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Radical substitution with azide: $TMSN_3$–$PhI(OAc)_2$ as a substitute of IN_3†

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$TMSN_3$ and $PhI(OAc)_2$ were found to promote high-yield azide substitution of ethers, aldehydes and benzal acetals. The reaction is fast and occurs at zero to ambient temperature in acetonitrile. However, it is essential for the reaction that $TMSN_3$ is added subsequent to the mixture of $PhI(OAc)_2$ and the substrate . A primary deuterium kinetic isotope effect was found for the azidonation of benzyl ethers both with $TMSN_3$–$PhI(OAc)_2$ and with IN_3. Also a Hammett free energy relationship study of this reaction showed good correlation with σ^+ constants giving with ρ-values of -0.47 for $TMSN_3$–$PhI(OAc)_2$ and -0.39 for IN_3. On this basis a radical mechanism of the reaction was proposed.

Introduction

The azido group is a highly useful functionality in organic synthesis due to its ready conversion to an amino group and its photochemical and cycloaddition reactions.[1] Besides the well known nucleophilic introduction of azide using azide ions, the introduction of azide by substitution of active hydrogen atoms employing azide radicals[2,3] has also been reported.[4–17] Thus, α-azidonation of enolic double bonds and amines with PhIO–$TMSN_3$ at low temperature have been reported,[5–8] while an azidoiodinane has also been shown to azidonate alkanes.[9] In these reactions an azidoiodine compound is believed to be the azidonating species. Kita *et al.* reported that $PhI(OOCCF_3)_2$–$TMSN_3$ can azidonate certain activated benzylic positions.[11] Chen showed that $PhI(OAc)_2$–NaN_3 transforms aldehydes to acyl azides in good yield, but also that the reaction appears only to work on aromatic aldehydes.[12] The mechanisms of these reactions have been suggested to occur through (1) formation of $PhI(N_3)_2$ (or equivalent), (2) homolysis of the I–N bond to form azide radicals, (3) abstraction of active hydrogen and (4) reaction of the carbon radical with a $PhIN_3^{\bullet}$ radical giving alkyl azide and iodobenzene.[11,12]

Related to this work with hypervalent iodine species, we have found that iodine azide can be used to promote radical azidonation (or azidation) of aldehydes,[13] benzal acetals[14] and ethers.[15–17] These reactions also follow radical mechanisms and have been proposed to occur by (1) bond homolysis of the weak I–N_3 bond to radicals, (2) attack of iodine or azide radical on active hydrogen atoms, (3) a propagating reaction step of the resulting carbon radical, with iodine azide forming an alkyl azide (or alternatively an alkyl iodide that is finally substituted by azide ions).

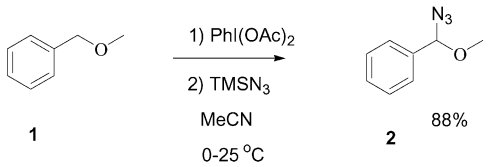
While the parallels in the above literature are obvious, it has been difficult to reach a clear-cut consistency in the methods. Thus, $PhI(OAc)_2$–NaN_3 has been reported only to azidonate aromatic aldehydes,[12] whereas IN_3 reacts well with aliphatic aldehydes,[13] and, unlike PhIO–$TMSN_3$, IN_3 does not give smooth azidonation of amines.[15] Since IN_3, perhaps not entirely justifiably, is notorious for being a hazardous reagent, we made attempts to see if substitution of iodine azide with hypervalent iodine reagents in the azidonation of benzyl ethers and aldehydes was possible, and here report that iodine azide can indeed be substituted with $PhI(OAc)_2$ and $TMSN_3$ in these reactions. This is a useful modification as it has the advantages of higher rate at milder conditions, higher yields in some cases and overall safer reaction conditions, since IN_3 is avoided. The only drawback is that PhI and excess reagent have to be removed by chromatography.

Results and discussion

While it occurred to us early on that azidonation of aldehydes, benzyl ethers and acetals might also be possible with $TMSN_3$ or NaN_3 and a hypervalent iodine species, attempts to carry out this reaction under many of the conditions published for successful azidonation of other substrates failed to give a satisfactory (or any) result. However it was found that the order of addition of the azide source, hypervalent iodine species and substrate is crucial in order to obtain a successful result. Mixing of $TMSN_3$ and $PhI(OAc)_2$ either at low or ambient temperature before adding the substrate completely fails to produce any products, presumably because the reagents decompose before reaction. However when $PhI(OAc)_2$ and substrate are mixed at room temperature and $TMSN_3$ is added subsequently, azidonation products are obtained in high yield.

Ethers

When benzyl methyl ether (**1**) and $PhI(OAc)_2$ are treated with $TMSN_3$ in MeCN at 0–5 °C and subsequently allowed to warm to room temperature, an 88% yield of azide **2** is formed in an essentially instantaneous reaction (Scheme 1). For comparison, IN_3 gives a 93% yield by 20 min reflux. A range of different benzyl ethers and related compounds were tried, and the results are shown in Table 1. $PhI(OAc)_2$ and $TMSN_3$ are used in equimolar amounts and in excess, between 1.3 to 4 equivalents, compared to the substrate; at least 1 equivalent of these reagents is necessary. In general the reaction gives similar yield to IN_3. Particularly noteworthy is the selectivity of monoazidonation of dibenzyl ether (**7**). The chiral silyl ethers **11** and **13** were also azidonated, but without induction of much diastereoselectivity: The diastereomeric ratio was 1 : 1 in **12** and 1 : 3 in **14**. Also it should be noted that, unlike IN_3, $PhI(OAc)_2$–$TMSN_3$ can convert a substrate like **15**. with a free OH group, as it is silylated

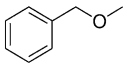
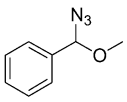
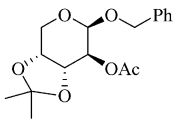
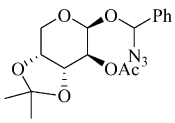
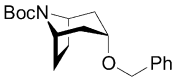
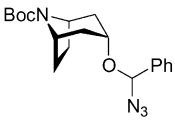
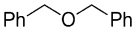
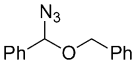
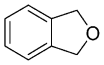
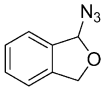
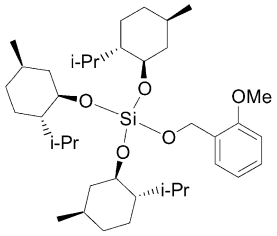
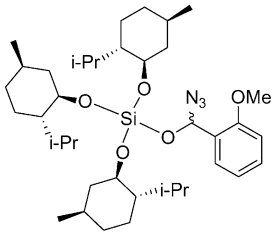
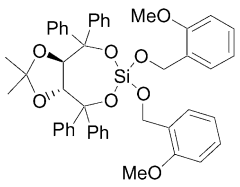
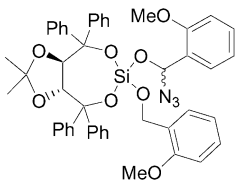
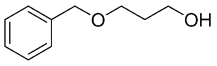
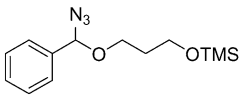


Scheme 1

† Electronic supplementary information (ESI) available: NMR spectra, Hammett plots and data, spectral data for known compounds. See http://www.rsc.org/suppdata/ob/b5/b500037h/

DOI: 10.1039/b500037h

Table 1 Substitution of ethers using $PhI(OAc)_2$–$TMSN_3$

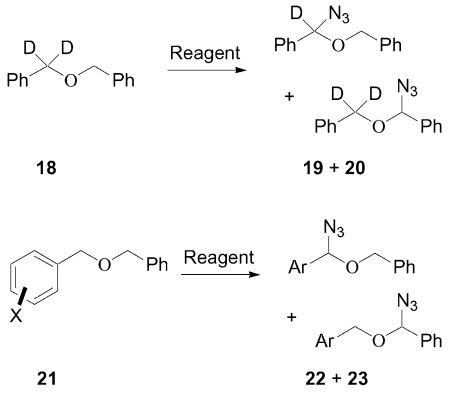
Substrate	Number	$PhI(OAc)_2$–$TMSN_3$	Product	Number	Yield with $PhI(OAc)_2$–$TMSN_3$/%	Yield with IN_3/%
	**1**	2.5 : 2.5		**2**	88	93[15]
	**3**	2 : 4		**4**	71	74[15]
	**5**	2.5 : 2.5		**6**	79	71[16]
	**7**	2 : 2		**8**	89	—
	**9**	1.3 : 1.3		**10**	50	—
	**11**	3 : 3		**12**	84	—
	**13**	5 : 5		**14**	51	—
	**15**	2.5 : 2.5		**16**	82	—

by $TMSN_3$. The optimal solvent is acetonitrile, though benzene and dichloromethane could also be used. THF gave no reaction presumably because of hydrogen abstraction from the solvent.[2]

Some mechanistic experiments were performed to provide an insight into the reaction and to compare it with other conditions. The reaction is inhibited by addition of *N*-*tert*-butyl-α-phenylnitrone in accordance with the radical nature of the mechanism. Adding more $TMSN_3$, beyond the first equivalent (compared to $PhI(OAc)_2$) has no positive effect. Also, $TMSN_3$ could not be replaced by sodium azide in this reaction even though NaN_3 has some solubility in acetonitrile. However, a product could be obtained with $PhI(OAc)_2$–NaN_3 in a slow overnight reaction, when 15-crown-5-ether was also added. Adding 1.5 equivalents of TMSCN to the reaction of **7** still only gave product **8** and no nitrile containing products, showing that no nucleophilic step was involved in the mechanism. On the other hand, when diphenyl diselenide (1.5 eq.) was added the corresponding selenide, PhCH(SePh)OBn (**17**), was obtained in varying amounts depending on how fast the $TMSN_3$ was added. The slower the addition of $TMSN_3$, the higher the proportion of **17** compared to **8**. This supports the presence of benzylic radicals in the mechanism.

Isotope effects in the reaction were investigated using the deuterated version of **7**,**18**[26] (Scheme 2). Reaction of **18** with $PhI(OAc)_2$–$TMSN_3$ (1.5 and 2 eq., MeCN, 25 °C, 50 min) gave a 1 : 5.2 ratio of **19** and **20** corresponding to a primary isotope effect. Reaction of **18** with IN_3 (2 eq., MeCN, 75 °C, 2 h.) gave a 1 : 5.0 ratio of **19** and **20**, also indicating a primary isotope effect in this reaction. This means that hydrogen abstraction is the rate determining step with both reagents.

Electronic effects were investigated using **21** and a series of monosubstituted analogues of **7** (Scheme 2). The ratio of isomeric products **22** and **23**, obtained from **21**, can be used to determine the influence of the substituent X on the reaction, *i.e.*, the isomeric ratio is identical to the ratio between rates of substituted and unsubstituted benzyl ethers. So isomeric ratios were determined for X = *p*-MeO, *m*-MeO, *p*-Br, *m*-Br, *m*-Cl, *p*-NO_2 and *m*-NO_2 and used to construct Hammett plots correlating log (ratio) with σ or σ^+. The reaction of **21** with $PhI(OAc)_2$–$TMSN_3$ (1.5 and 2 eq., MeCN, 25 °C, 1 h) gave the



Scheme 2

plots shown in Fig. 1 and S1. Plotting the data against σ^+ (Fig. 1) gives a better correlation ($r^2 = 0.97$) than the plot against σ ($r^2 = 0.85$, refer to the supplementary information) indicating that resonance from the substituent plays a role in the transition state. The ρ is −0.47, however, which is a very small value compared to a reaction involving an ionic transition state.

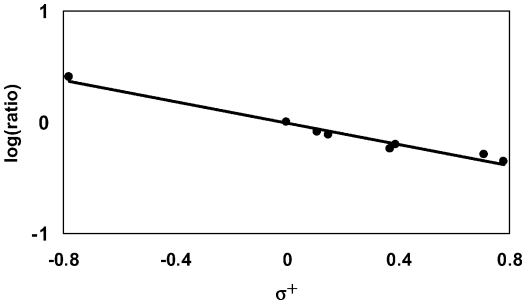


Fig. 1 Hammett plot for the reaction of **21** with $PhI(OAc)_2$–$TMSN_3$.

This Hammett analysis was also performed for IN_3 by reacting the compound series **21** with IN_3 in refluxing MeCN to generate the isomeric product ratios of **22** and **23**. Again, the Hammett plot against σ^+ gives the best correlation ($r^2 = 1.00$, Fig. 2), while the correlation *vs.* σ (supplementary information) is worse ($r^2 = 0.91$). The ρ is −0.39 and thus IN_3 behaves very similarly to $PhI(OAc)_2$–$TMSN_3$, with respect to the low degree of charge in the transition state.

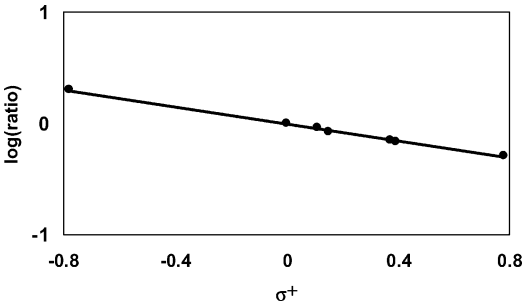
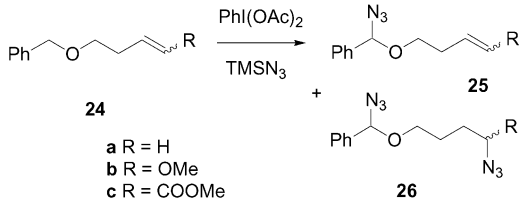


Fig. 2 Hammett plot for the reaction of **21** with IN_3.

To investigate possible intramolecular trapping of an intermediate benzylic radical, the three homoallylic substrates **24a–c**[22–25] were prepared (Scheme 3). Reaction of the unsubstituted derivative **24a**[24] gave 54% of monoazide **25a** and 41% of diazide **26a**, but with no cyclisation products being formed. Compound **26a** is a product of radical addition to the double bond. Reaction of enol ether **24b**[22,23] gave diazide **26b** in low yield (13%) as well as a number of by-products, none of which could be identified. The unsaturated ester **24c**[25] gave, according to mass spectrometry, monoazide **25c** together with an unidentified by-product that however did not fit with a cyclic structure. Since formation of

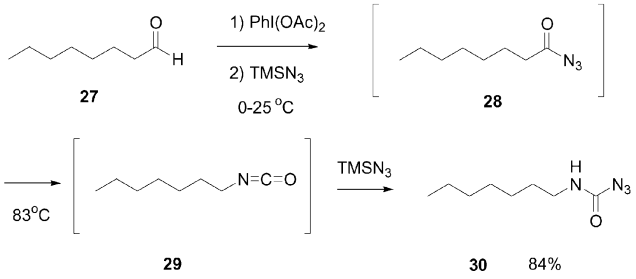


Scheme 3

a benzylic radical is beyond doubt, these experiments suggest that radicals formed from cyclisation cannot be converted into azides, but rather reconvert to the benzylic radical.

Aldehydes

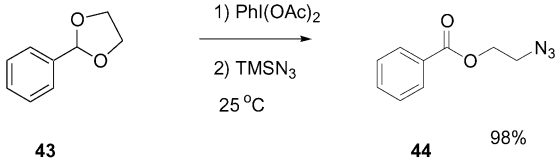
Aldehydes are also readily azidonated. From aliphatic aldehyde **27**, the acyl azide **28** is obtained, but due to its instability during work-up, this primary product was heated to 83 °C to give Curtius rearrangement to isocyanate **29** that, under these conditions, reacts with azide ions to give carbamoyl azide **30**, which was isolated in 84% yield (Scheme 4). For comparison an 86% yield was obtained with IN_3.[11] For the azidonation an excess of equimolar amounts of $PhI(OAc)_2$ and $TMSN_3$ was necessary, but an extra equivalent of $TMSN_3$ was added to form carbamoyl azide. A series of aliphatic and aromatic aldehydes were converted to carbamoyl azides in good yield with this procedure (Table 2). In general the yields with aromatic aldehydes are slightly lower than those obtained with IN_3. The preferred solvent was MeCN, while dichloromethane, benzene, EtOH and THF gave lower yields. The reaction is inhibited by the radical trap *N*-*tert*-butyl-α-phenylnitrone.



Scheme 4

Benzal acetal

Benzal acetal **43** also reacted with $PhI(OAc)_2$–$TMSN_3$ giving 2-azidoethyl benzoate **44** in 98% yield (Scheme 5), while IN_3 only gave 78% yield in this reaction.[15]

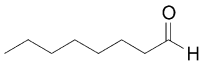
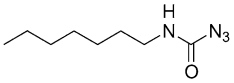
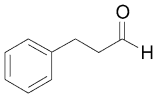
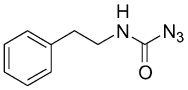
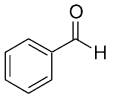
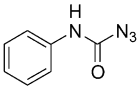
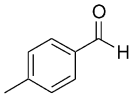
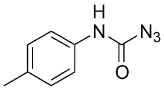
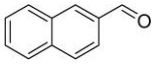
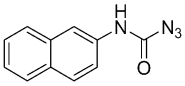
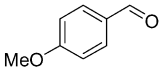
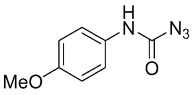
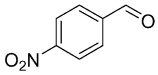
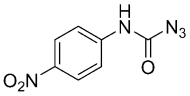


Scheme 5

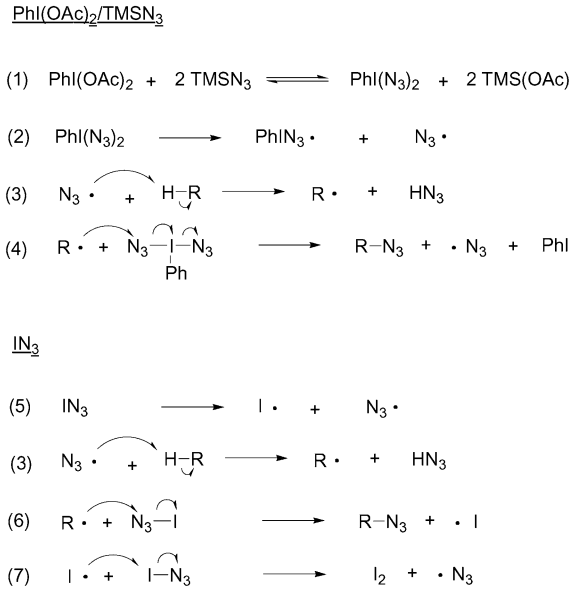
Mechanism

The inhibition of the reactions by addition of a radical trap and the deuterium primary kinetic isotope effect seen show that this is a radical mechanism with the rate determining step involving hydrogen abstraction. It is reasonable to suppose that this abstraction is being carried out by azide radicals as was suggested by others.[2,4,5] The very low negative value of ρ in the Hammett plot supports a purely radical reaction, as does the

Table 2 Conversion of aldehydes to carbamoyl azides using either (1) $PhI(OAc)_2$–$TMSN_3$ and heating or (2) IN_3 at 83 °C

Substrate	Number	$PhI(OAc)_2$–$TMSN_3$	Product	Number	Yield with $PhI(OAc)_2$–$TMSN_3$/%	Yield with IN_3/%
	**27**	1.5 : 2.5		**30**	84	86[13]
	**31**	1.5 : 2.5		**32**	77	73[13]
	**33**	1.5 : 2.5		**34**	81	97[13]
	**35**	1.5 : 2.5		**36**	84	96[13]
	**37**	1.5 : 2.5		**38**	58	—
	**39**	1.5 : 2.5		**40**	74	70[13]
	**41**	2 : 4		**42**	41	—

lack of any success in substituting azide with cyanide when TMSCN is added to the reaction. The better correlation of the Hammett data to σ^+ values suggest some ionic character of the transition state. These data fit the mechanism shown in Scheme 6, which is similar to what has been proposed previously, and is one of simplest that can be suggested. The mixture of $TMSN_3$ and $PhI(OAc)_2$ lead to formation of $PhI(N_3)_2$ that decomposes giving azide radicals. The chain propagating steps are reactions (3) and (4) with (3) being the rate determining step.



Scheme 6

Since the behaviour of $PhI(OAc)_2$–$TMSN_3$ and iodine azide is extremely similar in terms of reaction yields, kinetic isotope effect and Hammett correlations, it is compelling that the mechanism should be similar. It is therefore very probable that azide radicals are also involved in the hydrogen abstraction with this reagent and not iodine radicals as have previously been suggested.[13] We therefore propose the mechanism shown in Scheme 6. In this mechanism the chain propagating steps are (3), (6) and (7), the latter step being necessary to produce new azide radicals. Alternatively it might be suggested that in step (6) iodine was abstracted by the carbon radical producing azide radicals directly and giving an alkyl iodide. This iodide would subsequently be substituted by azide ions. However there is with IN_3 no evidence for the intermediacy of iodides or any indication of a ionic component in the reaction.

In summary $PhI(OAc)_2$–$TMSN_3$ is a valuable substitute for IN_3 in azidonation reactions. The reaction is faster and milder, and the reaction conditions are safer. The yields are slightly lower for aldehydes but higher for ethers and acetals.

Experimental

General procedure for benzyl ethers (A)

Into a 7 ml sample vial equipped with a septum, *ca.* 100 mg of benzyl ether was dissolved in 4 ml acetonitrile under a nitrogen atmosphere. 1.5 eq. of iodobenzene diacetate (with respect to ether) was added, and the mixture was stirred until complete dissolution. The vial was then cooled down on an ice bath, 2 eq. of $TMSN_3$ was added dropwise *via* syringe and the mixture was allowed to reach room temperature. After the gas had finished developing, the reaction mixture was concentrated *in vacuo* to give a crude oil containing the product and iodobenzene. The product was purified by column chromatography (iodobenzene was removed with pentane and the product was eluated with

pentane : dichloromethane, 5 : 1) and obtained as a colourless oil.

General procedure for aldehydes (B)

Into a 7 ml sample vial equipped with a septum, to a solution of *ca.* 100 mg aldehyde in 4 ml acetonitrile under nitrogen, iodobenzene diacetate (1.5 eq., with respect to aldehyde) was added and stirred until complete dissolution. The mixture was then cooled to 0 °C on an ice bath and $TMSN_3$ (2.5 eq.) was added dropwise to the mixture. After the resulting evolution of gas was completed, the reaction mixture was allowed to reach room temperature and the reaction was followed by TLC showing the formation of acyl azide. The vial was then heated to 83 °C for *ca.* 30 min to obtain the Curtius rearrangement followed by formation of carbamoyl azide. The reaction mixture was concentrated *in vacuo* and the product was isolated by column chromatography (pentane for removing the iodobenzene and than pentane : ethyl acetate, 10 : 1).

α-Azidobenzyl methylether (2)[15]. Prepared from commercially available **1** using general procedure A. Colorless oil. Yield: 123 mg (88%).

(*R*,*S*)-α-Azido-benzyl 2-*O*-acetyl-3,4-*O*-isopropylidene-β-D-arabinopyranoside (4)[15]. Prepared from **3**[18] using general procedure A. Colorless oil. Yield: 75 mg (71%).

3-(Azido-phenyl-methoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (6)[16]. Prepared from **5**[16] using general procedure A. Clear colourless oil. Yield: 89 mg (79%).

α-Azidobenzyl benzyl ether (8)[19]. Prepared from commercially available **7** using general procedure A. Colourless oil. Yield: 120 mg (89%).

α-Azidophthalan (10). Prepared from commercially available **9** using general procedure A. Colorless oil. Yield: 67 mg (50%). ^{1}H-NMR ($CDCl_3$): δ = 7.32–7.56 (m, 4H, Ar), 6.34 (s, 1H, N_3–C–*H*), 5.33 (d, J = 12.4, 1H, Ar–CH_a–O), 5.13 (d, J = 12.4, 1H, Ar–CH_b-O). ^{13}C-NMR ($CDCl_3$): δ = 139.3 (Ar-2), 136.4 (Ar-1), 129.8 (Ar-6), 128.3 (Ar-3), 122.7 (Ar-4). 121.4 (Ar-5), 96.0 (*C*–N_3), 73.9 (Ph*C*H_2). IR (NaCl)/cm^{-1}: ν = 3081, 3051 (Ar C–H sp^2), 2926, 2875 (C–H sp^3), 2099(vs) (N_3).

(α-Azido-(2-methoxybenzyl)oxy)tris(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)silane (12). Prepared from **11**[20] using general procedure A. Colorless oil. Yield: 89 mg (84%). ^{1}H-NMR($CDCl_3$): δ = 7.58 (dt, J = 1.6, J = 6.1, 1H, Ar), 7.31 (tt, J = 2.1, J = 7.8, 1H, Ar), 6.98 (dt, J = 3.4, J = 7.3, 1H, Ar), 6.88 (dd, J = 1.8, J = 8.0, 1H, Ar), 6.38/6.36 (s, 1H, BnH/BnH′), 3.86/3.85 (s, 3H, OMe/OMe′), 3.71 (m, 3H, H_{1a}), 2.24 (m, 3H, H_7), 2.1/2.0 (bd, J = 11.8, 2H, H_{2a}, H_{2a}′), 1.55–1.65 (m, 6H, H_6), 1.33 (m, 3H, H_{4e}), 1.20 (m, 3H, H_{3e}), 1.04 (m, 3H, H_{5a}), 0.84–1.0 (m, 24H, *Me*$_2$C–, H_{3a}, H_{4a}), 0.70/0.78 (d, 3H, Me/Me′). ^{13}C-NMR ($CDCl_3$): δ = 156.0 (Ar-1), 129.9 (Ar-5), 127.8 (Ar-2), 126.4 (Ar-3), 120.5 (Ar-4), 110.4 (Ar-6), 81.2 (*C*-N_3), 74.0 (C_1), 55.5 (OMe), 49.8/49.7 (C_2), 44.9 (C_4), 34.6, 31.8, 25.5, 22.8, 22.3, 21.3, 15.8/15.7 (C3, C5, C6, Me, *Me*$_2$C, Me$_2$*C*). IR (NaCl)/cm^{-1}: ν = 2954, 2923, 2870 (C–H sp^3), 2103(vs) (–N_3), 1604, 1592, 1494 (Ar C–H sp^2). MS(ES): calc. for (M + Na) = 694.5656, found 694.5656.

(6,6-bis(2-Methoxybenzyloxy)-2,2-dimethyl-4,4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxasilepine (13). Freshly distilled tetrachlorosilane (57 µl, 0.5 mmol) was added to a solution of *R*,*R*-TADDOL (0.233 mg, 0.5 mmol) in 20 ml of dry toluene under a nitrogen atmosphere. Pyridine (0.12 ml, 1.5 mmol) was then added and the reaction mixture was stirred overnight. After this, *o*-methoxy-benzylic alcohol (0.13 ml, 1 mmol) was added. The mixture was stirred overnight, filtered through celite and concentrated *in vacuo*. The product was purified by flash chromatography (pentane : ether 10 : 1 to 1 : 1) as a white solid (0.213 g, 56%). ^{1}H-NMR ($CDCl_3$): δ = 6.6–7.6 (m, 28H, Ar), 5.03 (s, 2H, H_{1a}/H_{1b}), 4.69 (d, J = 14, 2H, BnH_a), 4.54 (d, J = 14, 2H, BnH_b), 3.66 (s, 6H, O*Me*), 0.48 (s, 6H, *Me*$_2$C<). ^{13}C-NMR ($CDCl_3$): δ = 156.3 (Ar-1), 147.2 (Ar-2), 142.6 (Ph-), 129,5, 128.8, 128.2, 127.9, 127.6 127.5, 127.3, 127.2, 127.1 (Ar, Ph), 120.7 (Ar-4), 113.7 (Me$_2$*C*<), 109.8 (Ar-3), 82.5 (Ph$_2$*C*<), 81.2 (C_{1a}/C_{1b}), 61.0 (PhCH$_2$-), 55.4 (O*Me*), 27.3 (*Me*$_2$C<). IR (NaCl)/cm^{-1}: ν = 3059 (Ar C–H sp^2), 2992, 2935, 2836 (C–H sp^3), 1603, 1590, 1493 (Ar C–H sp^2). MS(ES): calc. for (M + Na) = 789.2859, found 789.5275.

6-(α-Azido-2-methoxybenzyloxy)-6-(2-methoxybenzyloxy)-2,2-dimethyl-4,4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]-dioxasilepine (14). Prepared from **13** using general procedure A. Colorless oil. Yield: 27 mg (51%). Diastereomeric ratio 1 : 3. ^{1}H-NMR ($CDCl_3$): δ = 6.6–7.6 (m, 28H, Ar), 6.0/6.1 (s, 1H, N_3-C-*H*/N_3–C–*H*′), 5.04 (m, 2H, H_1, H_2), 4.72/4.69 (d, J = 13.6, 1H, BnH_a/ BnH_a′), 4.55/4.53 (d, J = 13.6, 1H, BnH_b/BnH_b′), 3.66, 3.67, 3.68, 3.69 (s, 6H, –O*Me*), 0.43, 0.47, 0.48, 0.49 (s, 6H, *Me*$_2$C<). ^{13}C-NMR ($CDCl_3$): δ = 156.1 (Ar-1), 146.7 (Ar-2), 142.3 (Ph-), 130.0, 129.4, 129.3 128.3, 128.2 128.0, 127.9 127.5, 127.4, 127.3, 127.3, 127.1, 127.1 (Ar, Ph), 120.7 (Ar-4), 113.8 (Me$_2$*C*<), 110.3 (Ar-3), 109.7 (*C*–N_3), 82.9/81.9 (Ph$_2$*C*<), 81.1/81.0 (C_{1a}/C_{1b}), 61.3/61.1 (Ph*C*H$_2$–), 55.6/55.3 (O*Me*), 27.2 (*Me*$_2$C<). IR (NaCl)/cm^{-1}: ν = 2105 (–N_3), 1602, 1559, 1492 (Ar C–H sp^2). MS(ES): calc. for (M + Na) = 830.2874, found 830.1154.

α-Azidobenzyl 3-trimethylsilanoxypropyl ether (16). Prepared from **15**[21] using general procedure A. Colorless oil. Yield: 102 mg (82%). ^{1}H-NMR ($CDCl_3$): δ = 7.36–7.47 (m, 5H, Ar), 5.43 (s, 1H, N_3–C–*H*), 3.96 (m, 1H, H_{1a}), 3.65–3.75 (m, 3H, H_{1b}, H_3), 1.91 (m, 2H, H_2), 0.11 (s, 9H, OTMS). ^{13}C-NMR ($CDCl_3$): δ = 137.8(Ar-1), 129.2(H_3), 128.9(H_4), 126.6(H_2), 93.2 (>*C*–N_3), 66.4 (C_3), 59.7 (C_1), 33.1 (C_2), 0.0(TMS). IR (NaCl)/cm^{-1}: ν = 2956 (C–H sp^3), 2105(vs) (N_3) MS(ES): calc. for (M + Na) = 302.1322, found 302.1301.

General procedure for preparation of substituted dibenzyl ethers (21)

Substituted benzyl alcohol (1 eq.) was dissolved in dry DMF under nitrogen atmosphere. The mixture was cooled on an ice bath and pre-washed NaH (2 eq.) was slowly added. After stirring for 30 min, benzyl bromide (1.2 eq.) was added slowly by syringe, and the mixture was allowed to come to room temperature. After stirring overnight, the reaction was quenched with water and extracted with ether. The combined organic fractions were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (DCM : pentane, 1 : 3) to give colorless to pale yellow oils.

α,α-D_2 dibenzyl ether (**18**) was prepared according to literature procedures.[26]

Selectivity and isotope effect experiments with dibenzylethers (18/21)

General procedure for $PhI(OAc)_2$–$TMSN_3$

Into a 7 ml sample vial equipped with a septum, *ca.* 100 mg of benzyl ether was dissolved in 4 ml acetonitrile under a nitrogen atmosphere. 1.5 eq. of iodobenzene diacetate (with respect to ether) was added and the mixture was stirred until complete dissolution. $TMSN_3$ (2 eq.) was then added dropwise by syringe. After the gas had finished developing, the reaction mixture was concentrated *in vacuo* to give a crude oil containing the two products and iodobenzene. The ratio of products was determined by comparing integrals in ^{1}H-NMR.

General procedure for IN_3

In a 7 ml vial equipped with a septum, ICl (2 eq.) was dissolved in 4 ml dry acetonitrile under nitrogen atmosphere and cooled to −10 °C. Sodium azide (2.3 eq.) was added and the mixture

was stirred for 15 min, then *ca.* 100 mg benzyl ether (1 eq.) was added *via* syringe and the mixture was heated to 75 °C for 1 h. The crude mixture was transferred to a separation funnel containing *ca.* 15 ml $Na_2S_2O_3$ (5% solution), extracted 3 times with *ca.* 20 ml DCM. The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a colorless/pale yellow oil.

The ratio of products was determined by comparing integrals in ^{1}H-NMR.

1-((4-Methoxybut-3-enyloxy)methyl)benzene (24b)[22,23]. 4-Benzyloxybut-1-ene (**24a**) was prepared in a 92% yield according to the protocol of Six.[24] To a solution of 4-benzyloxybut-1-ene (5.13 g, 31.6 mmol) in 280 ml THF–H_2O (4 : 3) was added $NaIO_4$(14.9 g, 67.7 mmol). The reaction mixture was cooled in an ice bath, stirred for 30 min OsO_4 (0.6 ml 2% in ^{t}BuOH) was then added dropwise *via* syringe. After a while the solution turned light yellow and then white. The reaction was carefully followed by TLC and quenched with $NaHSO_3$ (10%) after *ca.* 2 h. The mixture was extracted with ether and the combined organic phases were washed with $Na_2S_2O_3$, brine and dried over $MgSO_4$. Flash chromatography (DCM–Pentane gradient, 1:1 to 1:0) provided 3-benzyloxy propanal as a colorless oil. Yield: 3.14 g (61%).

To a THF solution (10 ml) of di-isopropylamine (1.1 ml, 7.61 mmol) at 0 °C was added 5.1 ml *n*-BuLi (1.5 M in hexane, 7.61 mmol). After stirring at 0 °C for 5 min the mixture was transferred *via* syringe to a 10 ml solution of (methoxymethyl)-triphenylphosphonium chloride (2.61 g, 7.61 mmol). After stirring the mixture at 0 °C for 30 min and at room temperature for 30 min it was cooled to −78 °C and 3-benzyloxy propanal (0.50 g, 3.05 mmol) dissolved in 3 ml THF was added. The mixture was allowed to come to room temperature. When no more starting material appeared on TLC the mixture was quenched with water and extracted with ether. The combined organic phases were washed with NH_4Cl (sat.), brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Chromatography (pentane : EtOAc, 5 : 1) afforded 155 mg **24b** (26%) as an *E* : *Z* (2 : 1) mixture.

α-Azidobenzyl 3-butenyl ether (25a). Prepared from **24a**[24] using general procedure A. Isolated as the first product from flash chromatography in pentane to CH_2Cl_2–pentane, 1 : 1. Colorless oil. Yield: 74 mg (54%). ^{1}H-NMR ($CDCl_3$): δ = 7.35–7.47 (m, 5H, Ar), 5.87 (ddt, J = 17.1, J = 10.2, J = 6.7, 1H, H_a), 5.46 (s, 1H, N_3–C–*H*), 5.15 (ddd, J = 17.2, J = 3.25, J = 1.6, 1H, H_b), 5.09 (ddd, J = 10.2, J = 1.6, 1.1, 1H, H_c), 3.92 (dt, J = 9.3, J = 6.7, 1H, H_1), 3.66 (dt, J = 9.3, J = 6.7, 1H, H_1'), 2.47 (ddt, J = 6.6, J = 6.7, J = 1.1, 2H, H_2). ^{13}C-NMR ($CDCl_3$): δ = 137.2 (Ar-1), 134.8(C_3), 129.3(Ar-4), 128.7(Ar-3/Ar-3′), 126.3(Ar-2/Ar-2′), 117.1(C_4), 92.6(*C*–N_3), 68.4(C_1), 34.1(C_2). IR (NaCl)/cm^{-1}: ν = 2921 (C–H sp^3), 2104(vs) (–N_3). MS(ES): calc. for (M + Na) = 226.0956, found 226.0958.

α-Azidobenzyl 4-azidobutyl ether (26a). Prepared from **24a**[24] using general procedure A. Isolated as the second product from flash chromatography in pentane to CH_2Cl_2–pentane, 1 : 1. Colorless oil. Yield: 65 mg (41%). ^{1}H-NMR ($CDCl_3$): δ = 7.25–7.46 (m, 5H, Ar), 5.43 (s, 1H, N_3–C–*H*), 3.90 (ddd, J = 9.2, J = 5.6, J = 4.0, 1H, H_1), 3.62 (ddd, J = 9.2, J = 5.6, J = 4.0, 1H, H_1'), 3.27 (t, J = 6.0, 2H, H_4), 1.77 (m, 4H, H_2, H_3). ^{13}C-NMR ($CDCl_3$): δ = 137.2(Ar-1), 129.4(Ar-4), 128.9(Ar-3/Ar-3′), 126.3(Ar-2/Ar-2′), 92.7 (–O–*C*–N_3), 68.4 (C_1), 51.4 (C_4), 27.0, 26.0 (C_2, C_3). IR (NaCl)/cm^{-1}: ν = 3065, 3034 (Ar C–H sp^2), 2941, 2875 (C–H sp^3), 2102(vs) (N_3). MS(ES): calc. for (M + Na) = 269.1127, found 269.1137.

1-(Azido(3-azido-4-methoxy)methyl)benzene (26b). Prepared from **24b** using general procedure A. Colorless oil. Yield: 23 mg (13%). ^{1}H-NMR ($CDCl_3$): δ = 7.46–7.37 (m, 5H, Ar), 5.44 (s, 2H, PhCH_2), 4.37 (t, J = 5.8, 1H, H_4), 3.90 (ddt, J = 3.0, J = 6.4, J = 12.3, 1H, H_{1a}), 3.63 (m, 1H, H_{1b}), 3.48/3.47 (s, 3H, Me), 1.88 (m, 2H, H_3), 1.83 (m, 2H, H_2). ^{13}C-NMR ($CDCl_3$): δ = 137.1 (Ar-1), 129.3 (Ar-4), 128.8, 126.2 (Ar-2, Ar-3, Ar-5, Ar-6), 94.0 (Ph*C*N_3), 92.6 (C_4), 68.3 (C_1), 56.8 (Me), 31.5 (C_3), 24.9 (C_2). IR (NaCl)/cm^{-1}: ν = 3066, 3034 (Ar C–H sp^2), 2834, 2878 (C–H sp^3), 2105(vs) (N_3). MS(ES): calc. for (M + Na) = 299.1239, found 299.1254.

Heptyl carbamoylazide (30)[13]. Prepared from commercial **27** using general procedure B. Colourless oil. Yield: 120 mg (84%).

2-Phenylethyl carbamoylazide (32)[13]. Prepared from commercial **31** using general procedure B. White crystals. Yield: 108 mg (77%).

Phenyl carbamoylazide (34)[13]. Prepared from commercial **33** using general procedure B. White crystals. Yield: 124 mg (81%). mp = 107.1 °C.

4-Methylphenyl carbamoylazide (36)[13]. Prepared from commercial **35** using general procedure B. Light yellow crystals. Yield: 122 mg (84%).

Naphthyl carbamoylazide (38). Prepared from commercial **37** using general procedure B. Colorless oil. Yield: 78 mg (58%). ^{1}H-NMR ($CDCl_3$): δ = 8.05 (s, 1H, NH), 7.77 (m, 3H, c,e,h), 7.47 (c,f,g), 7.11 (s, 1H, a). ^{13}C-NMR ($CDCl_3$): δ = 154.4 (*C*=O), 134.5 (Ar-2), 133.9 (Ar-10), 131.0 (Ar-5), 129.3, 127.9, 127.8, 127.0, 125.6 (Ar-4, Ar-6, Ar-7, Ar-8, Ar-9), 119.3 (Ar-3), 115.4 (Ar-1). IR (NaCl)/cm^{-1}: ν = 3344(s) (NH), 3059 (Ar C–H sp^2), 2144 (N_3), 1699, 1681(vs) (C=O), 1588, 1560, 1502 (Ar). MS(ES): calc. for (M + Na) = 235.0596, found 235.0592

4-Methoxyphenyl carbamoylazide (40)[13]. Prepared from commercial **39** using general procedure B. White crystals. Yield: 100 mg (74%).

4-Nitrophenyl carbamoylazide (42). Prepared from commercial **41** using general procedure B. Yellow crystals. Yield: 55 mg (41%). ^{1}H-NMR ($CDCl_3$): δ = 8.22 (d, J = 8.9, 2H, Ar-2, Ar-2′) 7.63 (d, J = 8.9, 2H, Ar-3, Ar-3′), 7.30 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ = 154.3(*C*=O), 144.0, 143.1(Ar-1, Ar-2), 125.5(Ar-3/Ar-3′), 118.9(Ar-2, Ar-2). IR (NaCl)/cm^{-1}: ν = 3316 (NH), 3079 (Ar C–H sp^2), 2165, 2136 (N_3), 1691 (C=O), 1549, 1505, 1346 (–NO_2). MS(ES): calc. for (M + Na) = 219.0, found 219.0 ($C_8H_8N_2O_4$ from reaction with MeOH).

2-Azidoethyl benzoate (44)[14]. Prepared from commercial **43** using general procedure A. Colorless oil. Yield: 123 mg (98%).

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