Zn(OTf)_2$.

The present mild Zn-catalyzed solvolytic protocol was validated with substrates having a variety of substituents (Scheme 4).[22] While smooth solvolysis was observed for cinnamyl amide **6a** in MeOH and EtOH with as little as 2 mol% of $Zn(OTf)_2$ to give methyl and ethyl esters **7a**, **7ab**, formation of corresponding isopropyl ester **7ac** proceeded sluggishly, and $Cu(OTf)_2$ instead of $Zn(OTf)_2$ exhibited better catalytic activity. Bis(2-pyridyl)amides prepared from benzoic acid derivatives were then examined. This mild

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protocol was also applicable to benzamides and acid-labile *N*-Boc, *O*-MOM, and *O*-TBS groups were tolerated (**7b–d**). A ^{t}Bu ester group remained unchanged (**7e**). A substrate bearing a pyridyl group, which can potentially impair the chelating activation by $Zn(OTf)_2$, afforded desired methyl ester **7f** in high yield. Amides derived from sp^3-aliphatic carboxylic acid exhibited high reactivity and a γ-keto group had no detrimental effects (**7g**,**h**). The absence of racemization in the catalytic solvolysis of the amide α-amino acid derivative underscored the mild solvolytic protocol,[23] delivering Fmoc-Ala-OMe (**7h**) in high yield without undesired deprotection of base-sensitive Fmoc group.

In conclusion, we demonstrated that bis(2-pyridyl)amides are amenable to solvolytic cleavage to give the corresponding esters under mild catalytic conditions using Zn^{2+} or Cu^{2+} salts. The neutral and room-temperature protocol accommodates a variety of base- and acid-labile functional groups. The observed coordination mode in X-ray crystallographic analysis indicated that the amide functional group was not affected by metal cations, and the amide distortion driven by peripheral steric bias was crucially involved in engaging the amide in solvolysis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590932.

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(17) Although cation-driven solvolysis was much faster, partial solvolysis of amide **6a** proceeded under basic conditions: 1 equiv NaOH: 15%, 1 equiv DBU: 25% (identical conditions to Table 1: in CD_3OD, rt, 12 h). Compound **6a** was sufficiently stable under mild conditions and remained unchanged in the presence 1 equiv of Et_3N.
(18) See Supporting Information.
(19) Other designed amide cleavable by stoichiometric amount of $Zn(OTf)_2$ was developed. See ref. 15j.
(20) A part of the crsytal structure was disordered. See Supporting Information.
(21) For transesterification and transamidation of innate reactive amides, see: (a) Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2012**, *51*, 548. (b) Aubé, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3063. (c) Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. *Org. Lett.* **2017**, *19*, 1614; see also ref. 10b,d,k and 14a,b.
(22) **General Procedure: Catalytic Solvolysis of Amide 6**
A flame-dried 5 mL round-bottomed flask equipped with a magnetic stirring bar and a septum cap was charged with amide **6** (0.20 mmol) and $Zn(OTf)_2$ (0.01 mmol, 5 mol% or 0.004 mmol, 2 mol%; 0.02 mmol, 10 mol% or 0.01 mmol, 5 mol% of $Cu(OTf)_2$ were used for the synthesis of **7ac** or **7c**, respectively) in a glove box under Ar atmosphere. After adding anhydrous MeOH (2.0 mL; 2 mL of EtOH or ^{i}PrOH was used for the synthesis of **7ab** or **7ac**) at rt, the resulting clear solution was stirred for designated period of reaction time at the same temperature. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography to give esters **7**.
Methyl cinnamate (**7a**): white solid; yield 29.7 mg (92%).
Ethyl cinnamate (**7ab**): colorless oil; yield 33.5 mg (95%).
Isopropyl Cinnamate (**7ac**): colorless oil; yield 26.9 mg (71%).
Methyl 4-[(*tert*-butoxycarbonyl)amino]benzoate (**7b**): white solid; yield 41.4 mg (82%).
Methyl 4-(methoxymethoxy)benzoate (**7c**): clorless oil; yield 35.9 mg (91%).
Methyl 4-[(*tert*-butyldimethylsilyl)oxy]benzoate (**7d**): colorless oil; yield 51.2 mg (96%).
tert-Butyl methyl terephthalate (**7e**): white solid; yield 42.8 mg (91%).
Methyl picolinate (**7f**): colorless oil; yield 26.7 mg (97%).
Methyl 4-oxo-4-phenylbutanoate (**7g**): colorless oil; yield 36.4 mg (95%).
(*S*)-Methyl 2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino) propanoate (**7h**): white solid; yield 57.6 mg (89%).
(23) Determined by HPLC analysis.

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