Oxidations

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Synthesis of Imides, *N*-Acyl Vinylogous Carbamates and Ureas, and Nitriles by Oxidation of Amides and Amines with Dess–Martin Periodinane**

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The synthetic utility and pervasiveness of hypervalent iodine(v) reagents have become increasingly evident in recent decades, as underscored by a multitude of protocols that highlight the oxidative capabilities of λ^5-iodanes and their successful employment for the construction of diverse arrays of molecular targets.[1–3] As part of our explorations into the realm of hypervalent iodine(v) chemistry, we recently reported a number of useful applications involving both Dess–Martin Periodinane (DMP) and *o*-iodoxybenzoic acid (IBX). Included in these discoveries are the IBX-induced conversion of amines into imines[4] and the initiation of cascade reactions by DMP leading to a variety of imidoquinones and heterocycles from anilide precursors.[5,6] The intelligence gathered in the course of these investigations led us to hypothesize about additional modes of reactivity that could perhaps be unveiled through further explorations of the chemistry of such hypervalent iodine(v) reagents toward other classes of heteroatom-containing substrates. These speculations proved fruitful, and herein we report the direct oxidation of amides into imides and *N*-acyl vinylogous carbamates and ureas, the dehydrogenation of benzylic and related amines to aromatic nitriles by DMP, and applications thereof.

Imides are well represented in the literature, often appearing as productive components in a variety of reactions, ranging from condensations to alkylations and from acylations to cycloadditions.[7] This structural motif also appears in certain natural products such as fumaramidmycin,[8] coniothyriomycin,[9] and SB-253514.[10] Despite several procedures being available for their preparation, new methods for the synthesis of imides are nevertheless of considerable importance, especially when their direct access from readily available substrates could be secured under mild conditions.

The mechanistic rationale for the oxidation of amides to imides with DMP is shown in Scheme 1 A. Thus, it was anticipated that nucleophilic attack onto the iodine core of the reagent by the amide oxygen atom with concomitant expulsion of an acetate group may lead to intermediate **I**, whose spontaneous intramolecular rearrangement was anticipated to result in its collapse to Ac-IBA, AcOH, and *N*-acyl imine intermediate **3**. The latter, highly reactive, species **3** may then be transformed into imide **6**, either by addition of H_2O, with subsequent oxidation of the putative hemiaminal with DMP (Scheme 1 A, path A), or by the incorporation of Ac-IBX (**4**), to generate an intermediate of type **II** (Scheme 1 A, path B).

This hypothesis proved correct as secondary amides were smoothly oxidized to imides by heating with DMP in a mixture of fluorobenzene and DMSO at 80–85 °C. As seen by inspection of Table 1, an extensive range of functional groups is tolerated by this protocol, including aromatic halides, olefins, and acetates. Particularly significant are the results in Table 1, entries 3 and 5, which demonstrate the superiority of the present method over contemporary techniques employing RuO_4,[11] a reagent whose tolerance of the olefinic and ethereal sites of substrates **15** and **19**, respectively, would be questionable, at best.[12] Table 1, entries 7 and 8 are also noteworthy as they provide information regarding chemoselectivity preferences for the action of DMP on amide-containing substrates. Thus, carbamates are inert to these oxidation conditions (Table 1, entry 7), as are benzylic positions (Table 1, entry 8). The latter observation is expected as DMP is not, unlike IBX,[13] a willing single-electron-

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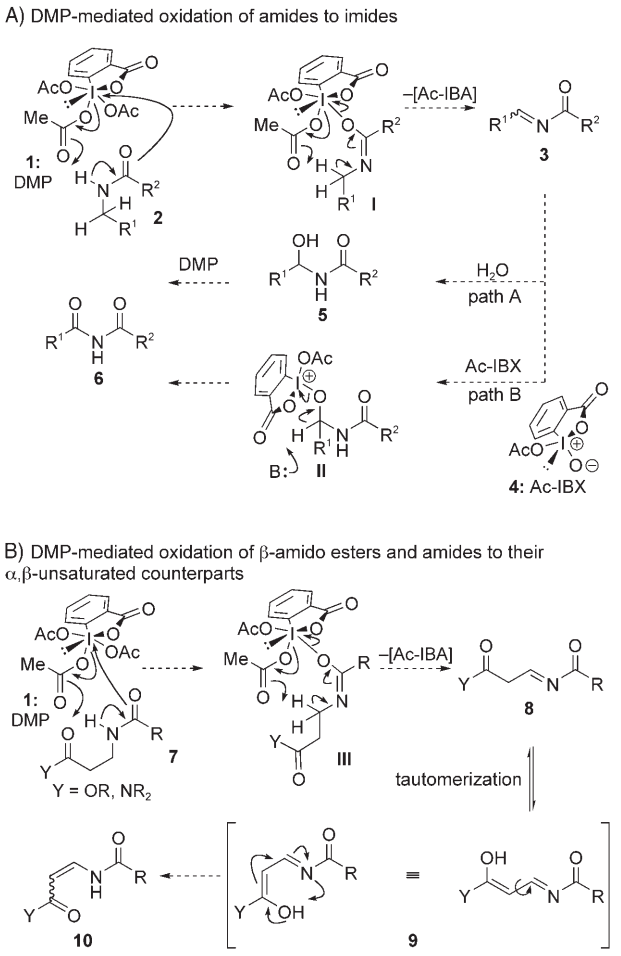


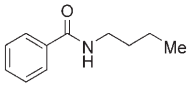
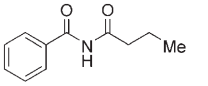
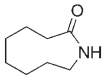
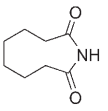
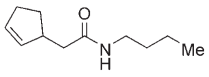
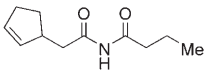
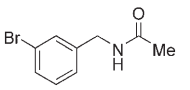
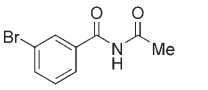
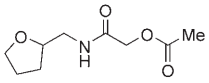
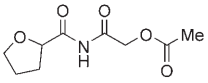
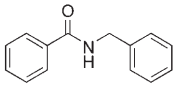
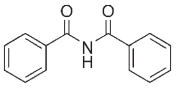
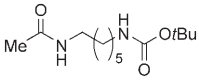
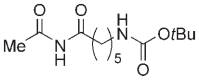
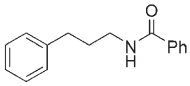
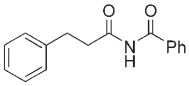
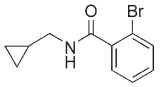
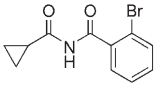
Scheme 1. Mechanistic rationale for the DMP-mediated oxidation of amides (A) and β-amido esters and amides (B). Ac-IBA = 1-acetoxy-1,2-benziodoxol-3(1*H*)-one; Ac-IBX = 1-acetoxy-1-oxide-1,2-benziodoxol-3(1*H*)-one.

transfer reagent. The minimal amount of DMSO is recommended for this reaction as it was found that larger amounts of this solvent (needed to ensure dissolution of certain substrates) proved deleterious (see Table 1, entry 5).

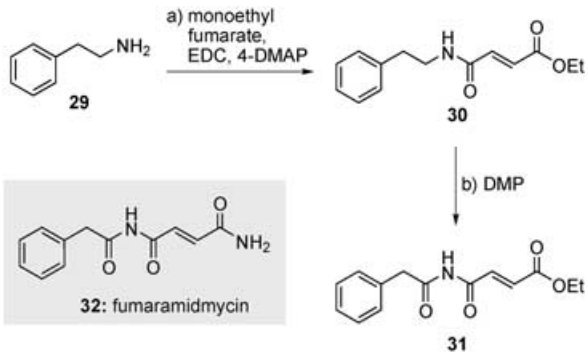
The relevance and potential utility of this novel route to imides is underscored by a facile synthesis of the ethyl ester analogue **31** of the antibiotic fumaramidmycin (**32**), as depicted in Scheme 2. Thus, coupling of monoethyl fumarate with amine **29** and subsequent oxidation of the resulting amide (**30**) with DMP led to the targeted fumaramidmycin analogue **31** (Table 4). This endeavor was instructive, as it not only resulted in the specific synthesis of **31** in a most expeditious manner but also hinted at the wealth of additional natural or designed structures that could be easily accessed through the developed technology.

Encouraged by these results, we further postulated that secondary amides equipped with *N*-β-carbonyl structural motifs could furnish vinylogous carbamates and ureas under suitable conditions. This speculation, which rested on the mechanistic rationale shown in Scheme 1 B, proved well founded as demonstrated in Table 2. Thus, the reaction conditions have been demonstrated to favor the *cis*-configured product, likely due to the stabilization provided by the

Table 1: Synthesis of imides by oxidation of amides with DMP.[a]

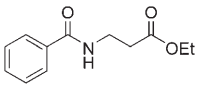
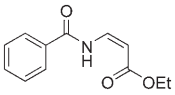
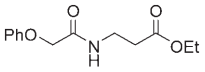
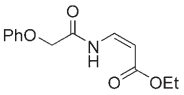
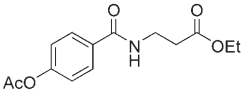
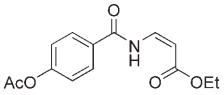
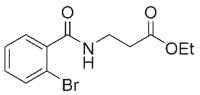
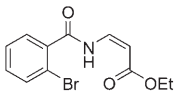
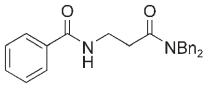
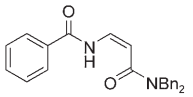
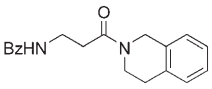
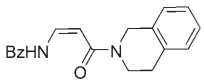
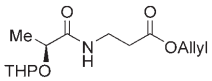
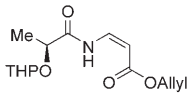
Entry	Substrate		Product		t [h]	Yield [%][b]
1		**11**		**12**	1.0	98
2		**13**		**14**	0.5	86
3		**15**		**16**	3.0	61
4		**17**		**18**	0.5	98
5		**19**		**20**	5.0	96[c]
6		**21**		**22**	1.0	86
7		**23**		**24**	3.5	86[d]
8		**25**		**26**	2.0	98
9		**27**		**28**	1.0	92

[a] Reactions were conducted on a 0.2–0.5 mmol scale in PhF/DMSO (minimal amount of DMSO) at 85 °C with DMP (2.0 equiv), unless otherwise noted. [b] Yield of isolated product with no chromatography necessary. [c] Based on 42% recovery of **19**. [d] DMP: 6.0 equiv. DMSO = dimethyl sulfoxide.



Scheme 2. Synthesis of the ethyl ester analogue of fumaramidmycin. Reagents and conditions: a) monoethyl fumarate (0.5 equiv), EDC (0.6 equiv), 4-DMAP (0.05 equiv), CH_2Cl_2, 25 °C, 19 h, 73%; b) DMP (2.0 equiv), $PhF/CH_2Cl_2/H_2O$ (40:20:1), 85 °C, 14 h, 96% (36% conversion). EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; 4-DMAP = 4-dimethylaminopyridine.

Table 2: Synthesis of *N*-acyl vinylogous carbamates and ureas by oxidation of β-amido esters and amides with DMP.[a]

Entry	Substrate		Product		*cis*/*trans*	Yield [%][b]
1		**33**		**34**	>25:1	98
2		**35**		**36**	19:1	55[b]
3		**37**		**38**	>25:1	67
4		**39**		**40**	23:1	59[c]
5		**41**		**42**	>25:1	52
6		**43**		**44**	>25:1	29
7		**45**		**46**	6:1	73

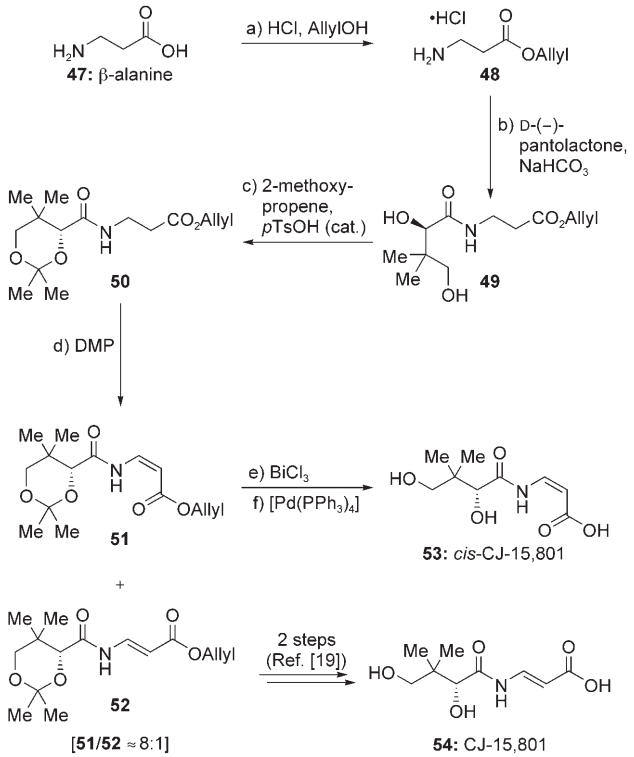
[a] Reactions were conducted on 0.1–0.3 mmol scale in PhF at 85 °C for 1 h with DMP (5.0 equiv). [b] Based on 45% recovery of **35**. [c] Based on 41% recovery of **39**. Bn = benzyl; Bz = benzoyl; THP = tetrahydropyranyl.

intramolecular hydrogen bond present within **9** and **10** (Scheme 1B) which is reinforced by the use of a nonpolar solvent (fluorobenzene);[14] these conditions also tolerate the presence of phenolic acetates (Table 2, entry 3) and *N*,*N*-dibenzylamides (Table 2, entry 5). The latter example, in particular, along with that in Table 2, entry 6, underscores the oxidative potential of DMP, as it represents a direct dehydrogenation between two amide functionalities, a task very few reagents, if any, can smoothly achieve. Possible applications of this type of synthetic transformation include the construction of the *N*-acyl vinylogous urea and carbamic acid structural domains found in palytoxin,[15] enamidonin,[16] and CJ-15,801,[17] as specifically highlighted in Table 2, entry 7, in which tetrahydropyranyl derivative **45** was oxidized with DMP to compound **46**, which could, in principle, be converted into a palytoxin-like side chain following, among other steps, *cis–trans* isomerization of the alkene.[14]

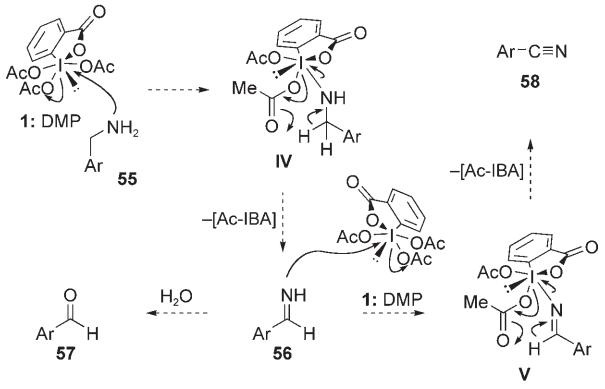
To highlight the applicability of this reaction further, a formal total synthesis of the antibiotic CJ-15,801, along with the construction of its *cis* isomer, was also completed from commercially available starting materials (Scheme 3). Thus, allylation of β-alanine (**47**),[18] followed by subsequent reaction of the resulting amino ester **48** with D-(−)-pantolactone in refluxing toluene, afforded diol **49**. Acetonide formation within **49** led to **50**, whose oxidation with DMP gave a mixture of the *N*-acyl vinylogous carbamates **51** (*cis* isomer) and **52** (*trans* isomer) in approximately 8:1 ratio in favor of the *cis* compound. While the arrival at **52** (Table 4) signals a formal total synthesis[19] of antibiotic CJ-15,801, the major isomer **51** was converted into *cis*-CJ-15,801 (**53**) by sequential cleavage of the acetonide ($BiCl_3$) and allyl ester ($[Pd(PPh_3)_4]$)[20] protecting groups (Scheme 3).

As a result of the aforementioned successes, we sought to test the reactivity of DMP on additional nitrogen-containing substrates, namely benzylic primary amines. We were attracted by the prospect of directly accessing nitrile compounds, intermediates and products whose ubiquitous applications in synthesis are well appreciated and documented.[21] Our reasoning for this expectation is encapsulated in Scheme 4. Thus, it was hypothesized that aromatic amine substrates such as **55** could associate with DMP to form complexes such as **IV** with concomitant loss of AcOH, followed by an intramolecular benzylic hydrogen abstraction by an acetate group. This would then result in a net dehydrogenation to afford aldimines of type **56**. These fleeting intermediates would then be expected to be either hydrolyzed by H_2O to aldehydes (e.g. **57**) or oxidized a second time by DMP to furnish nitriles (e.g. **58**).

Indeed, we were pleased to discover that an assortment of benzylic and related primary amines undergo the projected



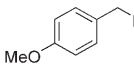
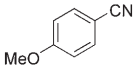
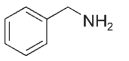
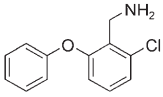
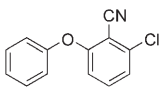
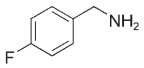
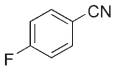
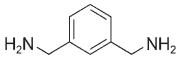
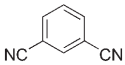
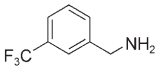
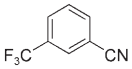
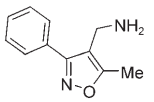
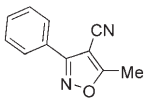
Scheme 3. Formal total synthesis of the antibiotic CJ-15,801 (**54**) and its *cis* isomer **53**. Reagents and conditions: a) see reference [18]; b) D-(−)-pantolactone (1.5 equiv), $NaHCO_3$ (5.0 equiv), PhMe, reflux, 20 h, 59% (23% of **48** was also observed by ^1H NMR prior to purification of crude mixture); c) 2-methoxypropene (10 equiv), *p*TsOH (0.1 equiv), acetone, 0 °C, 1 h, 78%; d) DMP (5.0 equiv), PhF, 85 °C, 2 h, 93% (based on 39% recovered **50**, *cis* and *trans* isomers isolated in ≈8:1 ratio, respectively); e) $BiCl_3$ (0.2 equiv), H_2O, MeCN, 25 °C, 14 h, 98%; f) $[Pd(PPh_3)_4]$ (0.2 equiv), dioxane/H_2O (4:1), 25 °C, 14 h, 87%. Ts = *p*-toluenesulfonyl.



Scheme 4. Mechanistic rationale for the oxidation of benzylic and related amines to aromatic nitriles with DMP.

transformation into nitriles upon reaction with DMP at 25 °C in CH_2Cl_2. The generality and scope of this reaction is demonstrated in Table 3 with examples of substrates containing halide (Table 3, entries 3, 4, and 6), ether (entries 1 and 3), electron-donating (entry 1), and electron-withdrawing (entries 4 and 6) groups, as well as isoxazoles (entry 7) and

Table 3: Dehydrogenation of amines to nitriles.[a]

Entry	Substrate		Product		*t* [min]	Yield [%]
1		**59**		**60**	10	95
2		**61**		**62**	10	71
3		**63**		**64**	15	94
4		**65**		**66**	10	77
5		**67**		**68**	15	90[b]
6		**69**		**70**	15	77
7		**71**		**72**	15	84

[a] Reactions were conducted on a 0.2–0.5 mmol scale in CH_2Cl_2 at 25 °C with DMP (2.0–3.0 equiv), unless otherwise noted. [b] DMP: 5.0 equiv.

bifunctional systems (entry 5). Aside from demonstrating considerable tolerance, this DMP dehydrogenation protocol has proven capable of affording nitriles through the implementation of brief reaction times, without excessive amounts of aldehyde by-products, unlike previously reported procedures employing iodosobenzene[22] or IBX.[4b]

The described chemistry expands the repertoire of reactions carried out by DMP, a versatile oxidant with ever-increasing utility in chemical synthesis. Among the reported examples of new reactivity for this hypervalent iodine reagent are the one-step oxidation of secondary amides to imides and *N*-acyl vinylogous carbamates or ureas, and the direct oxidation of benzylic and related primary amines to their nitrile counterparts. The relevance of the present new synthetic technology to a rapid synthesis of analogues of fumaramidmycin and antibiotic CJ-15,801 demonstrates the mildness and applicability of some of these protocols to chemical synthesis, and bodes well for their future utilization in other situations.

Experimental Section

General procedure (amides): Generation of imides: In a sealed tube the amide (0.1–0.3 mmol) was dissolved in fluorobenzene (0.15 M) and several drops of wet DMSO were added (or enough to ensure dissolution of substrate). After addition of DMP (2.0 equiv), the mixture was heated behind a blast shield at 80–85 °C until the starting material was consumed (monitored by TLC analysis). The resulting mixture was allowed to cool and was then quenched with saturated

Table 4: Selected physical properties for **31**, *cis*-**34**, **52**, **53**, and **64**.

31: $R_f = 0.50$ (silica gel, EtOAc/hexanes 1:2); IR (film): $\tilde{\nu}_{max} = 3282, 2981, 1723, 1690, 1508, 1453, 1367, 1300, 1157, 1031\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (br s, 1H), 7.46 (d, $J = 15.2$ Hz, 1H), 7.38–7.32 (m, 3H), 7.28–7.26 (m, 2H), 6.90 (d, $J = 15.5$ Hz, 1H), 4.27 (q, $J = 7.0$ Hz, 2H), 3.95 (s, 2H), 1.32 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.1, 165.0, 164.4, 134.8, 134.3, 133.0, 129.7, 129.1, 127.8, 61.7, 44.4, 14.2$ ppm; HRMS (ESI TOF): calcd for $C_{14}H_{15}NO_4Na^+$ $[M+Na]^+$: 284.0893; found: 284.0898

cis-**34**: $R_f = 0.78$ (silica gel, EtOAc/hexanes 1:2); IR (film): $\tilde{\nu}_{max} = 3311, 1673, 1616, 1480, 1395, 1378, 1220, 1030, 802, 695\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.53$ (br s, 1H), 7.97–7.95 (m, 2H), 7.74 (dd, $J = 8.9, 11.2$ Hz, 1H), 7.61–7.57 (m, 1H), 7.52–7.49 (m, 2H), 5.26 (d, $J = 9.0$ Hz, 1H), 4.24 (q, $J = 7.4$ Hz, 2H), 1.33 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 169.8, 164.7, 138.9, 133.1, 132.3, 129.1, 127.9, 97.4, 60.5, 14.4$ ppm; HRMS (ESI TOF): calcd for $C_{12}H_{13}NO_3Na^+$ $[M+Na]^+$: 242.0788; found: 242.0782

52: $R_f = 0.78$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D^{32} = +38$ ($CHCl_3$, $c = 0.13$); IR (film): $\tilde{\nu}_{max} = 3331, 2947, 1715, 1635, 1495, 1378, 1298, 1256, 1195, 1134\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.41$ (br d, $J = 11.9$ Hz, 1H), 8.00 (dd, $J = 13.8, 11.9$ Hz, 1H), 5.98–5.90 (m, 1H), 5.62 (d, $J = 13.8$ Hz, 1H), 5.33 (d, $J = 16.5$ Hz, 1H), 5.23 (d, $J = 10.1$ Hz, 1H), 4.65–4.64 (m, 2H), 4.20 (s, 1H), 3.71 (d, $J = 11.9$ Hz, 1H), 3.32 (d, $J = 11.9$ Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.05 (s, 3H), 1.00 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.1, 166.9, 136.5, 132.5, 118.1, 102.8, 99.7, 77.3, 71.4, 65.0, 33.6, 29.6, 22.0, 19.0, 18.8$ ppm; HRMS (ESI TOF): calcd for $C_{15}H_{23}NO_5Na^+$ $[M+Na]^+$: 320.1468; found: 320.1464

53: $[\alpha]_D^{32} = +18$ (MeOH, $c = 0.08$); IR (film): $\tilde{\nu}_{max} = 3317, 2960, 2873, 1655, 1625, 1467, 1402, 1320, 1243, 1108, 1044\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.37$ (d, $J = 8.4$ Hz, 1H), 5.18 (br s, 1H), 4.03 (s, 1H), 3.48 (d, $J = 11.0$ Hz, 1H), 3.39 (d, $J = 11.0$ Hz, 1H), 0.93 (s, 3H), 0.92 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 174.4$ (2C), 133.8, 129.9, 77.0, 70.0, 40.7, 21.4, 20.6 ppm; HRMS (ESI TOF): calcd for $C_9H_{14}NO_5^-$ $[M-H]^-$: 216.0877, found: 216.0875

64: $R_f = 0.68$ (silica gel, EtOAc/hexanes 1:2); IR (film): $\tilde{\nu}_{max} = 3449, 1570, 1488, 1449, 1262, 1199, 929, 765\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (dd, $J = 8.5, 7.4$ Hz, 2H), 7.36 (t, $J = 8.5$ Hz, 1H), 7.27–7.24 (m, 1H), 7.17 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.11–7.09 (m, 2H), 6.73 ppm (dd, $J = 8.8, 0.8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.5, 154.7, 138.3, 134.2, 130.4, 125.7, 123.5, 120.5, 114.6, 113.3$ ppm; HRMS (ESI TOF): calcd for $C_{13}H_8ClNOH^+$ $[M+H]^+$: 230.0367, found: 230.0359

aqueous $Na_2S_2O_3$ (2 mL) and stirred vigorously until the solution became clear. The mixture was poured into Et_2O (15 mL) and the ethereal phase was washed twice with 10% aq. $Na_2S_2O_3$/aq. $NaHCO_3$ (1:1 mixture, 15 mL) and brine (15 mL), and then dried ($MgSO_4$). Removal of the solvent in vacuo afforded the imide, often pure enough (by ^{1}NMR spectroscopic analysis) to forgo chromatography. Generation of *N*-acyl vinylogous carbamates and ureas: In a sealed tube the amide (0.1–0.3 mmol) was dissolved in fluorobenzene (0.1M) and DMP (5.0 equiv) was added. The mixture was heated at 80–85 °C until full consumption of starting material was noted (monitored by TLC analysis). The reaction mixture was then quenched and purified in the same manner as for the preparation of imides described above.

General procedure (amines): The amine (0.1–0.4 mmol) was dissolved in a small amount of CH_2Cl_2 and added dropwise over a period of 5–10 min to a homogeneous mixture of DMP (2.0 equiv) in CH_2Cl_2 to form a 0.15M solution with respect to the amine. The reaction mixture was stirred at 25 °C until the starting material was consumed (as observed by TLC analysis), at which time the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and the resulting mixture was stirred vigorously until it became clear. The mixture was then poured into Et_2O (15 mL) and the ethereal phase was washed twice with 10% aq. $Na_2S_2O_3$/aq. $NaHCO_3$ (1:1 mixture, 15 mL) and brine (15 mL) and then dried ($MgSO_4$). Removal of the solvent in vacuo afforded the nitrile, which was purified by silica-gel column chromatography.

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