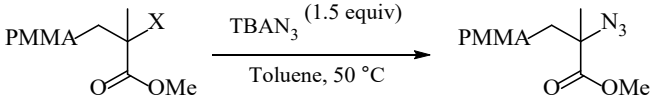
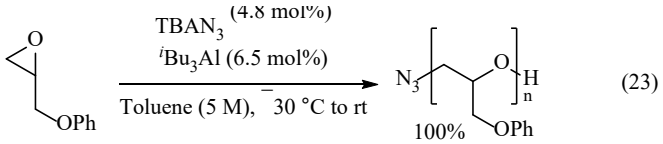
Nucleophilic Azidation of Alkyl Halides. The synthesis of alkyl azides commonly uses NaN_3 for the nucleophilic substitution of alkyl halides in polar solvents (e.g. DMF, DMSO). This method can be used to prepare azido-end polyacrylates and polystyrenes. However, polymethacrylates suffer from poor S_N2 reactivity due to the tertiary alkyl chain end, requiring a large excess of NaN_3 and long reaction times for quantitative azidation. An alternative method, using $TBAN_3$ in a non-polar solvent (toluene) has been developed, allowing nearly quantitative azidation of halide-end polymethacrylates with no large excess of azide (eq 22).[19]



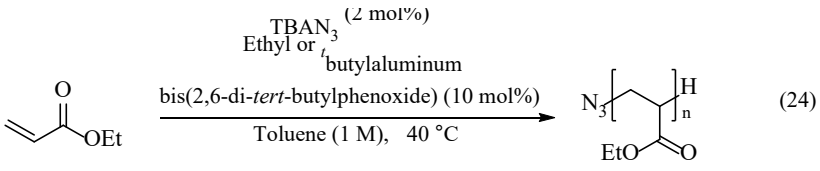
(22)

Initiation of Anionic Polymerization. $TBAN_3$ can initiate anionic ring-opening polymerization for the synthesis of linear poly(glycidylphenyl ether), and the resultant azide terminus can subsequently be derivatized *via* the copper-catalyzed alkyne-azide cycloaddition 'click' reaction. The presence of Lewis acid *i*-Bu_3Al during polymerization improved the end-group fidelity of the polymer chains, with azide ion opening the oxirane ring at the α-position (eq 23).[20]



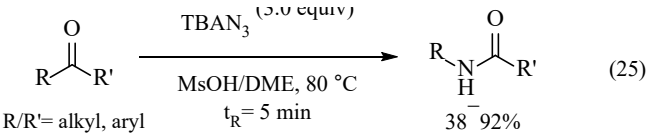
(23)

Similarly, $TBAN_3$ can be used to initiate the anionic polymerization of ethyl acrylate in the presence of alkyl-aluminium bisphenoxides, enabling the synthesis of azide-terminated poly(meth)acrylates for macrocycle synthesis *via* 'click' chemistry (eq 24).[21]



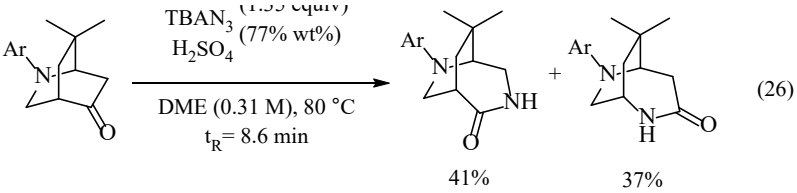
(24)

Schmidt Reaction. The Schmidt reaction, which enables *N*-insertive synthesis of secondary amides from ketones, typically uses NaN_3 under acidic conditions to generate hazardous hydrazoic acid (HN_3) *in situ*. By virtue, flow chemistry offers a safer method for utilising HN_3 in synthesis, given that it may be generated and consumed in small quantities in a continuous manner, without accumulation. However, the poor solubility of NaN_3 in many organic solvents provides an impetus for the use of $TBAN_3$ as an organic-soluble azide source in such applications, including Schmidt reactions in flow. Thus, the conversion of a range of cyclic and acyclic ketones to their corresponding amides can be achieved in DME using a continuous flow microreactor (eq 25).[22]



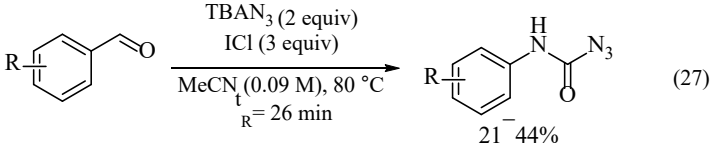
(25)

Similarly, a Schmidt rearrangement using $TBAN_3$ in continuous flow has been used as a ring expansion strategy for the synthesis of a bicyclic homopiperizine, although poor regioselectivity of the nitrogen insertion was observed (eq 26).[23]



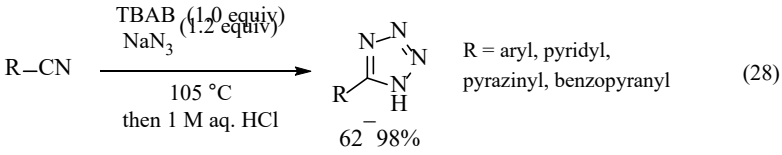
(26)

Synthesis of Iodine Azide. Iodine azide (IN_3) is a synthetically valuable but highly toxic and explosive reagent. However, it can be safely generated *in situ* from $TBAN_3$ and iodine monochloride (ICl) using continuous flow microreactors, where it has been used for the synthesis of carbamoyl azides from aldehydes.[24] Initial reaction of IN_3 with aldehydes generates acyl azide intermediates, which undergo Curtius rearrangement upon heating to give isocyanates. Trapping of these isocyanates by excess azide ion delivers the carbamoyl azide products (eq 27).



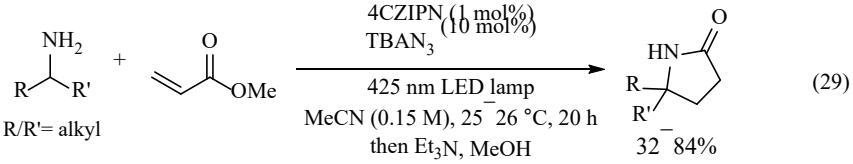
(27)

Tetrazole Synthesis. 5-Substituted 1*H*-tetrazoles can be accessed *via* the 1,3-dipolar cycloaddition of nitriles with azide ion, followed by acidification to neutralise the tetrazole anion. A solvent-free modification of this process with NaN_3 has been demonstrated using molten tetrabutylammonium bromide (TBAB) as the reaction medium, in which the *in situ* formation of $TBAN_3$ serves to bring azide ion into the melt phase. This procedure afforded a range of 5-(hetero)aryl-substituted 1*H*-tetrazoles, although alkyl aldehydes proved unsuccessful (eq 28).[25]

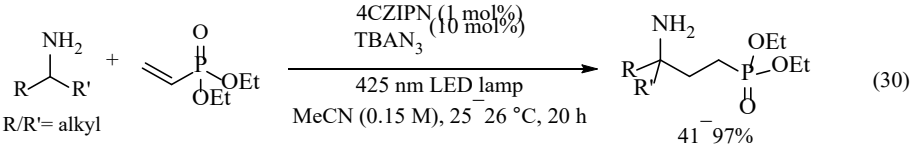


(28)

C(sp^3)–H Functionalizations and C=C Oxidations with Azidyl Radical. $TBAN_3$ can serve as an organic-soluble precursor to the azidyl radical ($N_3^{\bullet}$), which may be generated under photo- or electrooxidative conditions. This highly electrophilic radical species can engage readily with nucleophilic C–H or C=C bonds, and reactions that are catalytic in azide ion are possible. For example, $TBAN_3$ has been deployed as a hydrogen atom transfer (HAT) catalyst in the photoredox-catalyzed α-C–H alkylation of unprotected primary alkylamines, in which α-amino radicals are formed as key intermediates. Capture of the latter radicals with acrylates, followed by post-reaction lactamization, affords a direct synthesis of α,α-disubstituted (including spirocyclic) γ-lactams (eq 29).[26] A similar reaction using vinyl phosphonates as radicophiles can be used to synthesize γ-aminophosphonates (eq 30).[27]

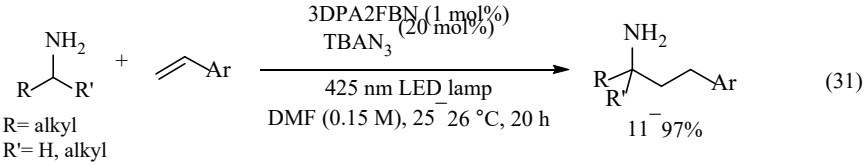


(29)



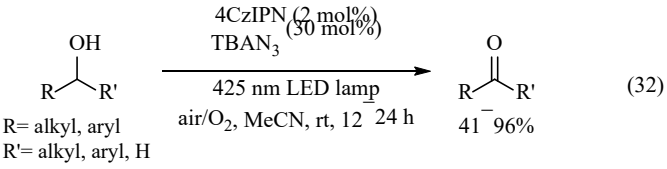
(30)

This chemistry can also be extended to non-electrophilic styrenes as radical acceptors, enabling a catalytic synthesis of unprotected γ-aryl primary amines (eq 31).[28] In all of the above C–H alkylation reactions, $TBAN_3$ was found to greatly outperform more commonly used HAT catalysts such as quinuclidine and tri(isopropyl)silanethiolate.

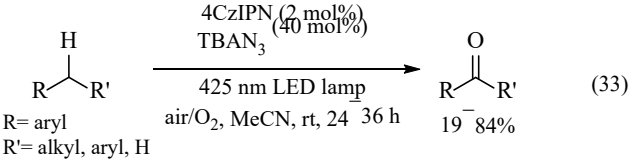


(31)

Hydrogen atom transfer catalysis with azide ion from $TBAN_3$ has also been exploited in the photoredox-catalyzed oxidation of alcohols (eq 32) and alkylarenes (eq 33) to give ketone (or aldehyde) products.[29] C–H abstraction by $N_3^{\bullet}$ followed by capture of the carbon-centred radicals with O_2 are key mechanistic steps in these processes.

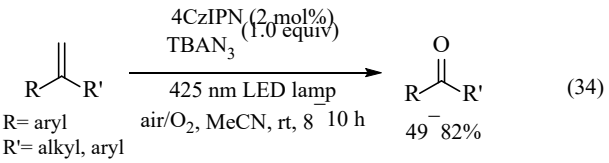


(32)



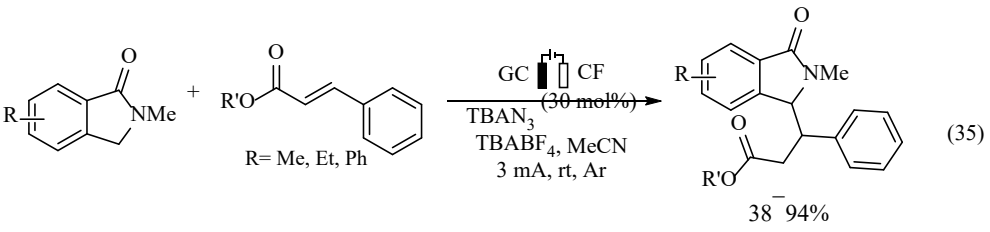
(33)

α-Substituted styrenes were also viable substrates in this ketone-forming process, albeit with stoichiometric $TBAN_3$, providing a practical alternative to ozonolysis (eq 34).[29] Here, addition of $N_3^{\bullet}$ to the C=C bond was envisaged to precede radical capture with O_2, although the precise mechanism of ketone formation is unclear.



(34)

Azidyl radical formation from $TBAN_3$ can also be achieved electrochemically *via* anodic oxidation, and this strategy has been used for the α-C–H amidoalkylation of γ-lactams, with various radical acceptors such as cinnamates, acrylates, and acrylonitrile (eq 35). Again, the $N_3^{\bullet}$ radical is thought to activate the α-C–H bond by hydrogen atom transfer, with HN_3 reacting at the cathode to evolve H_2 gas and regenerate the azide ion catalyst. *ortho*-Divinyl arenes were also exemplified as suitable radical acceptors, leading to spirocyclic scaffolds *via* tandem, sequential inter-intramolecular addition.[30]



(35)

References

[19] Wang, C.-G.; Chong, A. M. L.; Lu, Y.; Liu, X.; Goto, A. *Chem. Eur. J.* **2019**, *25*, 13025.

[20] Ochs, J.; Veloso, A.; Martínez-Tong, D. E.; Alegria, A.; Barroso-Bujans, F. *Macromolecules* **2018**, *51*, 2447.

[21] Kataoka, Y.; Kohsaka, Y.; Kitaura, T.; Domae, S.; Ishihara, S.; Kitayama, T. *Polym. Chem*. **2017**, *8*, 3858.

[22] Chen, Y.; Liu, B.; Liu, X.; Yang, Y.; Ling, Y.; Jia, Y. *Org. Process Res. Dev*. **2014**, *18*, 1589.

[23] Brown, M.; Aljarah, M.; Asiki, H.; Leung, L. M. H.; Smithen, D. A.; Miller, N.; Nemeth, G.; Davies, L.; Niculescu-Duvaz, D.; Zambon, A.; Springer, C. *Org. Process Res. Dev.* **2021**, *25*, 148.

[24] Brandt, J. C.; Wirth, T. *Beilstein J. Org. Chem*. **2009**, *5*, 30.

[25] Xie, A.; Cao, M.; Feng, L.; Dong, W. *J. Chem. Res*. **2013**, *37*, 665.

[26] Ryder, A. S. H.; Cunningham, W. B.; Ballantyne, G.; Mules, T.; Kinsella, A. G.; Turner-Dore, J.; Alder, C. M.; Edwards, L. J.; McKay, B. S. J.; Grayson, M. N.; Cresswell, A. J. *Angew. Chem*. *Int. Ed.* **2020**, *59*, 14986.

[27] Grayson, J. D.; Cresswell, A. J. *Tetrahedron* **2021**, *81*, 131896.

[28] Askey, H. E.; Grayson, J. D.; Tibbetts, J. D.; Turner-Dore, J. C.; Holmes, J. M.; Kociok-Kohn, G.; Wrigley, G. L.; Cresswell, A. J. *J. Am. Chem. Soc.* **2021**, *143*, 15936.

[29] Shee, M.; Singh, N. D. P. *Adv. Synth. Catal*. **2022**, *364*, 2032.

[30] Sim, J.; Ryou, B.; Choi, M.; Lee, C.; Park, C.-M. *Org. Lett.* **2022**, *24*, 4264.