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Nucleophile-Catalyzed Additions to Activated Triple Bonds. Protection of Lactams, Imides, and Nucleosides with MocVinyl and Related Groups

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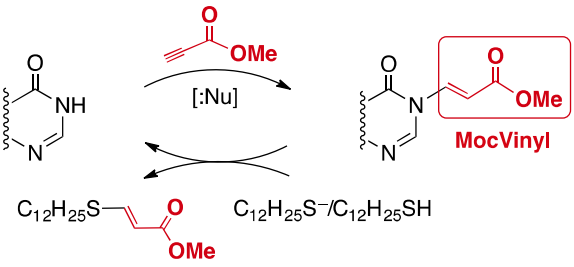


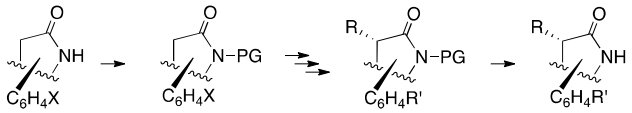
ABSTRACT: Additions of lactams, imides, (*S*)-4-benzyl-1,3-oxazolidin-2-one, 2-pyridone, pyrimidine-2,4-diones (AZT derivatives), or inosines to the electron-deficient triple bonds of methyl propynoate, *tert*-butyl propynoate, 3-butyn-2-one, *N*-propynoylmorpholine, or *N*-methoxy-*N*-methylpropynamide in the presence of many potential catalysts were examined. DABCO and, secondly, DMAP appeared to be the best (highest reaction rates and *E/Z* ratios), while $RuCl_3$, $RuClCp^*(PPh_3)_2$, AuCl, $AuCl(PPh_3)$, CuI, and $Cu_2(OTf)_2$ were incapable of catalyzing such additions. The groups incorporated (for example, the 2-(methoxycarbonyl)ethenyl group that we name MocVinyl) serve as protecting groups for the above-mentioned heterocyclic CONH or CONHCO moieties. Deprotections were accomplished via exchange with good nucleophiles: the 1-dodecanethiolate anion turned out to be the most general and efficient reagent, but in some particular cases other nucleophiles also worked (e.g., MocVinyl-inosines can be cleaved with succinimide anion). Some structural and mechanistic details have been accounted for with the help of DFT and MP2 calculations.

Introduction

The protection of the amide groups of the open-chain carboxamides RCONHR' is seldom needed in total synthesis of polyfunctional molecules since, from the point of view of the retrosynthetic analysis, the robust amide bond is a strategic bond that can be disconnected as soon as desired (that is, it can be formed as late as desired). On the other hand, cyclic amides (lactams, including unsaturated lactams such as 2-pyridone), imides, cyclic carbamates (e.g., oxazolidin-2-ones), and cyclic

ureas (e.g., imidazolin-2-one and pyrimidin-2-one derivatives), when embedded in alkaloids or in synthetic drugs, as well as uracil, thymine, and their corresponding nucleosides, very often do require protection of their reactive CONH moiety. In fact, almost all of the examples found in Greene's book[1] involve one or another of these types of heterocyclic compounds.[2] A representative sequence is shown in Scheme 1 with Boc as the PG, where (i) a cyclic CONH group is converted into CONBoc, (ii) the desired reactions are carried out (e.g., formation of a C–C bond at position α through alkylation in a basic medium and/or a Pd-catalyzed C–C or C–heteroatom coupling at a more remote position), and (iii) the Boc group is finally removed by treatment with a Lewis acid or with TFA. Other PGs have been used,[1] but the example in Scheme 1 is the most common.

Scheme 1. General Protection–Reaction(s)–Deprotection Sequence for Heterocyclic CONH Groups



PG = COO*t*-Bu, Boc
CH=CHCOOMe, MocVinyl, Mov (**a**)
CH=CHCOO*t*-Bu, BocVinyl, Bov (**b**)
CH=CHCOMe, AcVinyl, Acv (**c**)
CH=CHCON$(CH_2CH_2)_2$O, MorVinyl, Morv (**d**)
CH=CHCON(OMe)Me, WeinVinyl, Weiv (**e**)

Here, we report an alternative set of electron-withdrawing PGs for these heterocyclic CONH and CONHCO moieties (see Scheme 1): MocVinyl or, if preferred for the sake of simplification, Mov (**a**); BocVinyl or Bov (**b**); AcVinyl or Acv (**c**); MorVinyl or Morv (**d**); and WeinVinyl or Weiv (**e**). MocVinyl stands for 2-(methoxycarbonyl)ethen-1-yl, that is, a methoxycarbonylvinyl group. BocVinyl stands for the analogous *tert*-butoxycarbonylvinyl group. AcVinyl represents 3-oxo-1-buten-1-yl (or simply acetylvinyl). MorVinyl is the 2-(4-morpholinylcarbonyl)ethen-1-yl group, a 4-morpholinylcarbonylvinyl substituent. Finally, WeinVinyl represents 2-(*N*-methoxy-*N*-methylaminocarbonyl)ethen-1-yl, the group from the Weinreb amide of the corresponding propenoic or acrylic acid. Bioconjugation (ligation) of amides, imides, or related compounds with electron-deficient alkynes would be another potential application of the chemistry described here, although it is outside the scope of the present work.

These groups can be introduced by the addition of the CONH groups of lactams, imides, etc. to the triple bonds of HC≡C–COOMe (methyl propynoate, or methyl propiolate, which is a cheap, commercially available reagent), HC≡C–COO*t*-Bu (*tert*-butyl propynoate), HC≡C–COMe (3-butyn-2-one), HC≡C–CON$(CH_2CH_2)_2$O (*N*-propynoylmorpholine), or HC≡C–CON(OMe)Me (*N*-methoxy-*N*-methylpropynamide). The advantages are that their presence can clearly be observed via NMR spectroscopy (double bond) and their removal can be generally effected via an addition–elimination mechanism (exchange reactions), as explained below. In principle, we did not consider acetylvinyl (Acv) a real or practical group, due to the reactivity of its CO carbon atom. Moreover,

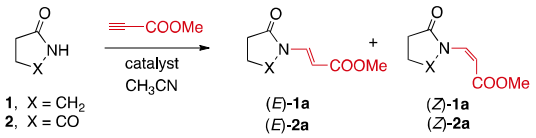
the MorVinyl and WeinVinyl groups, because of the feasibility of their conversion into CH=CH–COR and CH=CH–CHO groups by reaction with organolithium or organomagnesium compounds and with DIBALH, respectively,[3,4] may have applications other than the simple role of protecting groups. Nevertheless, these last three groups were included to compare the reactivity of lactams, imides, and related heterocyclic compounds with diverse electron-poor alkynes.

There are precedents of the addition of cyclic CONH groups to activated terminal triple bonds,[5] but the EWGs of the adducts were not specifically conceived as PGs. On the other hand, some applications have been found for the DMAP-catalyzed additions to methyl propynoate.[6,7] Here we provide a generalization and update of these concepts that includes unpublished work performed in our laboratory over the past decade in connection with several Master and PhD Theses.

Results and Discussion

We first studied the reaction of 2-pyrrolidinone (butyrolactam, **1**) and of succinimide (2,5-pyrrolidinedione, **2**), chosen as the most simple examples of a cyclic amide and a CONHCO substructure, respectively, with methyl propynoate (series **a**). Without a base, neither **1** nor **2** reacted at rt or even on heating to 70 °C (see Table 1, entries 1 and 6). A set of trisubstituted nitrogen bases were examined as catalysts, ranging from the quite basic but scarcely nucleophilic $^{i}Pr_2EtN$ (DIPEA) to the moderately basic but highly nucleophilic 4-(dimethylamino)pyridine (DMAP), and to the less basic but the most nucleophilic of the set, 1,4-diazabicyclooctane (DABCO).[8] The main products were *E*/*Z* mixtures of the desired **1a** and **2a**, respectively, in which the *E* isomer predominated. However, with **1** (with the less acidic CONH group) the reactions were slower than with **2** (and than with all the other compounds studied here, see below). In practice, in the case of **1** we had to add stoichiometric or relatively large amounts of DIPEA, Et_3N, or DMAP (entries 2–4), otherwise the conversions were too low (results not included for the sake of simplicity). With large amounts of DMAP, the percentage of dark, highly polar byproducts increased more than the yield of **1a**. DABCO (entry 5)[9] appeared to be the most appropriate catalyst for the conjugate addition of **1** to methyl propynoate. In the case of **2** (compare entries 7–13), the greater the nucleophilicity of the additive (from DIPEA to DABCO) or the larger the amount of DMAP, the faster the reaction rates and the higher the *E/Z* ratios of **2a** obtained. Other additives tested—Me_3P, DBU, and NHC—[9] were less selective than DABCO and DMAP. The effect of the solvents was not examined systematically, but we had noted in preliminary experiments that the reactions were slightly more rapid in polar solvents, such as CH_3CN or DMF, than in THF (**2**, 20 mol % of DABCO, 30 min, 95:5 *E/Z*) or toluene (**2**, which is only partially soluble, 20 mol % of DABCO, 45 min, 90:10 *E/Z*).

Table 1. Catalyzed Additions of 2-Pyrrolidinone (1) and Succinimide (2) to Methyl Propynoate[a]

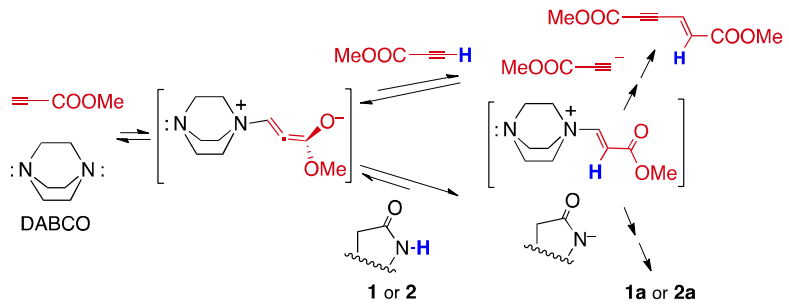


entry	substrate	base or catalyst (equiv)	T (°C)	time (h)	conv. (%)	adduct, yield (%)	*E*/*Z*[b]
1	**1**	—	70	15	0	—	—
2	**1**	DIPEA (1.0)	20	15	50	**1a**, 45	60:40
3	**1**	Et_3N (1.0)	20	2	100	**1a**, 82	95:5
4	**1**	DMAP (0.5)	20	1	100	**1a**, 52[c]	93:7
5	**1**	DABCO (0.2)[d]	20	0.2	100	**1a**, 98	99:1
6	**2**	—	70	4	0	—	—
7	**2**	NaH (0.2)	20	1	20	**2a**, 20	65:35
8	**2**	DIPEA (0.5)	20	4	100	**2a**, 90	75:25
9	**2**	Et_3N (0.5)	20	0.5	100	**2a**, 95	90:10
10	**2**	DMAP (0.1)	20	0.8	100	**2a**, 95	92:8
11	**2**	DMAP (0.5)	20	0.3	100	**2a**, 85	97:3
12	**2**	DMAP (1.0)	20	0.2	100	**2a**, 86	97:3
13	**2**	DABCO (0.2)[d]	20	0.2	100	**2a**, 97	97:3

[a] Standard conditions: **1** or **2** and the catalyst were dissolved in CH_3CN (0.1 M) under N_2 and the activated triple bond (1.2 equiv) was slowly added via syringe; stirring was maintained for the time indicated; the isolated yields of isomers *E*+*Z* are given. [b] *E*/*Z* ratios were determined by ^1H NMR. [c] Dark (presumably polymeric) material was also formed. [d] In fact, 20 mol %, as only one of the N atoms is active.

It is worth noting that the methyl propynoate dimer (see Scheme 2)[10] was never a major product in the preceding experiments. We detected this dimer by its characteristic NMR spectra in some cases, but only as a minor compound. Since it is well known that DABCO and other catalysts favor its formation[10]—in fact, we confirmed by ^1H NMR spectroscopy that a 1:2 mixture of DABCO and HC≡C–COOMe in CD_3CN at rt, without adding any lactam or imide, immediately gave such a dimer almost quantitatively—, it may be deduced that in the presence of a lactam- or imide-containing molecule, the first adduct (Scheme 2) may react either with HC≡C–COOMe or with the CONH/CONHCO group. The relative acidities of the methyne proton of the triple bond ($pK_a \approx 18.8$) and the amide/imide proton may be then crucial. As CONH/CONHCO protons are more acidic (in water but, presumably, in other polar solvents as well), the lactam/imide anions will predominate over MeOOC-C≡C$^-$, so the dimer will be formed in minor amounts and mainly at the end of the reaction, from the remaining methyl propynoate.

Scheme 2. Dimerization of Methyl Propynoate vs. Formation of 1a and 2a



Compound **1a** had previously been obtained as a 40:1 *E/Z* mixture by a Ru(III)-catalyzed reaction between 2-pyrrolidinone (**1**) and methyl propynoate (in toluene at 100 ºC for 15 h).[11] Since, in addition to 3% of $RuCl_3 \cdot xH_2O$, 9% of DMAP, 9% of Bu_3P, 15 mol % of K_2CO_3, and water or methanol were added to the reaction flask,[11] competition could have occurred between Ru-, nucleophile-, and base-catalyzed processes. In our experiments in toluene at 100 ºC, $RuCl_3$ did not cause the conjugate addition in the absence of DMAP and Bu_3P; on the other hand, 15 mol % of K_2CO_3 alone gave a conversion of 70%, and 9 mol % of DMAP alone gave a conversion of 50%. In short, $RuCl_3$ is not an appropriate catalyst for the conjugate additions of lactams to electron-poor alkynes.

As anticipated, 10 mol % of $RuCl_3 \cdot$hydrate failed to bring about the reaction of succinimide (**2**) with methyl propynoate, in refluxing CH_3CN. Lewis acids such as BF_3 or $Sc(OTf)_3$ did not work at all either. Strong bases gave rise to non-stereoselective additions (1.1 equiv of NaH in CH_3CN, full conversion, 60:40 *E/Z* of **2a**). The best catalyst, of those studied by us, was not a transition metal ion, a Lewis acid, or an electrophile in general, but a good nucleophile (much less basic than any trialkylamine), namely DABCO (Table 1).[9]

We also examined whether other transition-metal cations or complexes with high affinity for triple bonds, such as $RuClCp^*(PPh_3)_2$, AuCl, $AuCl(PPh_3)$, CuI, and $Cu_2(OTf)_2 \cdot$toluene, were capable or not of catalyzing the conjugate additions of **1** and **2** (as well as that of oxazolidinone **3**, see below) to methyl propynoate in the absence of bases. The desired adducts were never observed in either CH_3CN or toluene.[12] Some of these soft cations may generate acetylides[13] (M–C≡C–COOMe) and/or vinylidene complexes, but the polarity of these intermediates does not seem appropriate for nucleophile additions.

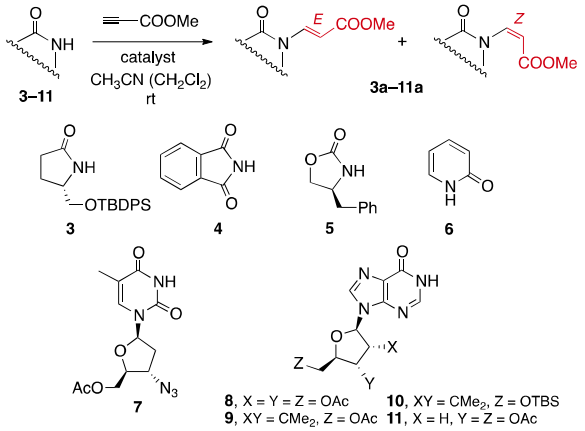
Once the conditions for the addition of a lactam and an imide to electron-poor triple bonds were optimized, we subjected a set of related substrates to these conditions. The results are summarized in Table 2. Lactam **3**, phthalimide (**4**), Evans' oxazolidinone **5** (taken as an example of a cyclic carbamate), and 2-pyridone (**6**) were converted into the expected addition products with excellent stereoselectivities (Table 2, entries 1–10). In general, the greater the amount of DMAP, the better the *E* selectivity obtained. The DABCO-catalyzed processes also delivered products very quickly, in excellent yields and with high stereoselectivities, with the advantage that ≤ 0.2 equiv of the catalyst was required. With the special case of **6** (2-pyridone/2-hydroxypyridine equilibrium), DABCO gave also rise to minor *O*-alkylation products (entry 9); this can be remedied by carrying out the reaction with smaller amounts of DABCO and at 0 °C (entry 10).

Thymidine derivative **7** (5'-*O*-Ac AZT) and inosine derivatives **8–11** also yielded the expected products with excellent conversions. In the case of **7**, the *E* isomer was obtained exclusively, with only 0.1 equiv of DMAP (entry 11). For the inosine

derivatives it was necessary to operate with at least 1.0 equiv of DMAP to obtain *E* exclusively (entry 15). Alternatively, 0.2 equiv of DABCO gave perfect diastereoselectivity (entry 18).

In short, the protecting group (*E*)-MocVinyl can quickly be introduced at rt (or below) in the presence of ≤ 20 mol % of DABCO or of sub-stoichiometric amounts of DMAP. The minor *Z* isomers that in some cases are formed concomitantly do not interfere. This would not be the case if nearly equimolar *Z*/*E* mixtures were always formed or if some substrates produced *Z* isomers and others *E* isomers. As explained below, there is no need for chromatographic separation or a post-reaction isomerization with further DABCO or DMAP,[14] as the major *E*- and minor *Z*-stereoisomers can be removed together later.

Table 2. DABCO- and DMAP-Catalyzed Additions of 3–11 to Methyl Propynoate[a]



entry	substrate	catalyst (equiv)	solvent	temper. (°C)	time (h)	adduct, yield (%)	*E*/*Z*
1	**3**	DABCO (0.2)	CH_3CN	20	0.2	**3a**, 95	>99:1
2	**4**	DMAP (0.5)	CH_3CN	20	1.0	**4a**, 97	97:3
3	**4**	DABCO (0.2)	CH_3CN	20	0.2	**4a**, 88	96:4
4	**5**	DMAP (0.5)	CH_3CN	20	0.8	**5a**, 99	93:7
4	**5**	DMAP (1.0)	CH_3CN	20	0.2	**5a**, 99	98:2
6	**5**	DABCO (0.2)	CH_3CN	20	0.2	**5a**, 97	95:5
7	**6**	DMAP (0.5)	CH_3CN	20	0.3	**6a**, 96	95:5
8	**6**	DMAP (1.0)	CH_3CN	20	0.2	**6a**, 99	97:3
9	**6**	DABCO (0.2)	CH_3CN	20	0.2	**6a**, 72[b]	93:7
10	**6**	DABCO (0.05)	CH_3CN	0	0.7	**6a**, 84[c]	95:5
11	**7**	DMAP (0.1)	mixture[d]	20	1.0	**7a**, 93	>99:1
12	**8**	—	mixture	20	72	**8a**, 20	80:20
13	**8**	DMAP (0.1)	mixture	20	4.0	**8a**, 90	86:14
14	**8**	DMAP (0.3)	mixture	20	1.2	**8a**, 85	91:9
15	**8**	DMAP (1.0)	mixture	20	0.1	**8a**, 92	>99:1
16	**9**	DMAP (0.3)	mixture	20	1.0	**9a**, 90	91:9
17	**9**	DMAP (0.5)	mixture	20	0.5	**9a**, 96	96:4
18	**9**	DABCO (0.2)	mixture	20	0.5	**9a**, 97	>99:1
19	**10**	DMAP (0.3)	mixture	20	1.0	**10a**, 90	91:9
20	**11**	DMAP (0.3)	mixture	20	1.2	**11a**, 85	90:10

[a] Standard conditions: **3–9** and the catalyst were dissolved in CH_3CN or CH_3CN:CH_2Cl_2 (1:1) (see table), under N_2, and methyl propynoate (1.2 equiv) was added via syringe; stirring was maintained at the temperature indicated. Most conversions are quantitative, unless otherwise mentioned; the isolated yields of isomers *E*+*Z* are given. [b] 20% of the (*E*)-*O*-substituted isomer was formed (^3J = 12.2 Hz). [c] 5% of the *O*-substituted isomer was formed. [d] Mixture of CH_3CN and CH_2Cl_2 (1:1 v/v) in which protected nucleosides showed enhanced solubility.

The NMR data for the addition products proved to be diagnostic, as anticipated. This is an advantage of this PG, since its introduction and removal can be simply evaluated by ^{1}H NMR. Scheme 3 shows representative parameters for the double bond of a selection of MocVinyl groups. (See Experimental Section and Supporting Information for data of other compounds.) The δH values of the CH doublets of the major *E* isomers (with standard $^3J_{HH}$ values) are clearly larger than those of the corresponding *Z* isomers. Only the most stable conformers are depicted in Scheme 3. These are the lowest-energy conformers predicted at three different levels of theory [B3LYP/6-31+G(d), MP2/6-31+G(d)//B3LYP/6-31+G(d), and MP2/6-311+G(d,p)//B3LYP/6-31+G(d)] with nearly identical results. In the case of (*E*)-**6a**, where the calculations (Supporting Information) suggest that its conformer (*E*)-**6a'** has practically identical energy, we have drawn both species (and the chemical shifts are probably means of values for both conformers). The same is true of the case (*E*)-**7a**/(*E*)-**7a'**, for which the calculations were carried out with models (*N*-Me derivative), and in the case of **8a** (where the calculated *N*-Me derivative is a model of **8a–11a**). The larger-than-usual chemical shifts of the olefin protons of the MocVinyl groups, due to the well-known anisotropy of the lactam or imide C=O groups in close vicinity to some of these protons, are worthy of note.

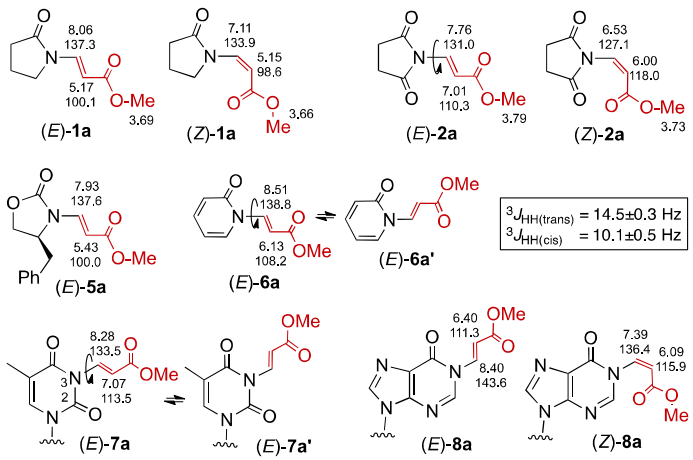
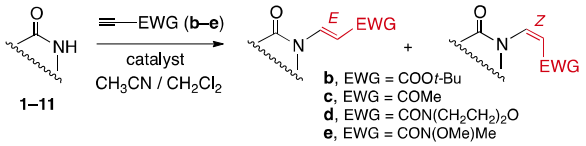


Figure 1. Representative NMR Data, in $CDCl_3$

The conjugate or Michael-type addition reactions worked equally well (see Table 3) with other electron-deficient triple bonds such as *tert*-butyl propynoate (series **b**, entries 1–5), 3-butyn-2-one (series **c**, entries 6–12), *N*-propynoylmorpholine (series **d**, examples of entries 13–17), or *N*-methoxy-*N*-methylpropynamide (series **e**, entries 18–20). For propynamides **d** and **e** the reactions were slower but feasible; heating was sometimes necessary, as anticipated assuming that the $CON(CH_2CH_2)_2O$ and CON(OMe)Me groups (entries 13–20) are weaker EWGs than ester or carbonyl groups. In general, the tendency of series **b–e** to give mainly stereoisomers *E* is similar to that noted for series **a**.

Table 3. Representative Reactions of Lactams, Imides, and Related Compounds with Other Electron-Deficient Alkynes[a]

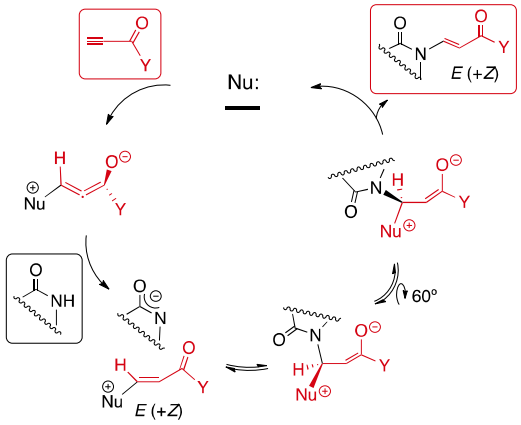


entry	starting compds	catalyst (equiv)	solvent	temper. (°C)	time (h)	adduct, yield (%)	*E/Z*
1	**1** + **b**	DABCO (0.2)	CH_3CN	20	0.2	**1b**, 98	99:1
2	**3** + **b**	DABCO (0.2)	CH_3CN	20	0.2	**3b**, 90	>99:1
3	**4** + **b**	DMAP (0.2)	CH_3CN	20	0.3	**4b**, 96	>99:1
4	**6** + **b**	DABCO (0.2)	CH_3CN	20	0.2	**6b**, 92	93:7
5	**10** + **b**	DMAP (0.3)	mixture[b]	20	0.8	**10b**, 91	94:6
6	**1** + **c**	DABCO (0.2)	CH_3CN	20	0.8	**1c**, 75[c]	>99:1
7	**5** + **c**	DABCO (0.2)	CH_3CN	20	0.2	**5c**, 75[c]	>99:1
8	**8** + **c**	—	mixture	20	24	**8c**, 20	—
9	**8** + **c**	DMAP (0.1)	mixture	20	2	**8c**, 93	>99:1
10	**9** + **c**	DMAP (0.1)	mixture	20	1	**9c**, 97	93:7
11	**10** + **c**	DMAP (0.1)	mixture	20	1	**10c**, 97	91:9
12	**11** + **c**	DMAP (0.1)	mixture	20	1	**11c**, 90	97:3
13	**2** + **d**	DABCO (0.2)	CH_3CN	20	2.5	**2d**, 92	93:7
14	**6** + **d**	DMAP (0.1)	CH_3CN	80	7	**6d**, 88	>99:1
15	**6** + **d**	DMAP (1.0)	CH_3CN	20	24	**6d**, 85	>99:1
16	**6** + **d**	DABCO (0.2)	CH_3CN	20	4	**6d**, 80[c]	91:9
17	**7** + **d**	DMAP (0.1)	CH_3CN	80	3	**7d**, 95	>99:1
18	**6** + **e**	DMAP (0.1)	CH_3CN	80	7	**6e**, 85	>99:1
19	**7** + **e**	DMAP (0.1)	CH_3CN	80	12	**7e**, 90	>99:1
20	**8** + **e**	DABCO (0.2)	mixture	80	6	**8e**, 80	91:9

[a] Standard conditions: **1–11** and the catalyst were dissolved in the corresponding solvent (0.1 M) under N_2; the activated triple bond (1.2 equiv) was added via syringe and stirring was maintained for the time indicated; conversions were quantitative unless otherwise is mentioned; the isolated yields of isomers *E*+*Z* are given. [b] Mixture of CH_3CN and CH_2Cl_2 (1:1, v/v) in which these protected nucleosides showed enhanced solubility at rt. [c] Plus 10–15% of *O*-substituted product of configuration *E* and other byproducts.

As most reactions in Tables 1–3 were very rapid, while the resulting *E/Z* mixtures were not quickly converted into stereopure *E* isomers or equilibrated by stirring them for a few hours with DMAP, the *E/Z* ratios are not a consequence of the final isomerization of the adducts in the reaction flasks. They seem to have a kinetic origin or depend on the relative stabilities of preceding reaction intermediates. In fact, nucleophilic catalysts such as DABCO and DMAP (weaker bases than trialkylamines, as is known) are the most efficient. Thus, the main mechanism may involve allenolate zwitterions as intermediates (see Scheme 3, which complements Scheme 2, and Supporting Information for DFT and MP2//DFT calculations of the two minima located; in these minimum-energy structures the CCC bond angles of the allene moieties are not linear, which can be explained by the partial negative charge, due to the resonance, on the allene central carbon atom). These intermediates take protons from the CONH- or CONHCO-containing substrates. After the addition of the lactam or imide anion, a small rotation around the $C(sp^3)$–$C(sp^2)$ bond (principle of minimum motion) would place Nu in the appropriate stereoelectronic arrangement for a nucleofuge, so its elimination occurs with retention of configuration (Scheme 3, right side).[15] This mechanistic proposal does not exclude the possibility that, with strong bases in very polar media, a substantial percentage of the products could arise from the direct addition of imide-like anions to the electron-deficient triple bonds.

Scheme 3. Mechanistic Proposal



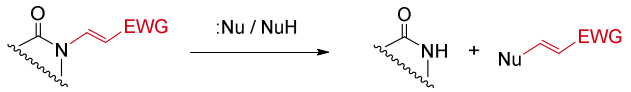
The stability of MocVinyl, BocVinyl, MorVinyl, and WeinVinyl against non-nucleophilic strong bases (required for the detachment of α protons to the CO group of the lactam, imide, and related groups) as well as against acidic media was examined in several examples: (i) **1a** was treated with LiHMDS in THF at –78 ºC and benzyl bromide was added, to give the corresponding Cα-alkylated derivative in good yield, without detaching the MocVinyl group; (ii) removal of the TBS group of **8a** was carried out with TBAF/AcOH at 0 °C, without affecting the MocVinyl, BocVinyl, and MorVinyl groups, respectively;[16] (iii) MocVinyl groups of **1a**–**8a** did survive after treatment with MeOH and 10 mol % of TsOH·H_2O (overnight at rt, which cleaved acetoxy groups by transesterification and silyl ethers by trans-silylation). BocVinyl derivative **10b** was stable during overnight treatment with AcOH/H_2O/THF; by adding a few drops of 2 M HCl the TBS group was removed but nothing else. MorVinyl derivative **7d** and WeinVinyl **7e** were stable in MeOH/TsOH at rt; on heating for 24 h, deacetylation occurred (transesterification) but the N–MorVinyl and N–WeinVinyl bonds were stable. In short, Mov, Bov, Morv, and Weinv are not sensitive to bases, provided that they are non-nucleophilic, and to acids (provided that these acidic conditions are incapable of cleaving the Boc group).

The last task was to examine the deprotection procedures. For the cleavage of the bond between the amide- or imide-like N atom and MocVinyl and related groups, we tested several nucleophiles that could remove the protecting group via an addition–elimination (AE) mechanism. Most experiments were carried out on series **a** (MocVinyl derivatives), for the sake of simplicity, but we obtained similar results with representative members of the other series. The most general reagent was 1-dodecanethiol (no stench) plus NaH in THF (Table 4), as this thiolate was effective with many substrates under mild conditions, and no trace of the *E* or *Z* isomers of the starting material remained. The major co-product was $CH_3(CH_2)_{11}$S-CH=CH-COOMe, usually in 90:10 to 95:5 *E*/*Z* ratios (when thiolate excesses were used, sometimes we also detected the double addition product, $(RS)_2CHCH_2COOMe$). On the other hand, simple lactam derivatives **1a** and **3a** underwent nucleophilic attack at the CO carbon atom rather than at C*β* under these conditions; as it was mandatory to use another procedure, we subjected them to a standard hydrogenation and

elimination protocol.[17] Simple imide derivatives **2a** and **4a** gave stable adducts (*N,S*-acetals, or hemithioaminal intermediates) at rt and, unfortunately, mixtures of products arising from the attack at the CO and at Cβ on heating. Thus, we also applied the classical hydrogenation/elimination protocol[17] to imides **2a** and **4a**, in very good yields. For **4a** (which turned out to be quite robust against strong bases) we developed another procedure, described in SI; it is based on the isolation of the primary adduct (*N,S*-acetal) followed by the decomposition of this *N,S*-acetal by addition of LiHMDS at 0 ºC.

The deprotection of the MocVinyl group with an excess of pyrrolidine in acetonitrile was also examined. With lactams **1a** and **3a**, as well as with oxazolidinone **5a**, pyrrolidine did not react, even on heating, whereas imides (**2a** and **4a)** were partially attacked at their CO groups. Pyrrolidine was successful with **6a** (entry 4) and **7a** (entry 7), but inosines (purine nucleosides) gave both deprotection and attack at C2. For a satisfactory deprotection of inosines, we developed an alternative method to that of the 1-dodecanethiolate ion explained in the preceding paragraph, that is, we deprotected them with succinimide anion, by means of an exchange reaction (for representative examples, see entries 10 and 11 of Table 4).

Table 4. Deprotection of MocVinyl and Related Groups



5–11

entry	starting compd	reagent,:Nu or NuH (no. equiv)	solvent	temper. (ºC)	time (h)	yield[a] (%)
1	**5a**	$C_{12}H_{25}SH$ (2), NaH (4)	THF	50	5	85
2	**5c**	$C_{12}H_{25}SH$/NaH (2)	THF	20	0.3	90
3	**6a**	$C_{12}H_{25}SH$/NaH (1.2)	THF	20	1	83
4	**6a**	pyrrolidine (4)	CH_3CN	20	2	95
5	**6e**	$C_{12}H_{25}SH$/NaH (3)	THF	20	2	92
6	**7a**	$C_{12}H_{25}SH$/NaH (1.2)	THF	20	2	96
7	**7a**	pyrrolidine (4)	CH_3CN	20	2	92
8	**7d**	$C_{12}H_{25}SH$/NaH (2)	THF	20	2	92
9	**8a**	$C_{12}H_{25}SH$/NaH (1.2)	THF	20	2	96
10	**8a**	succinimide (2), NaH (1.2)	CH_3CN[b]	60	4	91
11	**10a**	succinimide (2), NaH (1.2)	DMF[b]	20	24	85
12	**10b**	$C_{12}H_{25}SH$/NaH (1.2)	THF	20	2	85
13	**11a**	$C_{12}H_{25}SH$/NaH (1.2)	THF	20	1	97

[a] Isolated yields after removal of reagent excess and Nu–CH=CH–EWG by column chromatography. Conversions were complete. [b] Results were similar with potassium phthalimide in CH_3CN at 60 ºC.

Conclusions

A variety of heterocyclic compounds containing CONH and CONHCO groups react rapidly, fully, and stereoselectively, at rt, with methyl propynoate[18] and other compounds containing electron-poor triple bonds, to afford *N*-substituted Michael-like *E*-configuration adducts under nucleophilic catalysis, whereas transition metal catalysts and strong bases did not work or gave nearly equimolar *E/Z* mixtures, respectively. The best catalyst—shortest reaction times, largest scope—is DABCO, and secondly DMAP. However, no method or reagent is perfect. DABCO sometimes shows the handicap that with the most reactive substrates

it gives rise to a small percentage of *O*-substituted adducts, although these can be isomerized to the more stable *N*-MocVinyl isomers on heating (in the presence of DABCO itself). DMAP has to be added in larger amounts than DABCO to achieve the same performance. Other nucleophiles or bases cannot be recommended. It has been demonstrated that the MocVinyl group (Mov, series **a**) can advantageously be used as a protecting group for lactams, imides, oxazolidinones, nucleosides, and, in general, any kind of natural product containing heterocyclic CONH- or CONHCO-related moieties. It is quickly introduced at rt (or below) and easily detected chromatographically and by NMR, it is stable against acids in general, and can be removed by a standard procedure (catalytic hydrogenation followed by treatment with base) or with a thiolate ion via an AE mechanism; depending on the EW features of the substrates, we have used alternative nucleophiles (either pyrrolidine or the succinimide ion). As anticipated, the BocVinyl group (Bov, series **b**), the analogous morpholine amide (MorVinyl, Morv, series **d**), and the analogous Weinreb amide (WeinVinyl, Weinv, series **e**) can similarly be added and removed, but not so quickly; the last groups have been less exhaustively studied because of the well-known role of Weinreb and morpholine amides as surrogates for aldehydes and ketones (so the removal of MorVinyl and WeinVinyl may lack practical interest). We hope that MocVinyl and some of its partners will have applications in stepwise syntheses of complex natural products and medicinal drugs containing heterocyclic substructures such as those examined here.

EXPERIMENTAL SECTION

General Information. Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers and used without further purification. All reactions were conducted in oven-dried glassware, under dry nitrogen or argon atmosphere with anhydrous solvents, which were dried and distilled before use according to standard procedures. Solvents used for isolation of products and chromatography were glass distilled. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (F_{254}). Retention factors (R_f) are approximate. Flash column chromatography was performed on silica gel 60 (35–70 μm). Yields were determined after purification of the desired compound by column chromatography on silica gel. ^{1}H NMR spectra were recorded in $CDCl_3$ on 400 MHz spectrometers. Melting points have been obtained with a Gallenkamp apparatus. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as usual: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br s = broad singlet, m = multiplet), coupling constants (in Hz), integration. ^{13}C NMR spectra were recorded in $CDCl_3$ on the above-mentioned spectrometers (100.6 MHz for ^{13}C) with complete proton decoupling. Chemical shifts are reported in ppm ($CDCl_3$, δ 77.0 ppm). Where necessary, 2D NMR experiments (HSQC and NOESY, mainly) were carried out to assist in structure elucidation and signal assignments. IR spectra were obtained as thin films on NaCl plates or KBr discs. Only the more relevant frequencies (cm^{-1}) are reported. HRMS were obtained by using ESI–TOF techniques.

General procedure for the nucleophile-catalyzed addition of lactams, imides, and related compounds to electron-poor alkynes. The substrate and either DMAP or DABCO were dissolved in CH_3CN or CH_3CN/CH_2Cl_2 (0.1 M) under a N_2 atmosphere. The electron-poor alkyne (esters of propynoic acid, 3-butyn-2-one, amides of propynoic acid) (1.2 equiv) was then slowly added via syringe and the reaction was stirred until TLC analysis indicated complete consumption of the substrate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel.

1a (99:1 *E*:*Z*, 100 mg, 98%) was obtained using 0.2 equiv of DABCO; **1-[(*E*)-2-(Methoxycarbonyl)vinyl]-2-pyrrolidinone,** (*E*)-**1a**: white solid; mp 77–79 °C; R_f = 0.67 (CH_2Cl_2/MeOH, 96:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15–2.24 (m, 2H), 2.56 (t, J = 8.2, 2H), 3.57 (t, J = 7.3, 2H), 3.74 (s, 3 H), 5.21 (d, J = 14.2, 1H), 8.10 (d, J = 14.2, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.3, 30.8, 44.8, 51.3, 100.1, 137.3, 167.5, 174.2; IR (ATR) ν 2946, 1725, 1710, 1626; HRMS (ESI+) *m*/*z* calcd for $C_8H_{12}NO_3^+$ $[M+H]^+$ 170.0812, found 170.0813. NMR data agree with those reported.[11, 19] **1-[(*Z*)-2-(Methoxycarbonyl)vinyl]-2-pyrrolidinone,** (*Z*)-**1a**: oil; R_f = 0.74 (CH_2Cl_2/MeOH, 96:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (m, 2H), 2.48 (t, J = 8.1, 2H), 3.69 (s, 3H), 3.94–4.00 (m, 2H), 5.15 (d, J = 10.6, 1H), 7.11 (d, J = 10.6, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.5, 30.2, 48.5, 51.2, 98.6, 133.9, 167.8, 176.0; IR (ATR) ν 2945, 1716, 1626; HRMS (ESI+) *m*/*z* calcd for $C_8H_{12}NO_3^+$ $[M+H]^+$ 170.0812, found 170.0807.

2a (97:3 *E*:*Z,* 90 mg, 97%) was obtained using 0.2 equiv of DABCO; ***N*-[(*E*)-2-(Methoxycarbonyl)vinyl]succinimide,** (*E*)-**2a**: white solid; mp 81–83 °C; R_f = 0.62 (CH_2Cl_2/MeOH, 97:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.83 (s, 4H), 3.79 (s, 3H), 7.01 (d, J = 14.8, 1H), 7.76 (d, J = 14.8, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.7, 51.8, 110.3, 131.0, 167.1, 174.3; IR (ATR) ν 1723, 1643. NMR data agree with those published.[5f, 20] ***N*-[(*Z*)-2-(Methoxycarbonyl)vinyl]succinimide,** (*Z*)-**2a**: oil; R_f = 0.50 (CH_2Cl_2/MeOH 98:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.82 (s, 4H), 3.73 (s, 3H), 6.00 (d, J = 9.4, 1H), 6.53 (d, J = 9.4, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.4, 51.8, 118.0, 127.1, 164.6, 174.0; IR (ATR) ν 2930, 1732, 1641. NMR data agree with those reported.[5f]

(*E*)-**3a** (59 mg, 95%) was obtained using 0.2 equiv of DABCO; **(*S*)-5-*tert*-Butyldiphenylsilyloxymethyl-*N*-[(*E*)-2-(methoxycarbonyl)vinyl]-2-pyrrolidinone,** (*E*)-**3a**: white solid; mp 108-110 ºC; R_f = 0.62 (CH_2Cl_2/MeOH, 97:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9H), 2.19–2.27 (m, 2H), 2.46 (m, 1H), 2.78 (dt, J = 17.7, J = 10.3, 1H), 3.66 (dd, J = 10.8, J = 2.6, 1H), 3.73 (s, 3H), 3.87 (dd, J = 10.8, J = 3.9, 1H), 3.95–4.00 (m, 1H), 5.06 (d, J = 14.6, 1H), 7.33-7.49 (m, 6H), 7.56 (m, 2H), 7.63 (m, 2H), 8.01 (d, 1H, J = 14.6); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.1, 21.9, 26.7, 30.6, 51.3, 57.7, 62.3, 100.0, 127.8, 130.0, 132.1, 132.7, 135.5, 135.6, 136.6, 167.5, 174.8; HRMS (ESI+) *m*/*z* calcd for $C_{25}H_{32}NO_4Si$ $[M+H]^+$ 438.2095, found 438.2091.

4a (96:4 *E*:*Z,* 69 mg, 88%) was obtained using 0.5 equiv of DMAP; ***N*-[(*E*)-2-(Methoxycarbonyl)vinyl]phthalimide,** (*E*)-**4a**: white solid; mp 126–128 °C; R_f = 0.50 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 7.00 (d, J = 14.8, 1H), 7.82 (m, 2H), 7.95

(d, J = 14.8, 1H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.7, 108.2, 124.2, 131.1, 135.2, 165.4, 167.5; HRMS (ESI+) *m/z* calcd for $C_{12}H_{10}NO_4^+$ $[M+H]^+$ 232.0604, found 232.0612. NMR data agree with those reported.[5f]

5a (97:3 *E*:*Z,* 260 mg, 99%) was obtained using 0.5 equiv of DMAP; **(*S*)-4-Benzyl-3-[(*E*)-2-(methoxycarbonyl)vinyl]-1,3-oxazolidin-2-one,** (*E*)-**5a**: white solid, mp 80–82 ºC; R_f = 0.62 (CH_2Cl_2/ MeOH, 97:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.81–2.86 (m, 1H), 3.20 (dd, J = 13.8, J = 2.4, 1H), 3.77 (s, 3H), 4.25–4.33 (m, 3H), 5.43 (d, J = 14.4, 1H), 7.16–7.18 (m, 2H), 7.30–7.37 (m, 3H), 7.93 (d, J = 14.4, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.9, 51.5, 54.7, 66.7, 100.0, 127.6, 129.0, 129.2, 134.2, 137.6, 154.2, 167.0; IR (ATR) ν 2946, 1766, 1701, 1633; HRMS (ESI+) calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074, found 262.1081. NMR data agree with those reported.[20]

6a (97:3 *E*:*Z,* 177 mg, 99%) was obtained using 1.0 equiv of DMAP; **1-[(*E*)-2-(Methoxycarbonyl)vinyl]-2-pyridone,** (*E*)-**6a**: orange solid; mp = 114–116 °C; R_f = 0.55 (CH_2Cl_2/MeOH, 97:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 6.13 (d, J = 14.7, 1H), 6.25 (m, 1H), 6.61 (d, J = 9.3, 1H), 7.33 (ddd, J = 9.3, J = 6.5, J = 2.0, 1H), 7.43 (dd, J = 7.2, J = 1.7, 1H), 8.51 (d, J = 14.7, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.8, 107.5, 108.2, 122.4, 131.3, 138.8, 140.0, 160.8, 166.2; IR (ATR) ν 2949, 1726, 1701, 1626; HRMS (ESI+) *m/z* calcd for $C_9H_{10}NO_3^+$ $[M+H]^+$ 180.0655, found 180.0660.

(*E*)-**7a** (183 mg, 93%) was obtained using 0.1 equiv of DMAP; **5'-*O*-Acetyl-3'-azido-3'-deoxy-1-[(*E*)-2-(methoxycarbonyl)vinyl]thymidine,** (*E*)-**7a**: white solid; mp 77–78 ºC; R_f = 0.7 (CH_2Cl_2/EtOAc, 1:1); R_f = 0.4 (CH_2Cl_2/MeOH, 98:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (d, J = 1.2, 3H), 2.14 (s, 3H), 2.39 (ddd, J = 13.8, J = 7.6, J = 5.5, 1H), 2.54 (ddd, J = 13.8, J = 6.7, J = 5.7, 1H), 3.79 (s, 3H), 4.10 (dt, J = 5.6, J = 4.1, 1H), 4.20 (dt, J = 7.6, J = 5.7, 1H), 4.36 (ddd, J = 20.0, J = 12.3, J = 4.1, 2H), 6.10 (t, J = 6.1, 1H), 7.06 (d, J = 14.8, 1H), 7.29 (q, J = 1.2, 1H), 8.26 (d, J = 14.8, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.5, 20.8, 37.9, 51.8, 60.3, 63.1, 82.1, 86.7, 110.1, 113.7, 133.7, 134.4, 149.2, 161.8, 167.6, 170.2. Also see ref 21.

(*E*)-**8a** (220 mg, 92%) was obtained using 1.0 equiv of DMAP; **2',3',5'-tri-*O*-Acetyl-1-[(*E*)-2-(methoxycarbonyl)vinyl]inosine,** (*E*)-**8a**: foam; R_f = 0.59 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 3.83 (s, 3H), 4.35–4.55 (m, 3H), 5.57 (t, J = 5.1, 1H), 5.86 (t, J = 5.3, 1H), 6.11 (d, J = 5.1, 1H), 6.40 (d, J = 14.7, 1H), 7.89 (s, 1H), 8.24 (s, 1H), 8.40 (d, J = 14.7, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.3, 20.5, 20.7, 52.1, 62.9, 70.3, 73.3, 80.3, 86.6, 111.3, 125.0, 136.9, 139.0, 143.6, 146.3, 154.6, 165.6, 169.2, 169.5, 170.2; IR (ATR) ν 3101, 1714, 1651, 1544. HRMS (ESI+) *m/z* calcd for $C_{20}H_{23}N_4O_{10}^+$ $[M+H]^+$ 479.1409, found 479.1406.

(*E*)-**9a** (60 mg, 97%) was obtained using 0.2 equiv of DABCO; **5'-*O*-Acetyl-2',3'-di-*O*-isopropylidene-1-[(*E*)-2-(methoxycarbonyl)vinyl]inosine,** (*E*)-**9a**: foam; R_f = 0.51 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H),

1.64 (s, 3H), 2.04 (s, 3H), 3.84 (s, 3H), 4.24 (dd, J = 5.6, J = 12.0, 1H), 4.16 (dd, J = 4.2, J = 12.0, 1H), 4.50–4.53 (m, 1H), 4.93 (dd, J = 3.5, J = 6.3, 1H), 5.22 (dd, J = 6.3, J = 2.4, 1H), 6.10 (d, J = 2.4, 1H), 6.38 (d, J = 14.7, 1H), 7.91 (s, 1H), 8.22 (s, 1H), 8.41 (d, J = 14.8, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.6, 25.3, 27.1, 52.1, 63.9, 81.3, 84.6, 84.8, 90.9, 111.2, 114.9, 124.9, 136.9, 139.2, 143.5, 145.9, 154.6, 170.3, 170.2. HRMS (ESI+) m/z calcd for $C_{19}H_{23}N_4O_8^+$ $[M+H]^+$ 435.1510, found 435.1507.

10a (91:9 *E*:*Z,* 108 mg, 90%) was obtained using 0.3 equiv of DMAP; **5'-*O*-*tert*-Butyldimethylsilyl-2',3'-di-*O*-isopropylidene-1-[(*E*)-2-(methoxycarbonyl)vinyl]inosine,** (*E*)-**10a**: foam; R_f = 0.69 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H) 1.40 (s, 3H), 1.64 (s, 3H), 3.81 (dd, J = 3.3, J = 1.5, 1H), 3.83 (s, 3H), 3.90 (dd, J = 3.0, J = 11.4, 1H), 4.46-4.48 (m, 1H), 4.90 (dd, J = 2.2, J = 6.1, 1H), 5.03 (dd, J = 6.1, J = 2.8, 1H), 6.14 (d, J = 2.8, 1H), 6.34 (d, J = 14.7, 1H), 8.10 (s, 1H), 8.22 (s, 1H), 8.45 (d, 1H, J = 14.7); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ –5.6, –5.5, 18.3, 25.3, 25.8, 27.2, 52.0, 63.5, 81.2, 85.7, 87.1, 91.6, 110.8, 114.2, 124.5, 137.1, 139.8, 143.4, 146.0, 154.7, 165.4; IR (ATR): ν 2952, 1713, 1649, 1575; HRMS (ESI+) m/z calcd for $C_{23}H_{35}N_4O_7Si^+$ $[M+H]^+$ 507.2270, found 507.2266.

11a (90:10 *E*:*Z,* 84 mg, 85%) was obtained using 0.5 equiv of DMAP; **3',5'-di-*O*-Acetyl-2'-deoxy-1-[(*E*)-2-(methoxycarbonyl)vinyl]inosine,** (*E*)-**11a**: foam; R_f = 0.54 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 2.15 (s, 6H), 2.64 (ddd, J = 2.8, J = 6.1, J = 14.2, 1H), 2.86 (ddd, J = 6.6, J = 7.7, J = 14.2, 1H), 3.84 (s, 3H), 4.30–4.40 (m, 3H), 5.40–5.44 (m, 1H), 6.36 (dd, J = 6.3, J = 7.7, 1H), 6.39 (d, J = 14.7, 1H), 7.98 (s, 1H), 8.20 (s, 1H), 8.42 (d, J = 14.7, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7, 20.8, 37.9, 52.1, 74.2, 63.6, 82.7, 84.7, 111.1, 124.7, 136.9, 138.6, 143.4, 146.2, 154.6, 165.7, 170.2, 170.3; IR (ATR) ν 2949, 1712, 1650; HRMS (ESI+) m/z calcd for $C_{18}H_{21}N_4O_8$ $[M+H]^+$ 421.1354, found 421.1356.

1b (99:1 *E*:*Z,* 122 mg, 98%) was obtained using 0.2 equiv of DABCO; **1-[(*E*)-2-(*tert*-Butoxycarbonyl)vinyl]-2-pyrrolidinone**, (*E*)-**1b**: mp 61–62 ºC; R_f = 0.57 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 1.41 (s, 9H), 2.10 (quin, J = 7.8, 2H), 2.46 (t, J = 8.2, 2H), 3.47 (t, J = 7.2, 2H), 5.06 (d, J = 14.2, 1H), 7.91 (d, J = 14.2, 1H); ^{13}C NMR δ 17.3, 28.1, 30.9, 44.9, 80.1, 102.6, 136.3, 166.4, 174.0. NMR data agree with those already reported.[22]

(*E*)-**3b** (61 mg, 90%) was obtained using 0.2 equiv of DABCO; **1-[(*E*)-2-(*tert*-Butoxycarbonyl)vinyl]-(*S*)-5-*tert*-butyldiphenylsilyloxymethyl-2-pyrrolidinone**, (*E*)-**3b**: white solid; mp 134-136 °C; R_f = 0.80 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 1.03 (s, 9H), 1.49 (s, 9H), 2.16–2.25 (m, 2H), 2.40–2.47 (m, 1H), 2.76 (dt, J = 17.7, J = 10.2, 1H), 3.64 (dd, J = 10.8, J = 2.7, 1H), 3.85 (dd, J = 10.8, J = 3.9, 1H), 3.94–3.98 (m, 1H), 5.01 (d, J = 14.6, 1H), 7.34–7.47 (m, 6H), 7.54–7.56 (m, 2H), 7.62–7.64 (m, 2H), 7.92 (d, J = 14.6, 1H); ^{13}C NMR δ 19.0, 21.9, 26.7, 28.3, 30.6, 57.7, 62.4, 80.0, 102.4, 127.8, 127.9, 130.0, 132.1, 132.7, 135.5, 135.6, 166.4, 174.7; IR (ATR) ν 3067, 2999, 2886, 2858, 1681; HRMS (ESI+) m/z calcd for $C_{56}H_{74}N_2NaO_8Si_2^+$ $[2M+Na]^+$ 981.4876, found 981.4872.

(*E*)-**4b** (89 mg, 96%) was obtained using 0.2 equiv of DMAP; ***N*-[(*E*)-2-(*tert*-Butoxycarbonyl)vinyl]phthalimide**, (*E*)-**4b**: white solid; mp 124-126 ºC; R_f = 0.71 (hexanes/EtOAc, 20:80); ^{1}H NMR δ 1.53 (s, 9H), 6.89 (d, J = 14.7, 1H), 7.80–7.86 (m, 3H), 7.93–7.95 (m, 2H); ^{13}C NMR δ 28.2, 80.8, 110.7, 124.1, 130.1, 131.4, 135.4, 165.5, 166.3; HRMS (ESI+) *m/z* calcd for $C_{15}H_{15}NNaO_4^+$ $[M+Na]^+$ 296.0893, found 296.0901.

6b (93:7 *E*:*Z,* 107 mg, 92%) was obtained using 0.2 equiv of DABCO; **1-[(*E*)-2-(*tert*-Butoxycarbonyl)vinyl]-2-pyridone**, (*E*)-**6b**: mp 68–69 ºC; R_f = 0.50 (CH_2Cl_2/MeOH, 96:4); ^{1}H NMR δ 1.52 (s, 9H), 6.05 (d, J = 14.7, 1H), 6.25 (ddd, J = 7.2, J = 6.5, J = 1.2, 1H), 6.59 (dd, J = 9.2, J = 1.2, 1H), 7.34 (ddd, J = 9.3, J = 6.5, J = 1.9, 1H), 7.46 (dd, J = 7.2, J = 1.9, 1H), 8.38 (d, J = 14.7, 1H); ^{13}C NMR δ 28.0, 81.1, 107.3, 110.9, 122.2, 131.6, 137.8, 139.9, 160.9, 164.9. HRMS (ESI+) *m/z* calcd for $C_{12}H_{16}NO_3^+$ $[M+H]^+$ 222.1125, found 222.1123.

10b (94:6 *E*:*Z,* 118 mg, 91%) was obtained using 0.3 equiv of DMAP; **1-[(*E*)-2-(*tert*-Butoxycarbonyl)vinyl]-5'-*O*-*tert*-butyldimethylsilyl-2',3'-*O*-isopropylideneinosine**, (*E*)-**10b**: foam; R_f = 0.43 (hexanes/EtOAc, 60:40); ^{1}H NMR δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.41 (s, 3H), 1.54 (s, 9H), 1.64 (s, 3H), 3.80 (dd, J = 11.4, J = 3.4, 1H), 3.90 (dd, J = 11.4, J = 3.1, 1H), 4.47 (m, 1H), 4.90 (dd, J = 2.2, J = 6.1, 1H), 5.04 (dd, J = 2.8, J = 6.1, 1H), 6.13 (d, J = 2.7, 1H), 6.23 (d, J = 14.6, 1H), 8.09 (s, 1H), 8.19 (s, 1H), 8.30 (d, J = 14.7, 1H); ^{13}C NMR δ −5.6, −5.5, 18.3, 25.3, 25.8, 27.2, 28.1, 63.5, 81.3, 81.7, 85.6, 87.1, 91.6, 113.7, 114.2, 124.5, 136.2, 138.8, 143.5, 146.1, 154.8, 164.4. HRMS (ESI+) *m/z* calcd for $C_{26}H_{41}N_4O_7Si^+$ $[M+H]^+$ 549.2739, found 549.2738.

(*E*)-**1c** (68 mg, 75%) was obtained using 0.2 equiv of DABCO; **1-[(*E*)-2-(3-Oxo-1-butenyl)vinyl]-2-pyrrolidinone**, (*E*)-**1c**:[19] oil; R_f = 0.48 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 2.16–2.27 (m, 2H), 2.29 (s, 3H), 2.58 (t, J = 8.2, 2H), 3.59 (t, J = 7.2, 2H), 5.54 (d, J = 14.7, 1H), 7.99 (d, J = 14.7, 1H); ^{13}C NMR δ 17.4, 26.5, 31.0, 45.0, 111.4, 137.1, 174.6, 197.8.

(*E*)-**5c** (57 mg, 75%) was obtained using 0.2 equiv of DABCO; **(*S*)-4-Benzyl-3-[(*E*)-2-(3-oxo-1-butenyl)vinyl]-1,3-oxazolidin-2-one**, (*E*)-**5c**: white solid; mp = 108–110 °C; R_f = 0.59 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 2.31 (s, 3H), 2.77–2.87 (m, 1H), 3.21 (m, 1H), 4.26–4.37 (m, 3H), 5.75 (d, J = 14.9, 1H), 7.16–7.19 (m, 2H), 7.27–7.39 (m, 3H), 7.80 (d, J = 14.9, 1H); ^{13}C NMR δ 26.7, 36.2, 54.8, 66.9, 111.0, 127.7, 129.1, 129.2, 134.1, 137.3, 154.4, 196.9; IR 3448, 3072, 2963, 1766, 1626, 1416, 1211; HRMS (ESI+) *m/z* calcd for $C_{14}H_{16}NO_3^+$ $[M+H]^+$ 246.1125, found 246.1118.

(*E*)-**8c** (116 mg, 93%) was obtained using 0.1 equiv of DMAP; **2',3',5'-Tri-*O*-acetyl-1-[(*E*)-2-(3-oxo-1-butenyl)vinyl]inosine**, (*E*)-**8c**: foam; R_f = 0.57 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR δ 2.11 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 2.43 (s, 3H), 4.34–4.48 (m, 3H), 5.56 (t, J = 5.1, 1H), 5.85 (t, J = 5.3, 1H), 6.10 (d, J = 5.1, 1H) 6.61 (d, J = 15.1, 1H), 7.98 (s, 1H), 8.24 (s, 1H), 8.31 (d, J = 15.2, 1H); ^{13}C NMR δ

20.3, 20.4, 20.7, 27.8, 62.9, 70.3, 73.3, 80.3, 86.6, 119.7, 124.8, 136.9, 139.0, 143.5, 146.4, 154.7, 169.2, 169.5, 170.2, 196.6. HRMS (ESI+) *m/z* calcd for $C_{20}H_{23}N_4O_9^+$ $[M+H]^+$ 463.1460, found 463.1457.

9c (93:7 *E*:*Z,* 101 mg, 97%) was obtained using 0.1 equiv of DMAP; **5'-*O*-Acetyl-2',3'-*O*-isopropylidene-1-[(*E*)-2-(3-oxo-1-butenyl)vinyl]inosine**, (*E*)-**9c**: white solid; mp 151–153 ºC; R_f = 0.52 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR δ 1.40 (s, 3H), 1.64 (s, 3H), 2.04 (s, 3H), 2.44 (s, 3H), 4.25 (dd, *J* = 12.0, *J* = 5.6, 1H), 4.35 (dd, *J* = 12.0, *J* = 4.2, 1H), 4.51–4.54 (m, 1H), 4.94 (dd, *J* = 6.3, *J* = 3.4, 1H), 5.22 (dd, *J* = 6.3, *J* = 2.4, 1H), 6.11 (d, *J* = 2.4, 1H), 6.61 (d, *J* = 15.1, 1H), 7.93 (s, 1H), 8.25 (s, 1H), 8.32 (d, *J* = 15.2, 1H); ^{13}C NMR δ 20.7, 25.3, 27.1, 27.8, 63.9, 81.3, 84.6, 84.8, 91.0, 115.0, 119.6, 124.9, 135.9, 139.3, 140.0, 143.4, 154.7, 170.3, 196.6. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}N_4O_7^+$ $[M+H]^+$ 419.1561, found 419.1555.

10c (91:9 *E*:*Z,* 95 mg, 97%) was obtained using 0.1 equiv of DMAP; **5'-*O*-*tert*-Butyldimethylsilyl-2',3'-*O*-isopropylidene-1-[(*E*)-2-(3-oxo-1-butenyl)vinyl]inosine**, (*E*)-**10c**: foam; R_f = 0.56 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR δ 0.06 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.41 (s, 3H), 1.64 (s, 3H), 2.43 (s, 3H), 3.81 (dd, 1H, *J* = 11.4, *J* = 3.3), 3.91 (dd, 1H, *J* = 11.4, *J* = 3.0), 4.46–4.49 (m, 1H), 4.90 (dd, 1H, *J* = 6.1, *J* = 2.2), 5.03 (dd, 1H, *J* = 6.1, *J* = 2.8), 6.14 (d, 1H, *J* = 2.8), 6.57 (d, 1H, *J* = 15.1), 8.11 (s, 1H), 8.24 (s, 1H), 8.35 (d, 1H, *J* = 15.1); ^{13}C NMR δ −5.6, −5.4, 18.3, 25.3, 25.9, 27.2, 27.2, 63.6, 81.3, 85.8, 87.2, 91.8, 114.3, 118.0, 119.5, 136.2, 139.0, 154.8, 196.8. HRMS (ESI+) *m/z* calcd for $C_{23}H_{35}N_4O_6Si^+$ $[M+H]^+$ 491.2320, found 491.2318.

11c (97:3 *E*:*Z,* 90 mg, 90%) was obtained using 0.1 equiv of DMAP; **3',5'-Di-*O*-acetyl-2'-deoxy-1-[(*E*)-2-(3-oxo-1-butenyl)vinyl]inosine**, (*E*)-**11c**: foam; R_f = 0.56 (CH_2Cl_2/MeOH, 90:10); ^{1}H NMR δ 2.10 (s, 3H), 2.15 (s, 3H), 2.44 (s, 3H), 2.65 (ddd, *J* = 6.1, *J* = 4.2, *J* = 2.8, 1H), 2.83 (ddd, *J* = 14.2, *J* = 7.7, *J* = 6.5, 1H), 4.31–4.41 (m, 3H), 5.40–5.44 (m, 1H), 6.36 (dd, *J* = 7.7, *J* = 6.2, 1H), 6.61 (d, *J* = 15.1, 1H), 8.00 (s, 1H), 8.23 (s, 1H), 8.33 (d, *J* = 15.1, 1H); ^{13}C NMR δ 20.7, 20.8, 37.8, 63.5, 74.1, 82.7, 84.6, 119.5, 124.6, 135.9, 138.6, 143.3, 146.3, 154.7, 165.7, 170.1, 170.2, 196.6. HRMS (ESI+) *m/z* calcd for $C_{18}H_{21}N_4O_7^+$ $[M+H]^+$ 405.1405, found 405.1400.

***N*-Propynoylmorpholine** was prepared according to ref 23: ^{1}H NMR δ 3.19 (s, 1H), 3.62–3.74 (m, 6H), 3.76–3.81 (m, 2H); ^{13}C NMR δ 41.8, 47.1, 66.3, 66.7, 75.0, 79.7, 151.8.

2d (93:7 *E*:*Z,* 111 mg, 92%) was obtained using 0.2 equiv of DABCO; ***N*-[(*E*)-2-(4-Morpholino)carbonylvinyl]succinimide**, (*E*)-**2d**: orange solid; mp 146–148 ºC; R_f = 0.64 (hexanes/EtOAc, 20:80); ^{1}H NMR δ 2.82 (s, 4H), 3.70–3.74 (m, 8H), 7.50 (d, *J* = 14.1, 1H), 7.78 (d, *J* = 14.1, 1H); ^{13}C NMR δ 27.7, 66.8, 109.0, 130.1, 164.9, 174.6; HRMS (ESI+) *m/z* calcd for $C_{11}H_{15}N_2O_4^+$ $[M+H]^+$ 239.1026, found 239.1034.

(*E*)-**6d** (105 mg, 85%) was obtained using 1.0 equiv of DMAP; **1-[(*E*)-2-(4-Morpholino)carbonylvinyl]-2-pyridone,** (*E*)-**6d**: amorphous; R_f = 0.41 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 3.65 (br s, 8H), 6.20 (ddd, *J* = 7.1, *J* = 6.5, *J* = 1.4, 1H), 6.53 (dd, *J* = 9.3, *J* = 1.4, 1H), 7.07 (d, *J* = 13.9, 1H), 7.26 (ddd, *J* = 9.3, *J* = 6.5, *J* = 1.9, 1H), 7.36 (dd, *J* = 7.1, *J* = 1.9. 1H), 8.01 (d, *J* = 13.9, 1H); ^{13}C NMR δ 42.5, 46.5, 66.8, 107.2, 110.0, 122.6, 134.3, 139.2, 139.4, 162.0, 164.8; HRMS (ESI+) *m*/*z* calcd for $C_{12}H_{15}N_2O_3^+$ $[M+H]^+$ 235.1077, found 235.1079.

(*E*)-**7d** (172 mg, 95%) was obtained using 0.1 equiv of DMAP; **5'-*O*-Acetyl-3'-azido-2'-deoxy-1-[(*E*)-2-morpholinocarbonylvinyl]thymidine**,[24] (*E*)-**7d**: white solid; mp 45–47 °C; R_f = 0.50 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 1.97 (d, *J* = 1.1, 3H), 2.14 (s, 3H), 2.38 (ddd, *J* = 14.0, *J* = 7.6, *J* = 5.6, 1H), 2.55 (ddd, *J* = 14.0, *J* = 6.6, *J* = 5.7, 1H), 3.60 (br s, 2H), 3.71 (br s, 6H), 4.10 (m, 1H), 4.21 (dt, *J* = 7.6, *J* = 5.6, 1H), 4.34 (dd, *J* = 12.2, *J* = 3.8, 1H), 4.39 (dd, *J* = 12.2, *J* = 4.4, 1H), 6.12 (t, *J* = 6.1, 1H), 7.30 (q, *J* = 1.1, 1H), 7.56 (d, *J* = 14.2, 1H), 8.19 (d, *J* = 14.2, 1H); ^{13}C NMR δ 13.4, 20.7, 37.8, 42.4 46.2, 60.3, 63.1, 66.8, 82.0, 86.5, 110.1, 112.8, 133.1, 133.4, 149.4, 162.1, 165.4, 170.1; HRMS (ESI+) *m*/*z* calcd for $C_{19}H_{25}N_6O_7^+$ $[M+H]^+$ 449.1779, found 449.1780.

***N*-Methoxy-*N*-methylpropynamide** was prepared according to ref 23: ^{1}H NMR δ 3.11 (s, 1H), 3.24 (br s, 3H), 3.78 (s, 3H).

(*E*)-**6e** (93 mg, 85%) was obtained using 0.1 equiv of DMAP; **1-[(*E*)-2-(*N*-Methoxy-*N*-methylaminocarbonyl)vinyl]-2-pyridone**, (*E*)-**6e**: white solid; mp 110–111 ºC; R_f = 0.40 (CH_2Cl_2/ MeOH, 95:5); ^{1}H NMR δ 3.23 (s, 3H), 3.69 (s, 3H), 6.20 (ddd, *J* = 7.2, 6.6, 1.3, 1H), 6.53 (dd, *J* = 9.0, *J* = 1.3, 1H), 6.84 (d, *J* = 14.4, 1H), 7.27 (ddd, *J* = 9.0, 6.6, 2.1, 1H), 7.44 (dd, *J* = 7.2, 1.9, 1H), 8.31 (d, *J* = 14.4, 1H); ^{13}C NMR δ 32.3, 61.8, 107.1, 107.5, 122.3, 132.5, 138.6, 139.6, 161.2, 165.7. HRMS (ESI+) *m*/*z* calcd for $C_{10}H_{13}N_2O_3^+$ $[M+H]^+$ 209.0921, found 209.0918.

(*E*)-**7e** (126 mg, 90%) was obtained using 0.1 equiv of DMAP; **5'-*O*-Acetyl-3'-azido-3'-deoxy-3-[(*E*)-2-(*N*-methoxy-*N*-methylaminocarbonylvinyl]thymidine**,[25] (*E*)-**7e**: white solid; mp 111–113 ºC; R_f = 0.44 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 1.98 (d, *J* = 1.2, 3H), 2.14 (s, 3H), 2.40 (ddd, *J* = 14.1, *J* = 7.6, *J* = 5.6, 1H) 1H), 2.53 (ddd, *J* = 14.1, *J* = 6.7, *J* = 5.6, 1H), 3.28 (s, 3H), 3.75 (s, 3H), 4.10 (dt, *J* = 5.6, *J* = 4.1, 1H), 4.21 (dt, *J* = 7.6, *J* = 5.6, 1H), 4.34 (dd, *J* = 12.2, *J* = 3.8, 1H), 4.39 (dd, *J* = 12.2, *J* = 4.4, 1H), 6.14 (t, *J* = 6.2, 1H), 7.30 (q, *J* = 1.2, 1H), 7.60 (d, *J* = 14.6, 1H), 8.21 (d, *J* = 14.6, 1H); ^{13}C NMR δ 13.5, 20.7, 32.5, 37.8, 60.3, 61.8, 63.1, 81.9, 86.5, 110.1, 112.1, 133.4, 133.4, 149.3, 162.0, 167.0, 170.1. HRMS (ESI+) *m*/*z* calcd for $C_{17}H_{23}N_6O_7^+$ $[M+H]^+$ 423.1623, found 423.1619.

8e (91:9 *E*:*Z,* 53 mg, 80%) was obtained using 0.2 equiv of DABCO; **2',3',5'-Tri-*O*-acetyl-1-[(*E*)-2-(*N*-methoxy-*N*-methylaminocarbonyl)vinyl]inosine**, (*E*)-**8e**: foam; R_f = 0.68 (hexanes/EtOAc, 20:80); ^{1}H NMR δ 2.10 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 3.32 (s, 3H), 3.78 (s, 3H), 4.42–4.46 (m, 4H), 5.59 (t, *J* = 5.2, 1H), 5.89 (t, *J* = 5.2, 1H), 6.08 (d, *J* = 4.9, 1H),

7.18 (d, J = 14.3, 1H), 7.95 (s, 1H), 8.22–8.27 (m, 2H); ^{13}C NMR δ 20.3, 20.5, 20.7, 62.1, 62.9, 70.3, 73.2, 80.2, 110.9, 125.1, 136.6, 137.6, 139.1, 144.8, 146.2, 155.1, 165.1, 169.3, 169.5, 170.3; HRMS (ESI+) *m/z* calcd for $C_{21}H_{26}N_5O_{10}^+$ $[M+H]^+$ 508.1674, found 508.1682.

Removal of MocVinyl and related groups. To the protected substrate (0.20 mmol) in anhyd THF (2 mL) was added a suspension of sodium 1-dodecanethiolate in THF (2 mL). Depending on the easiness or difficulty of the deprotection (see Table 4), 0.24–0.40 mmol (1.2–2.0 equiv) of 1-dodecanethiol plus 48 mg, 0.24–0.80 mmol (i.e. 1.2–4.0 equiv) of NaH were used. After stirring the mixture in a bath at rt or 50 ºC, for a few minutes up to 5 h, TLC indicated complete consumption of the starting material. Quenching with water and neutralization with 0.1 M HCl was followed by extraction with an organic solvent (EtOAc or CH_2Cl_2 depending on the case, several times, until all the organic products went to the organic phase). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel.

Nucleoside **7a** (79 mg, 0.20 mmol) was added to pyrrolidine (57 mg, 0.80 mmol) in CH_3CN (2 mL) and the solution was stirred at rt under N_2 for 2 h (when TLC indicated the full disappearance of the starting material). Evaporation under vacuum gave a residue that was purified by flash column chromatography on silica gel, with CH_2Cl_2 and then CH_2Cl_2/EtOAc mixtures as the eluents. The less polar methyl 3-(pyrrolidin-1-yl)propenoate was eluted first; afterwards, the desired product, **7**, was isolated and dried (57 mg, 92%).

Nucleoside **8a** (95 mg, 0.20 mmol) was added to a flask containing sodium succinimide (from 40 mg, 0.40 mmol, of succinimide and 5.8 mg, 0.24 mmol, of NaH) in CH_3CN (2 mL); DMF gave the same result. The suspension was stirred at 60 ºC (bath temperature) for 4 h (when TLC indicated the full disappearance of **8a**). After dilution with water and several extractions with EtOAc, the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (with 95:5 CH_2Cl_2–MeOH, **2a** was eluted first, and later **8**, 72 mg, 91% yield).

Characterization of *N,S*-acetals. Example. MocVinyl derivative **4a** (100 mg, 0.43 mmol) in THF (4 mL) was added to a flask in which 1-dodecanethiol (174 mg, 0.86 mmol) and NaH (42 mg, 1.72 mmol) were mixed at rt. After stirring for 0.2 h, TLC indicated that the starting material had disappeared to give a less polar product. The reaction was quenched with aqueous HCl (0.5 M, 10 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated. The aqueous phase was re-extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to yield **4a**·$\mathbf{C_{12}H_{26}S}$ (130 mg, 70%): oil; R_f = 0.73 (CH_2Cl_2); ^{1}H NMR δ 0.86 (t, J = 6.9,

3H), 1.19–1.29 (m, 19H), 1.50–1.63 (m, 2H), 2.51–2.58 (m, 1H), 2.63–2.70 (m, 1H), 3.15 (dd, J = 16.7, J = 6.2, 1H), 3.44 (dd, J = 16.7, J = 9.2, 1H), 3.63 (s, 3H), 5.69 (dd, J = 9.2, J = 6.2, 1H), 7.72 (m, 2H), 7.86 (m, 2H); ^{13}C NMR δ 14.1, 28.7, 29.1, 29.3, 29.4, 29.42, 29.5, 29.59, 29.6, 31.9,51.1, 51.9, 123.5, 131.6, 134.2, 167.2, 170.1; HRMS (ESI+) *m/z* calcd for $C_{24}H_{36}NO_4S^+$ $[M+H]^+$ 434.2360, found 434.2357. Treatment of this adduct (217 mg, 0.5 mmol) with lithium hexamethyldisilylamide (LHMDS, 500 μL, 1 M in THF, 0.5 mmol) at 0 ºC for 15 min, followed by neutralization with dil. HCl, evaporation to dryness under vacuum, and purification by column chromatography, gave **4** (50 mg, 0.33 mmol, 61%).

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of the new compounds, DFT and MP2 calculations of all possible conformations of **1a**, **2a**, **5a**, and **6a** and of models of **7a** and **8a–11a**, predicted energies for selected exchange reactions, and predicted energies for relevant initial intermediates (from DABCO and methyl propynoate). This material is available free of charge at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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[14] Compound (*Z*)-**1a** isomerized to its *E* isomer in refluxing toluene, overnight, in the presence of DABCO (1 equiv). On the other hand, nucleoside (*Z*)-**8a** isomerized to its isomer *E* much more easily, since an 86:14 *E/Z* mixture (Table 2, entry 13) was converted to >99:1 by simple treatment for 1 day with DMAP at rt. The *O*-substituted derivatives (2-pyridyl-O-CH=CH-COOMe, for example), which were formed as impurities in some experiments, can be removed by chromatography or, even better, can be rearranged to their major *N*-MocVinyl isomers (to **6a**, for example) with DABCO in refluxing CH_3CN for two days.

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[16] TBAF alone ($Bu_4N^+F^-\cdot 3H_2O$), due to the basicity of the tetrabutylammonium alkoxide that is generated in the medium, causes a N-to-O MocVinyl transfer (from the imide-like N to the O atom that was deprotected) in some cases examined.

[17] After the Pd-catalyzed hydrogenation of the conjugated double bond (with a balloon of H_2, which required less than 1 h for completion), the purification of the crude product by treatment with a strong base to produce an elimination reaction—we used 1.2 equiv of LiHMDS in THF at 0 ºC—immediately furnished the deprotected compounds. Many cleavages of RR'N–CH_2CH_2COOMe and RR'N–CH_2CH_2CN (to give rise to RR'NH and CH_2=CH–EWG) can be found in the chemical literature. For representative examples

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[18] Ethyl propynoate (ethyl propiolate) has a similar price and is also sold by many companies; it can be used in the same way, as an alternative.

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[20] Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7333–7336.

[21] Other usual protecting groups for nucleosides were compatible with the reaction conditions. For example, the 5'-*O*-TBS analog of **7a** could be similarly prepared in excellent yield: 3'-azido-5'-*O*-*tert*-butyldimethylsilyl-1-[(*E*)-2-(methoxycarbonyl)vinyl]thymidine; oil; R_f = 0.80 (CH_2Cl_2/EtOAc, 80:20); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 6H), 0.93 (s, 9H), 1.96 (d, J = 1.2, 3H), 2.25 (m, 1H), 2.49 (m, 1H), 3.78 (s, 3H), 3.81 (m, 1H), 3.99 (m, 2H), 4.23 (td, J = 7.2, J = 4.3, 1H), 6.21 (t, J = 6.4, 1H), 7.07 (d, J = 14.8, 1H), 7.50 (d, J = 1.2, 1H), 8.28 (d, J = 14.8, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.4, −5.4, 13.4, 18.4, 25.9, 38.2, 51.7, 60.2, 62.8, 84.8, 85.7, 109.8, 113.5, 133.5, 134.6, 149.4, 161.9, 167.7; IR (ATR) ν 3085, 2952, 2110, 1750, 1711, 1667, 1633. For an application, see: Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 7515–7517.

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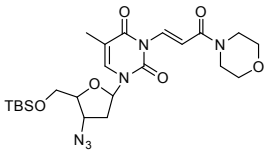
[23] Delamarche, I.; Mosset, P. *Tetrahedron Lett.* **1993**, *34*, 2465–2468.

[24] These reactions are of general scope. For example, a 5'-*O*-TBS group was also stable under the reaction conditions, as we have similarly prepared the morpholine amide-containing 5'-OTBS-AZT analog of **7d** (0.1 M in CH_3CN, 0.1 equiv of DMAP, 1.5 equiv of *N*-propynoylmorpholine, refluxing CH_3CN for 4 h, 90% yield after column chromatography): ^{1}H NMR δ 0.12 (s, 6H), 0.91 (s, 9H), 1.94 (d, J = 1.1, 3H), 2.23 (dt, J = 13.7, J = 6.9, 1H), 2.47 (ddd, J = 13.7, J = 6.1, J = 4.4, 1H), 3.35–3.74 (m, 8H), 3.80 (dd, J = 11.4, J = 2.2, 1H), 3.92–4.00 (m, 2H), 4.21 (dt, J = 7.3, J = 4.2, 1H), 6.20 (t, J = 6.4, 1H), 7.49 (q, J = 1.1, 1H), 7.56 (d, J = 14.2, 1H), 8.20 (d, J = 14.2, 1H); ^{13}C NMR δ −5.5, −5.4, 13.4, 18.3, 25.9, 38.2, 42.4, 46.2, 60.3, 62.7, 66.8, 84.7, 85.6, 109.8, 112.5, 133.3, 149.5, 162.3, 165.5.



[25] The Weinreb amide-containing AZT derivative with a trityl group, not included in Table 3 of the main text for the sake of simplification, was also prepared without loss of 5'-*O*-Tr group, under similar conditions (0.1 M in CH_3CN, 0.1 equiv of DMAP, 1.5 equiv of *N*-methoxy-*N*-methylpropynamide, refluxing for 3 h, 91% yield after chromatography): ^{1}H NMR δ 2.39–2.48 (m, 1H), 2.49–2.58 (m, 1H), 3.25 (s, 3H), 3.44 (dd, J = 11.1, J = 2.9, 1H), 3.56 (dd, J = 11.1, J = 2.8, 1H), 3.71 (s, 3H), 3.95 (ddd, J = 5.9, J = 2.8, 1H), 4.34 (q, J = 6.8, 1H), 5.45 (d, J = 8.2, 1H), 6.18 (dd, J = 4.8, J = 6.4, 1H), 7.22–7.36 (m, 9H), 7.37–7.42 (m, 6H), 7.58 (d, J = 14.6, 1H), 7.87 (d, J = 8.2, 1H), 8.21 (d, J = 14.6, 1H); ^{13}C NMR δ 32.4, 38.4, 59.0, 61.7, 61.9, 83.6, 85.7, 87.6, 101.3, 112.0, 127.4, 128.0, 128.4, 133.0, 137.8, 142.8, 149.4, 161.0, 166.8.