PART I

CLICK CHEMISTRY STRATEGIES AND DECOUPLING

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1

PARADIGM AND ADVANTAGE OF CARBOHYDRATE CLICK CHEMISTRY STRATEGY FOR FUTURE DECOUPLING

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1.1 INTRODUCTION

When discussing click chemistry, the exceptionally successful methodology of connecting molecules, it seems natural to look at ways of disconnecting them. Thus, while preparing a symposium on applications of the click chemistry in carbohydrates, we began thinking about effective methods of disconnecting molecular units from each other. It turns out that the number of options is rather limited. We reasoned that the need for such reactions must be rather rare. However, it is easy to list several situations that require decoupling after certain experiments or procedures had been completed. Recently, we discussed circumstances calling for a design of coupling of the molecular units that takes into account a future necessity for the decoupling of these units [1]. The review lists almost a dozen such situations. Examples include releasing of the radio part from the radiotherapeutic or the chemo part from the chemotherapeutic after the treatment had been completed; decoupling of molecular units to enable or facilitate analytical procedures; decoupling various constructs from the surface either to produce a specific structure on the surface or to release a product from the surface after its special properties had been taken advantage of; and cleavage of the synthesis's product from the solid support.

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For a variety of reasons, coupling is performed much more often than decoupling. The language gives strong support to this notion. While there are at least five words describing various types of coupling processes leading to the increase in the molecular weight (bioconjugation, derivatization, labeling, ligation, tagging), there are only two words describing decoupling processes (cleavage, scission). There are, additionally, at least three words whose negation is a proper word (coupling, protection, connection).

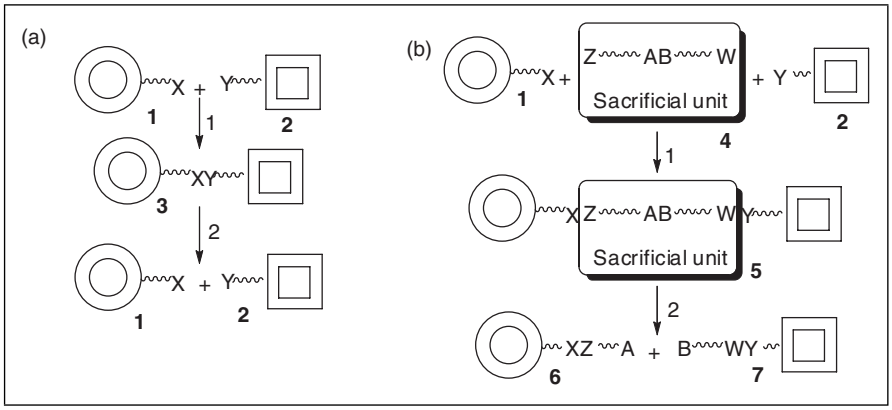
Let us consider possible protocols of coupling molecular units when it is known that the decoupling will be necessary later on. Let the molecules of interest potentially include large biomolecules. One obvious option is to couple molecular units by taking advantage of the click chemistry reactions, and later, utilize processes that are the reverse of the click reactions. Unfortunately, most click processes are not reversible or the retro reactions require conditions that cannot be applied to most (bio)macromolecular structures. Recently, Bielawski and coworkers [2] published an interesting paper showing that in the presence of ultrasound the popular click products, cyclic triazoles, can be transformed back to an azide and an alkyne. However, at this point, it seems unlikely that the ultrasound-generated reverse Huisgen cycloaddition process can find a broad application.

Since click reactions are usually not reversible, one has to develop other strategies. At least, two potentially successful strategies can be devised:

- One strategy asks for the use of reversible reactions (not belonging to click chemistry) such as formation of esters, amides, benzyl ethers during the coupling process and hydrolysis or debenzylation during the decoupling process (Scheme 1.1a). While such an option is often useful and effective, it is worth noting that hydrolysis of a specific ester or amide group from a construct containing protein(s) with many peptide bonds or polysaccharide with many acetal and/or ester groups may be problematic. The same applies to debenzylation, which may not be sufficiently regio- or chemoselective for various constructs.
- An alternative strategy asks for the introduction of a unit that is coupled (preferably via the click chemistry forming XZ and WB connections) to two (or more) molecular units and contains an easy cleavable functionality (AB) somewhere in the middle (Scheme 1.1b). We call such a unit a "sacrificial unit" containing a "sacrificial functionality." We coined the term for such chemistry—coupling and decoupling chemistry (CAD) [1]. The advantage of this option is that the sacrificial functionality (AB) can be tailor-made for specific molecular units; that is, it can be a functionality that is not found in the molecular units and thus can be safely decoupled when needed.

A construct **5** containing a sacrificial functionality can be synthesized on a step-by-step basis that comprises the introduction of appropriate linkers and other necessary components of sacrificial units. However, taking advantage of the pre-synthesized sacrificial units **4** equipped with all the required linkers, as shown in Scheme 1.1b, seems to be a better approach.

First, let us discuss the requirements of the reactive groups Z and W which are to connect the sacrificial unit to (macro)molecules of interest. Of course, the choice



SCHEME 1.1 Possible approaches to the issue of future decoupling of connected molecular units: (a) use of reversible reactions; (b) use of sacrificial units.

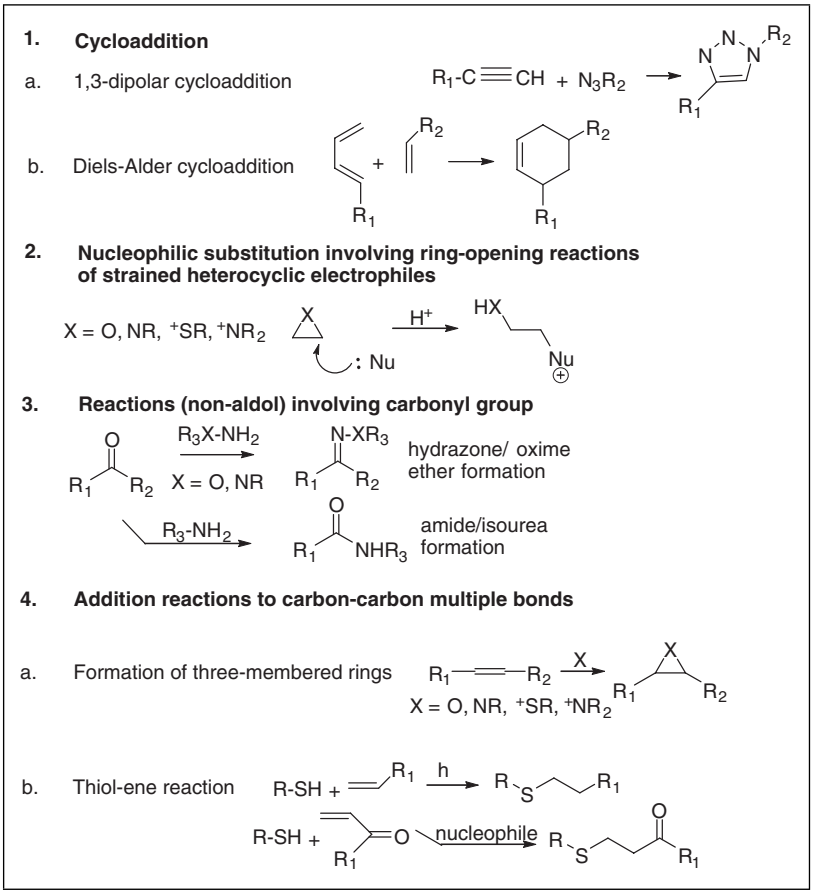
of Z and W depends very strongly on the type of available X and Y groups and on reactivity of the various other functional groups present in molecular units **1** and **2**. It must be emphasized that the click chemistry should be used to connect the molecular units whenever possible. Besides all the virtues of the click chemistry reactions, the products of these reactions are, as a rule, very stable and we may be sure that unexpected and undesired disconnections will not happen.

While experts disagree on the exact scope of the click chemistry and what reactions truly belong to the click chemistry domain [3], it is probably worth at least listing the chemical reactions considered to belong there. Carvalho, Field, and coworkers recently reviewed applications of Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) "click chemistry" in carbohydrate drug and neoglycopolymer synthesis [4]. In the review, they list four categories of "click reactions" (Scheme 1.2).

The Huisgen addition of azides to terminal alkynes (1A) is, by far, the most popular click reaction. The second most often employed click reactions is the addition of thiols to double (and triple) bonds. Depending on the substituents of the double bond, the reaction mechanism can be free radical or nucleo or electrophilic. Only a few of other reactions listed by Carvalho and Field [4] fulfill the conditions that open a door to a "distinguished" club of click processes. There are two more reviews of click-related carbohydrate chemistry. One of them discusses the impact of click chemistry on the carbohydrate-based drug development and glycobiology [5]. The other one, recently published by Lucas and coworkers [6], describes novel developments of click chemistry in polysaccharides. The authors are mainly focused on the catalyzed version of Huisgen 1,3-dipolar cycloaddition between terminal alkynes and azides.

Interestingly, the list of click reactions utilized in polymer chemistry [7] (Scheme 1.3) is slightly different from the one outlined in Reference 4.

Luckily, there are more than one click processes. It is important because taking advantage of a single click process (to form XZ and WY connections—see Fig. 1.1b) is rather problematic. Assume that a square is a functionality forming the



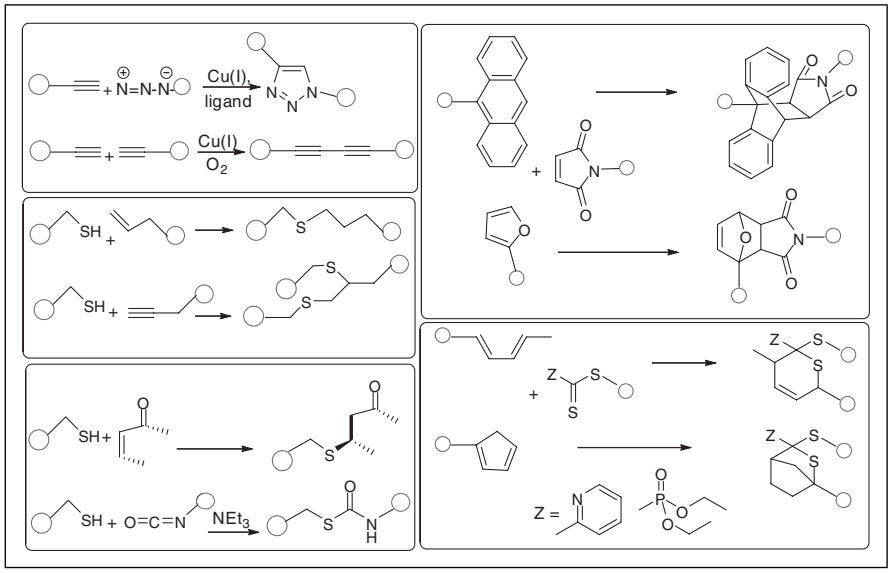
SCHEME 1.2 Click reactions according to Carvalho, Field, et al. [4].

click reaction product with the "open square." Figure 1.4 shows clearly that both functionalities involved in a click process should not be attached to a sacrificial unit. In such a case, the molecule of a sacrificial unit will react with another molecule of a sacrificial unit to form a polymer (Scheme 1.4a). Even if the same functionalities are attached to the sacrificial units, certain amounts of undesired symmetrical products will be formed (Scheme 1.4b).

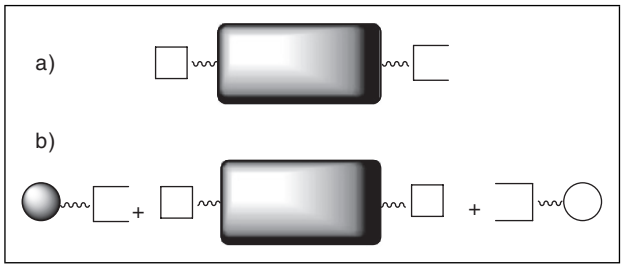
Employing two different click reactions solves the problem (Scheme 1.5).

What chemical functionalities can act as sacrificial functionalities? The answer depends mainly on the structure of molecular units that are to be coupled. If one (or more) of the molecular units to be connected is a (poly)saccharide, such functionalities as acetals and esters should be rather avoided since polysaccharides usually have an abundance of such groups.

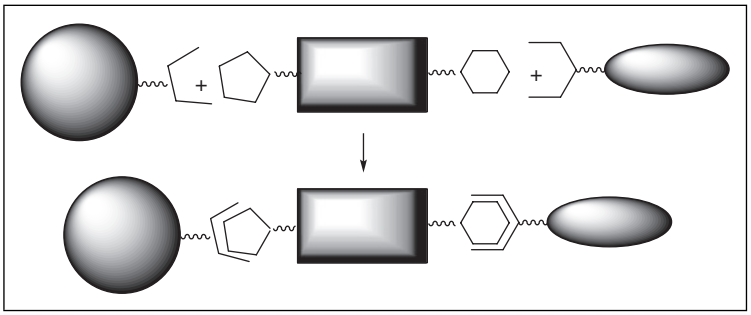
Let us take a look at a few applicable examples of click chemistry reactions. It has been already more than 10 years since the concept was introduced [8]. Since then,



SCHEME 1.3 Click reactions in polymer chemistry according to Becer, Schubert, et al. [7].



SCHEME 1.4 The use of the same click process on both sides of the sacrificial unit: (a) different functionalities attached to the sacrificial unit; (b) same functionalities on both sides of the sacrificial unit.



SCHEME 1.5 Use of two different click reactions.

thousands of papers employing click reactions have been published. Thus, there is a plethora of data describing the connection of large and small, natural and non-natural molecules equipped with a variety of functional groups. For many click reactions, their scope is well known and it is relatively easy to choose the one that will be effective at the given circumstance. The following carbohydrate examples are meant to serve as an illustration only.

1.2 COUPLING USING HUISGEN DIPOLAR CYCLOADDITION

Let us begin with [3 + 1] dipolar cycloaddition of azides to acetylenes. These reactions are usually very easy to perform, particularly since the use of copper-containing catalysts was introduced [9,10]. Since copper salts are not always applicable, Bertozzi et al. [11] and Boons et al. [12] developed methodologies employing no copper catalyst, but offering most of the advantages of CuAAC reactions. Both methodologies use a substituted cyclooctyne.

As we already mentioned, the Cu(I)-catalyzed [3 + 1] dipolar cycloaddition of azides to acetylenes (CuAAC) is, by far, the most popular click process. A few years ago, Marmuse, Nepogodiev, and Field [13] synthesized starch fragments analogs. The results of 1,3-dipolar cycloaddition of dipropargylated maltosides and azidoglucosides are shown in Figure 1.1. All reactions were carried out using $(Ph_3P)_3{\cdot}CuBr$

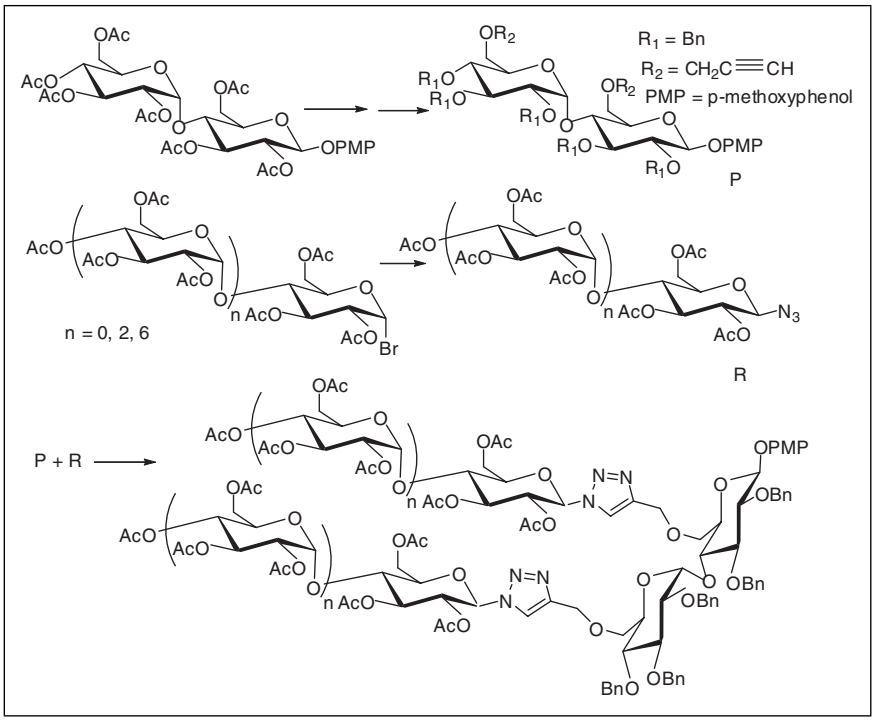


FIGURE 1.1 Example of rapid assembly of starch fragment analogs using CuAAC "click chemistry."

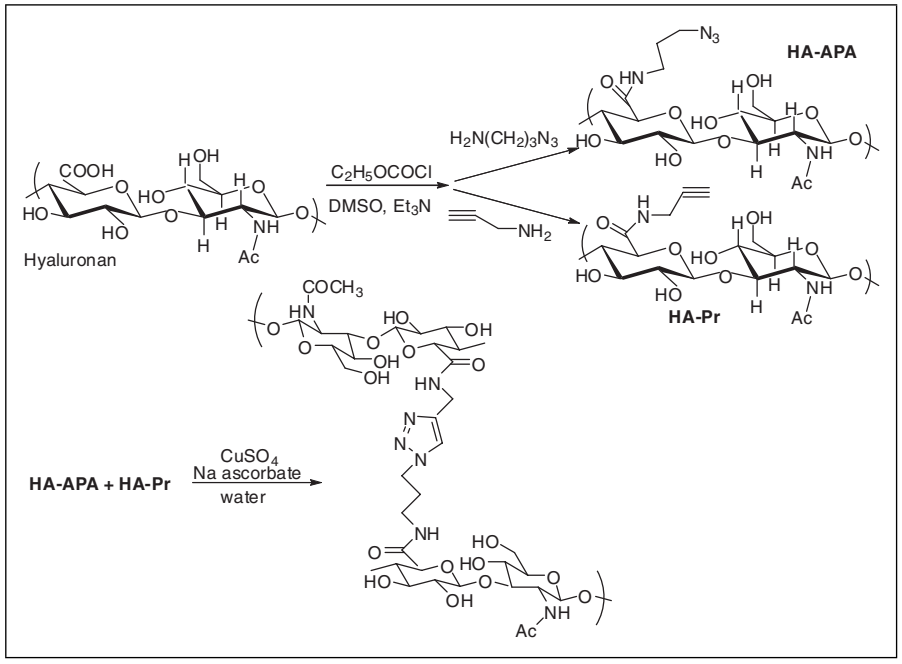


FIGURE 1.2 Use of CuAAC reaction as cross-linking to form HA-based hydrogels.

as a catalyst in the presence of DIPEA as a base for a relatively long reaction time (12 hours) at room temperature. The yields of cycloaddition reactions varied between 65% and 27%, decreasing with increasing length of the azidooligosaccharide chain.

Huerta-Angeles et al. [14] also synthesized truly large molecules by taking advantage of the Cu(I)-assisted AAC. Actually, they used the formation of the cyclic triazole as the cross-linking reaction to form hyaluronan (HA)-based hydrogels with well-defined 3D-molecular architecture for potential application in tissue engineering. Figure 1.2 shows the relevant chemistry.

Maillard and coworkers [15] synthesized a series of porphyrins each containing three glycosyl units using microwave activation. The products were designed as photodynamic therapy (PDT) agents. They are linked by a triazole group to chromophore in the aim to target tumor cells overexpressing lectin-type membrane receptors. Figure 1.3 shows the synthesis of the constructs. Importantly, zinc(II) cations in porphyrins are sufficiently stable under Cu-assisted azide acetylene cycloaddition click reaction conditions to avoid replacement by a copper(II) ions. The products turned out to be less active than analogs containing no triazole rings. The yields were very reasonable.

Chapleur and coworkers [16] synthesized more than a dozen neoglycopeptides via a direct functionalization of cysteine. The employed monosaccharides include acetylated and unprotected glucose, mannose, galactose, and 6-deoxy-6-fluoroglucose. Interestingly, the reaction of the fluoro compound equipped with the azido group and

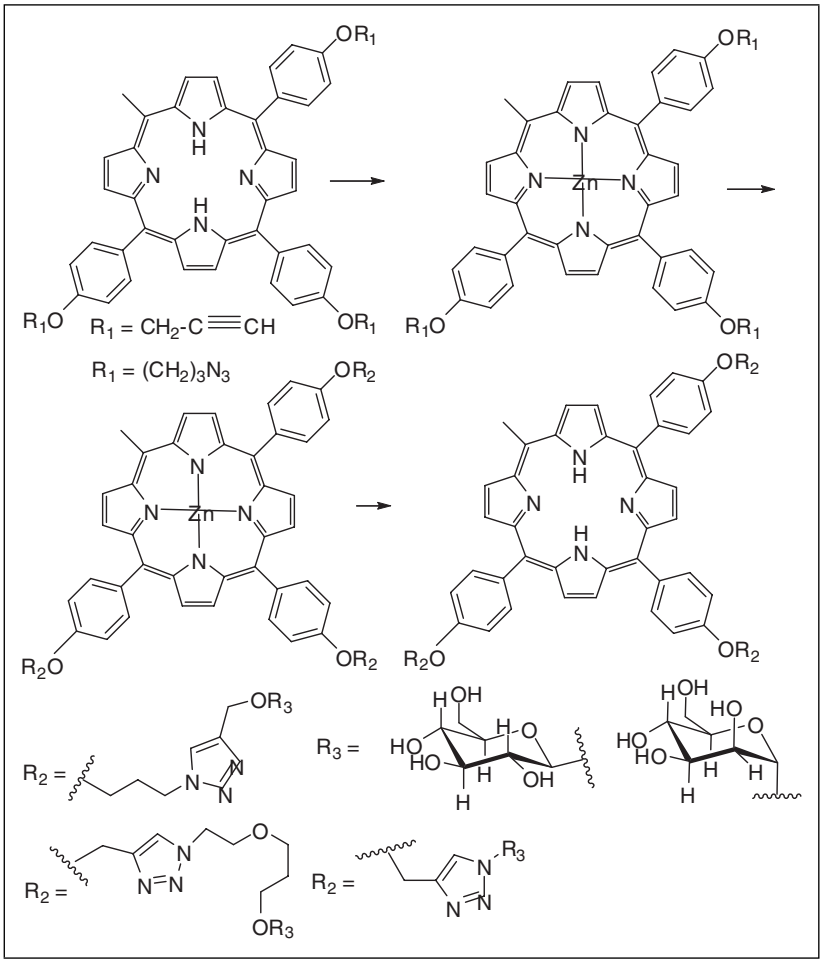


FIGURE 1.3 Porphyrin-based constructs synthesized by Maillard et al.

the tetrapeptide, Arg-Gly-Asp-Cys (RGDC) substituted with the propargyl group gave the highest yield. The synthetic strategy is shown in Figure 1.4.

1.3 COUPLING USING THIOL-ENE COUPLING CLICK CHEMISTRY

In recent years, another reaction, thiol-ene coupling (TEC), joined the exclusive club of click chemistry processes [17–19]. It is worth noting that the TEC reaction has been known for more than 100 years [20]. The addition of thiols to simple alkenes (and alkynes) is almost always free radical and can be initiated either thermally or photolytically.

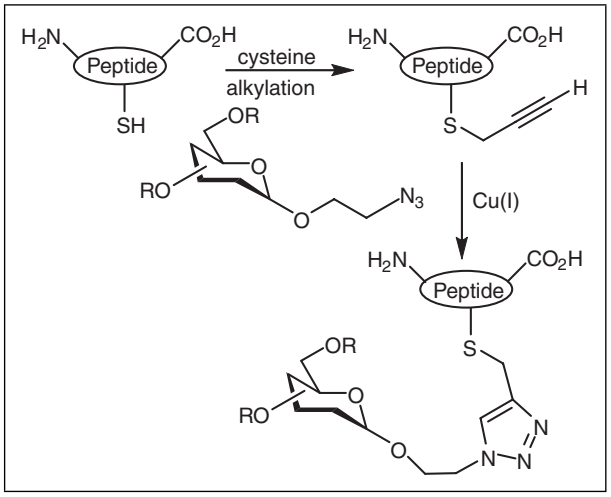


FIGURE 1.4 Chapleur et al.'s synthetic strategy for neoglycopeptides construction.

Fiore, Marra, and Dondoni [21] took advantage of photoinduced coupling of anomeric sugar thiols with sugar alkenes to synthesize 1,6-linked *S*-disaccharides in good to excellent yields (76–92%) and high diastereoselectivities (up to 99%). Figure 1.5 shows a typical example of the synthesized disaccharide.

Stenzel and coworkers [22] synthesized a block copolymer containing di(ethylene glycol) methyl ether methacrylate (DEGMA) and 2-hydroxyethyl methacrylate (HEMA) by reversible addition-fragmentation chain transfer (RAFT) polymerization, which was subsequently modified with glucothiose. Glucothiose was introduced via UV-promoted TEC process. The resulting glycosylated block copolymer led to the formation of thermoresponsive micelles, a potential candidate for targeted drug delivery. Figure 1.6 illustrates the methodology.

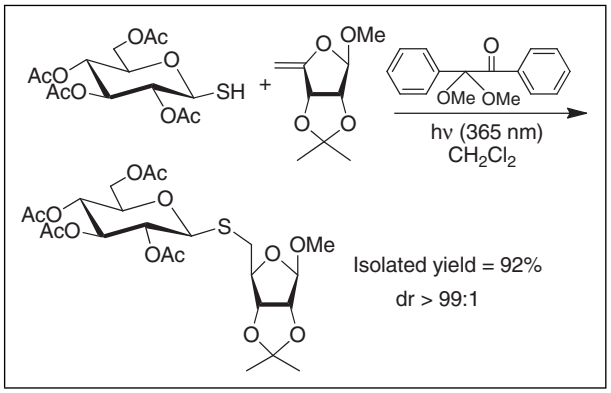


FIGURE 1.5 Example of Dondoni et al.'s [21] photoinduced TEC as a click ligation tool for thiodisaccharide synthesis.

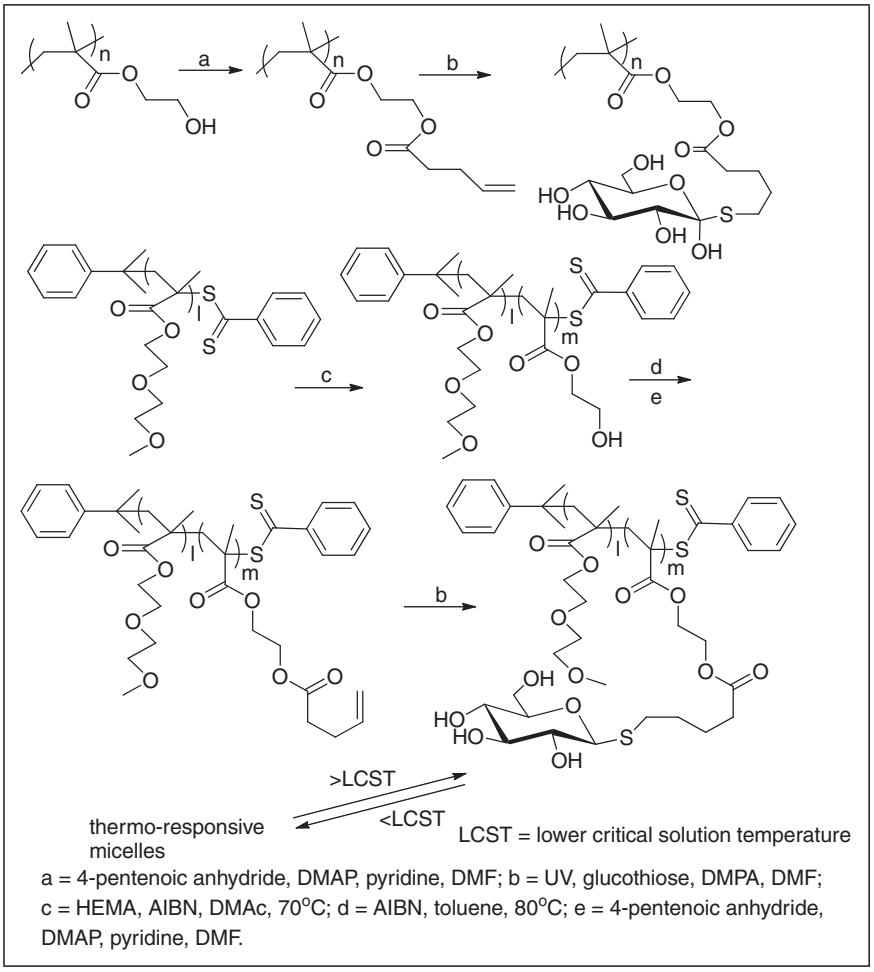


FIGURE 1.6 Stenzel et al.'s [22] synthetic strategies for the preparation of glucose functionalized (co)polymers.

Most Michael additions of thiols to double bonds conjugated to carbonyl and similar groups are reversible. Nevertheless, some of the Michael additions of thiols have been shown to offer stable and easy-to-isolate products. For example, Chandrasekaran et al. [23] synthesized several thioglycosides and other thiosugar analogs using benzyltriethylammonium tetrathiomolybdate [$(BnNEt_3)_2MoS_4$] or ammonium tetrathiomolybdate as a sulfur-transfer reagent. The reagent reacts with sugar halides to give sugar disulfides, which then undergo reductive cleavage *in situ* to provide the corresponding thiolates, followed by Michael addition to give the corresponding thioglycosides or other monosaccharides containing sulfur. Alternatively, the authors also made sugar enones to react with disulfides to form thiosugars, often with

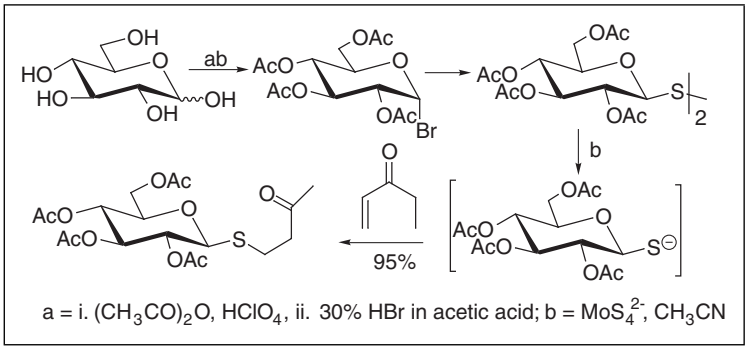


FIGURE 1.7 Thio-glucoside forming tandem sulfur transfer/reduction/Michael addition assisted by tetrathiomolybdate [23].

excellent diastereoselectivity (but sometimes the ratio of diastereoisomers was 1:1). The process is simple, offers good to excellent yields, and is performed in one pot. While the authors did not consider the process to belong to click chemistry, it definitely shows most features of the click chemistry. Figures 1.7 and 1.8 illustrate the methodology.

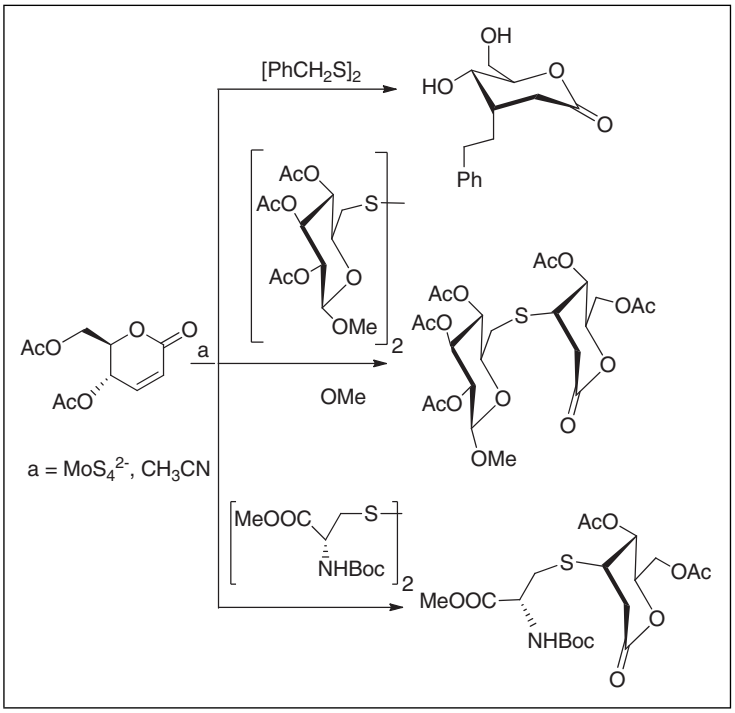


FIGURE 1.8 Synthesis of 3-deoxy-3-thiosugar derivatives via Michael addition according to Reference 23.

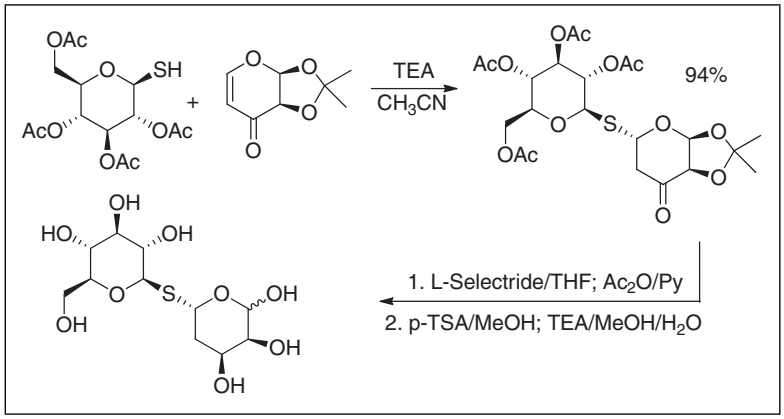


FIGURE 1.9 Witczak et al.'s [24] synthesis of thiodisaccharide using Michael addition of monosaccharide with a thiol functionality.

Witczak et al. [24] synthesized an interesting thiodisaccharide presented in Figure 1.9. The synthesis takes advantage of a click chemistry reaction, the (Michael) addition of a thiol to the enone system.

1.4 PROCESSES WHERE BOTH CuAAC AND TEC CLICK CHEMISTRIES ARE USED

Perrier et al. [25] synthesized highly branched and hyperbranched glycopolymers via RAFT polymerization and click chemistry which includes Cu(I)-catalyzed Huisgen 1,3-cycloaddition of azides and alkynes (CuAAC), thiol-ene addition, and thiol-yne addition. The authors explain that in some circumstances, the drawback of the RAFT approach is the poor availability and compatibility of specific functional monomers. They circumvent the problem by introducing functionalities via post-polymerization modification employing click chemistry. The TEC reactions were performed in the presence of HCl using glucothione sodium salt as the carbohydrate component and 2,2-dimethoxy-2-phenylacetophenone (DMPA) as a photoinitiator, under UV at room temperature. 2-azidoethyl-β-D-galactopyranoside served as a carbohydrate component of CuAAC reactions. Figure 1.10 shows the relevant products.

Haddleton and coworkers [26] also synthesized polymers capable of forming click products deriving from both CuAAC and thiol-ene reactions. They took advantage of the catalytic chain transfer polymerization (CCTP) to form alkyne-functional macromonomers which were subsequently functionalized with sugar azides (CuAAC) and thiols. Interestingly, the addition of thiol was a Michael-type reaction and benzyl mercaptan in the presence of dimethylphenylphosphine (DMPP) was employed as a thiol. Figure 1.11 shows this convenient synthesis of end-functionalized glycopolymers and the utilized carbohydrate azides.

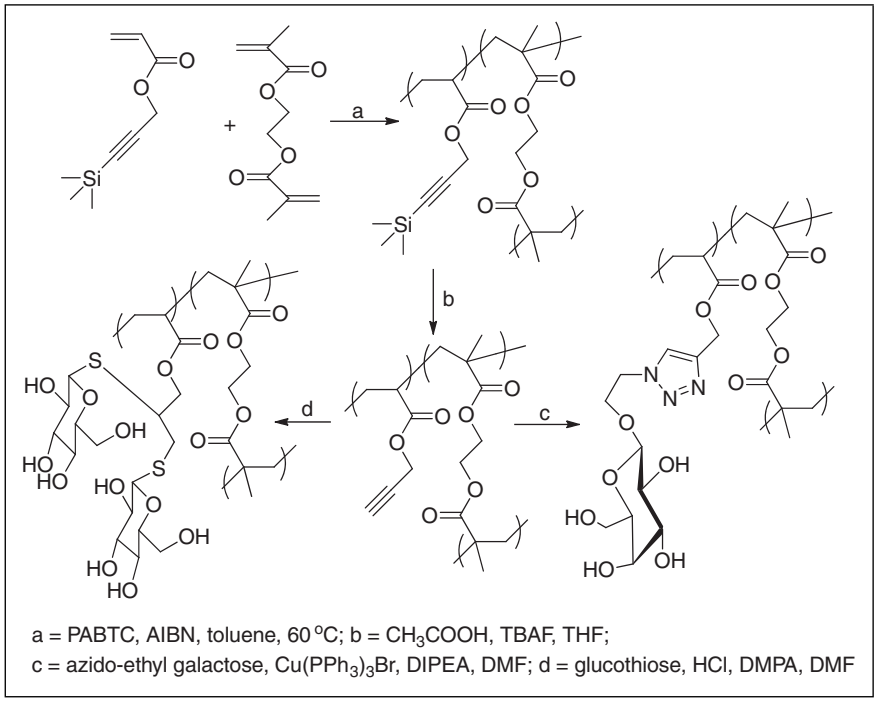


FIGURE 1.10 Synthetic strategy for the preparation of highly branched glycopolymers devised by Perrier et al. [25].

Marra, Dondoni, et al. [27] also use both CuAAC and TEC chemistries when synthesizing calix[4]arene-based *S*-glycoclusters. They describe the dual clustering at the upper and lower rim of a calix[4]arene with two different sugars (galactose and glucose) via sequential copper(I)-catalyzed azide–alkyne cycloaddition and photoinduced TEC. Figure 1.12 illustrates the approach.

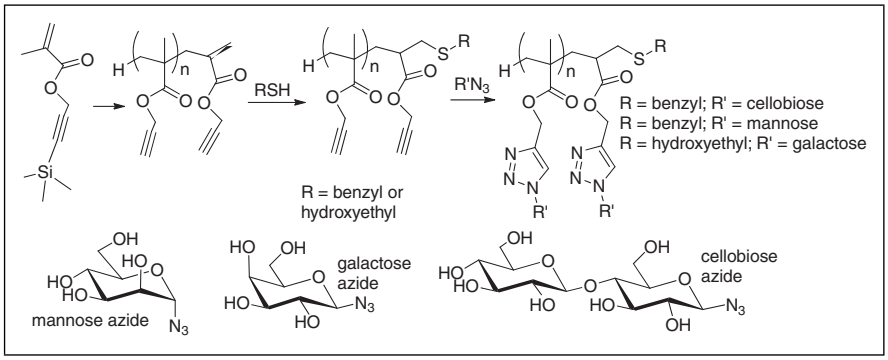


FIGURE 1.11 Haddleton and coworkers' [26] synthetic approach to end-functionalized glycopolymers and structures of utilized carbohydrate azides.

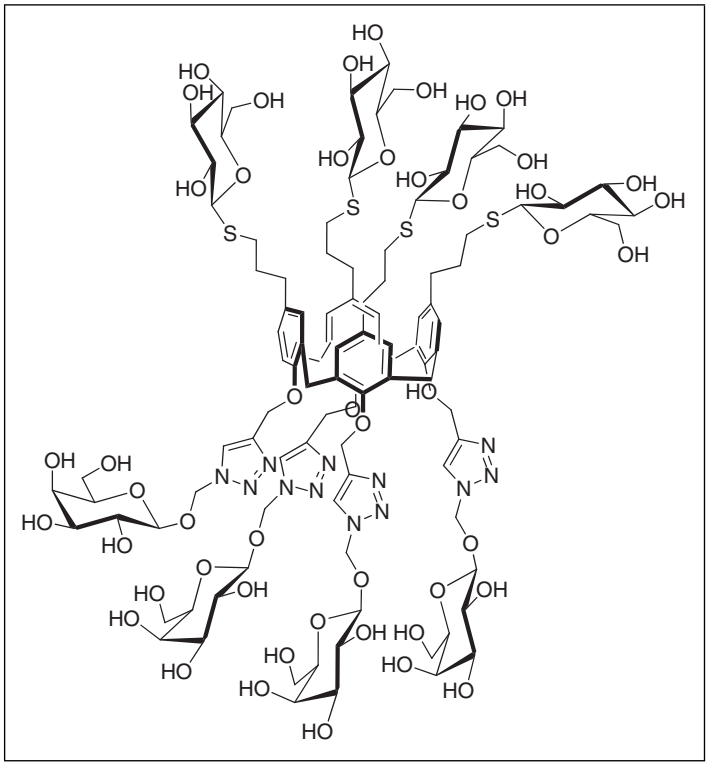


FIGURE 1.12 Structure of one of the dual clusters at the upper and lower rim of a calix [4] arene with two different sugars (galactose and glucose) synthesized by Dondoni et al. [27].

1.5 DECOUPLING

It should be very strongly emphasized that the number of literature examples of decoupling large molecules is very limited. At this point, we must rely on examples of decoupling in which small molecules were split to smaller fragments. We hope that soon there will be many examples of decoupling reactions applied to large molecules consisting of two or, at least, one macromolecule. It will help researchers to understand the scope and limitations of various reactions and will minimize guessing (or extrapolating) whether a specific coupling or decoupling reaction is applicable in a specific situation.

The following examples show some of the decoupling which includes carbohydrates sacrificial functionalities that can be found in the literature.

1.5.1 Enzymatic Cleavage

Let us start with decoupling processes that are triggered by enzymes. It is well known that enzymes are highly sensitive to the structure of reactants. Thus, one has to be

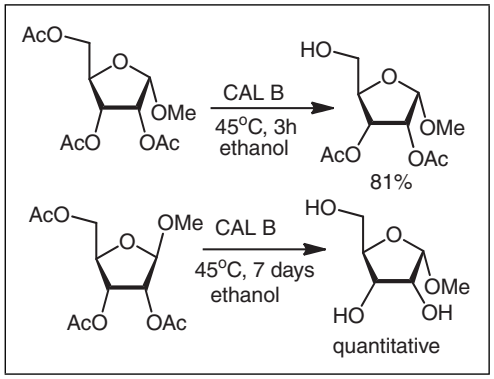


FIGURE 1.13 Highly regioselective and exhaustive deacetylation using lipases described by Iglesias and coworkers [28].

exceptionally cautious when trying to expand the use of specific enzymes to other categories of compounds. It applies particularly to reactions performed on small molecules. It may not translate well to much larger (macro) molecules even when the specific part of the molecule is the same. We can only hope that with time our understanding of specific enzymatic processes will improve and there will be the abundance of literature data enabling successful application of enzymatic decoupling to specific situations. The following examples derive from small molecule chemistry, but hopefully will find application in decoupling processes as well.

Iglesias and coworkers [28] studied alcoholysis of methyl 2,3,5-tri-*O*-acetyl-α-D-ribofuranoside and methyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside using the *Candida antarctica lipase* B (CAL B). The reaction of the α-anomer lead to the isolation of the monodeacetylated product. The reaction of the β-anomer lead to a variety of partially deacetylated products but eventually provided the fully deacetylated product in a quantitative yield (Fig. 1.13).

Italian and Spanish researchers [29] performed selective hydrolysis of peracetylated β-monosaccharides using immobilized lipases from different sources [*Thermomyces lanuginosa* (TLL), *Aspergillus niger* (ANL), and *Candida antarctica* B (CAL B)]. Figure 1.14 shows some of the results. The shown yields represent isolated yields. The results illustrate a crucial role played by the procedure applied to the immobilization of enzymes. The paper is an example of a larger series of papers devoted to studying regioselectivity of various enzymatic hydrolyses [30] and references quoted therein. The acquired knowledge was employed to a very elegant synthesis of linear oligosaccharides by a simple monoprotective, chemoenzymatic approach.

Baba and Yoshioka [31] prepared 1-β-*O*-acyl glucuronides of three nonsteroidal, anti-inflammatory drugs, diclofenac (DF), mefenamic acid (MF), and (*S*)-naproxen (NP) (their structures are shown in Fig. 1.15). Next, after some screening, they employed selected commercial enzymes—lipase AS Amano LAS: (from ANL), and porcine liver esterase (PLE). LAS hydrolyses the *O*-acetyl groups with high

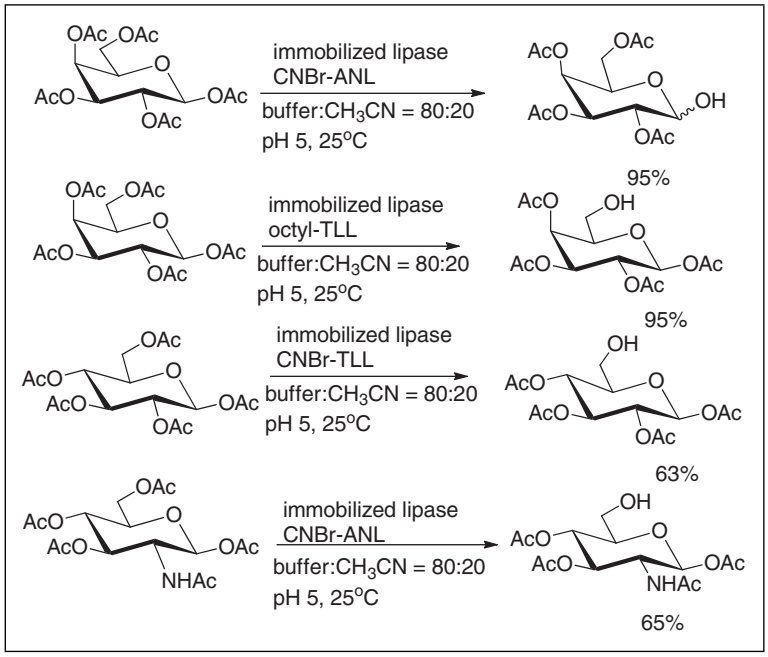


FIGURE 1.14 Specific and regioselective hydrolysis of different 1,2,3,4,6-penta-*O*-acetyl-D-glycopyranoses using immobilized lipases [29].

chemoselectivity to provide the methyl ester equipped with three OH groups and PLE hydrolyses the methyl ester groups with high chemoselectivity to provide glucuronic acid containing three acetyl groups. Any combination of two esters leads to high yields (90% or more) of glucuronic acids with unchanged substituent at the aglycone position (Fig. 1.15).

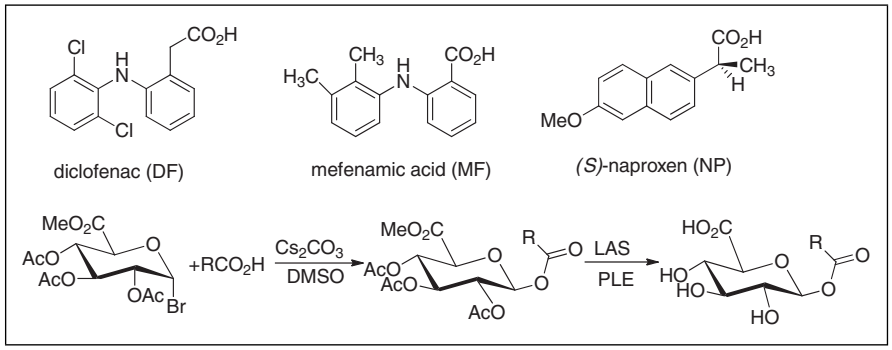


FIGURE 1.15 Chemo-enzymatic synthesis of 1-β-*O*-acyl glucuronides described by Baba and Yoshioka [31].

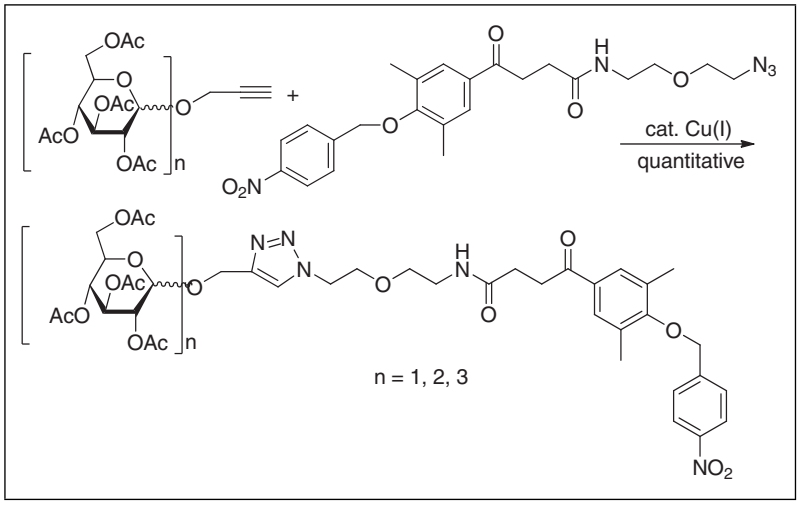


FIGURE 1.16 Maki and Ishida's [32] synthesis of compounds containing carbohydrate and photocleavable parts.

1.5.2 Photocleavage

Maki and Ishida [32] designed and synthesized photocleavable molecules for laser desorption ionization-mass spectrometry (LDI-MS). The authors envisaged that a photocleavable molecule, which affords an MS-detectable ion upon irradiation without matrix assistance, would simplify the ionization mechanism and be a reliable and selective labeling device for LDI-MS. As expected, the connection takes advantage of the click chemistry. The final step of the synthetic procedure is shown in Figure 1.16. The cleavage takes place under the laser pulse at 337 nm.

Ju and coworkers [33] designed and synthesized a 3′-modified photocleavable fluorescent nucleotide, 3′-*O*-allyl-dUTP-PC-Bodipy-FL-510 (PC-Bodipy, photocleavable 4,4-difluoro-4-bora-3α,4α-diaza-s-indacene), as a reversible terminator for DNA sequencing by synthesis (SBS). Figure 1.17 shows the design and synthesis of the product.

1.5.3 Chemical Cleavage

Manabe, Ueki, and Ito [34] developed a very convenient method of deprotecting propargyl ethers using the samarium–amine–water system. The method requires little time (usually 15 minutes), reactions take place at room temperature, offer good yields, and chemoselectivity (Fig. 1.18). The method was applied to the solid state synthesis of oligosaccharides (Fig. 1.19).

At this point, it is impossible to say if the same decoupling can be applied to a propargyl group in which one of the hydrogen atoms (in either of the two possible positions) was replaced with a large (macromolecular) substituent.

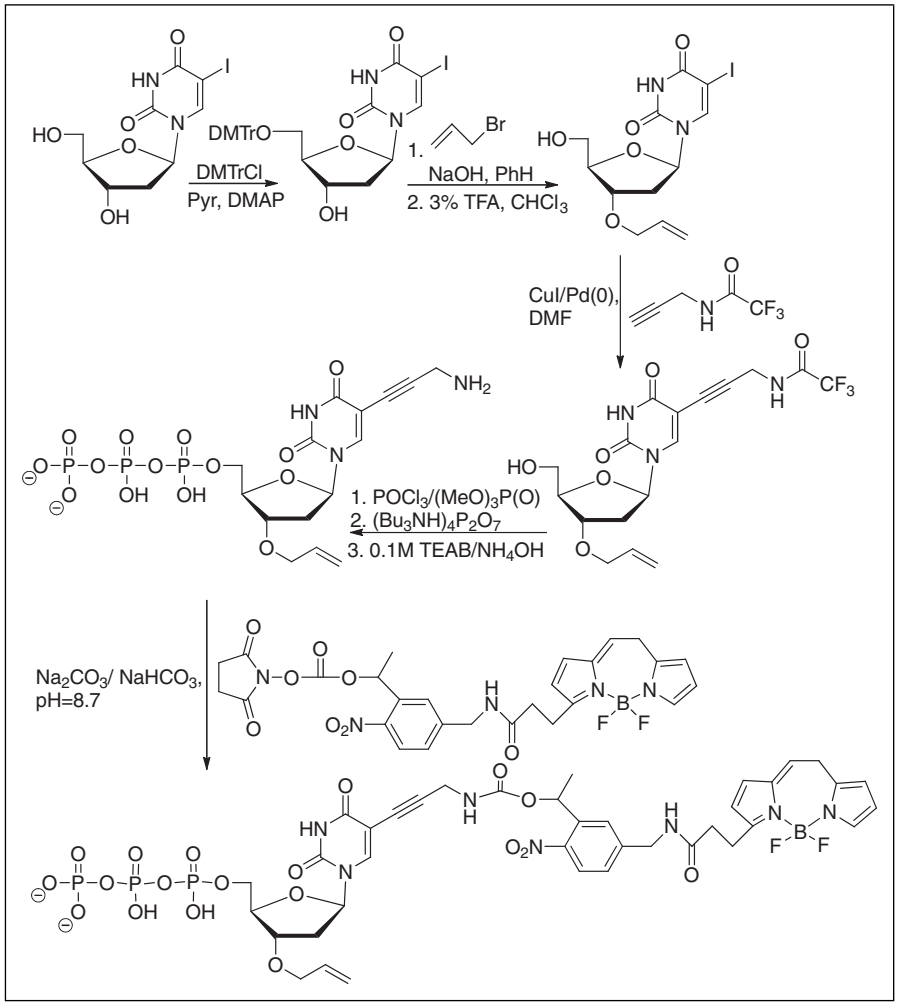


FIGURE 1.17 Ju and coworkers' [33] design and synthesis of a 3′-*O*-allyl photocleavable fluorescent nucleotide as a reversible terminator for DNA sequencing by synthesis.

Chen and coworkers [35] developed a novel method of selective deacylation using dioxomolybdenum dichloride as a catalyst. The conditions are mild and the yields are very high. Figure 1.20 shows more spectacular examples of removal of acyl group in the presence of other protecting functionalities.

Padrón, Bermejo, and collaborators [36] used as simple reagent as *p*-toluenesulfonic acid (or 10-camphorsulfonic; CSA) to selectively cleave acetates in the presence of benzoates and *p*-bromobenzoates. The reactions are performed in DCM/methanol at 40°C and yields are high. The examples shown in Table 1.1 illustrate the methodology.

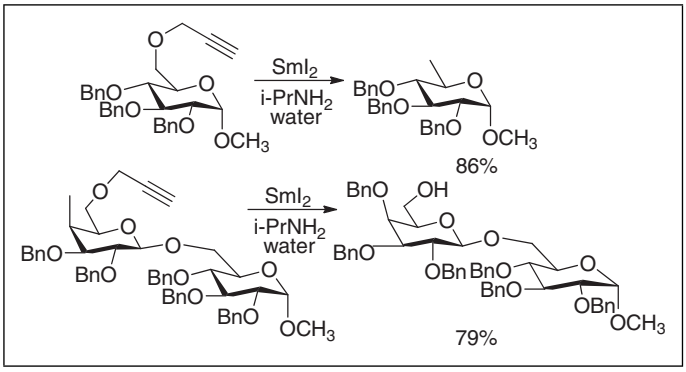


FIGURE 1.18 Examples of selective deprotection of propargyl ethers using samarium–amine–water system [34].

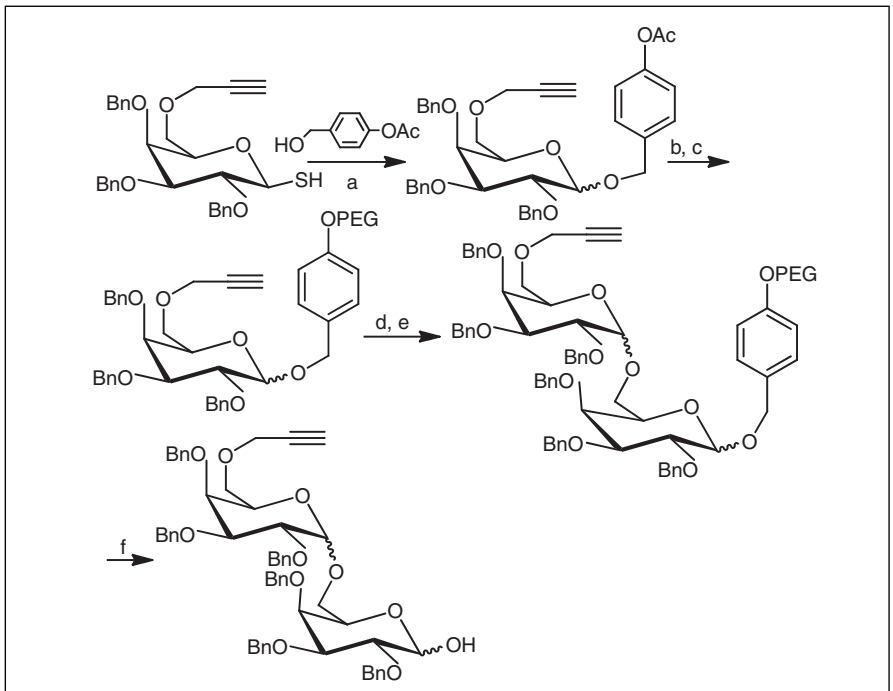


FIGURE 1.19 Polymer-supported disaccharide synthesis according to Manabe, Ueki, and Ito [34].

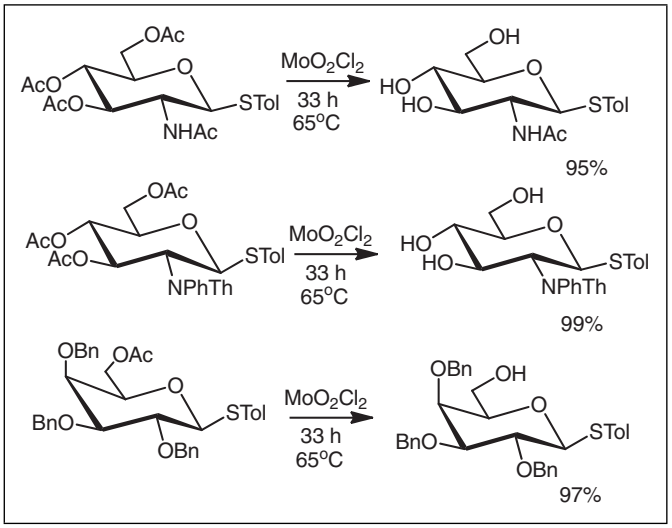
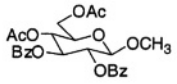
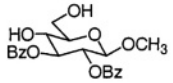
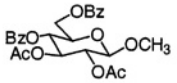
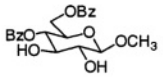
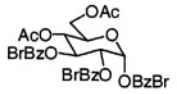
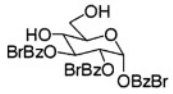
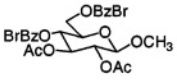
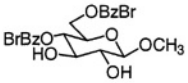
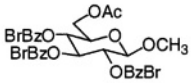
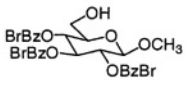
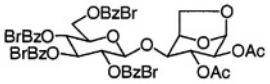
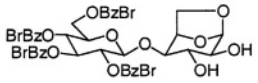


FIGURE 1.20 Effective deacetylation developed by Chen et al.

TABLE 1.1 Selective Deacetylation Described by Padrón, Bermejo et al.

Entry	Substrates	Conditions	Products[a]	Yield[b]
1		***p*-TsOH (2 equiv) 40°C, 7 h CSA (2 equiv) rt, 72 h**		91% 88%
2		***p*-TsOH (2 equiv) rt, 24 h**		65%
3		***p*-TsOH (2 equiv) rt, 24 h**		90%
4		***p*-TsOH (2 equiv) 40°C, 24 h**		70%
5		***p*-TsOH (1 equiv) 40°C, 24 h**		88%
6		***p*-TsOH (2 equiv) 40°C, 24 h**		70%

[a] All products were characterized by ^{1}H NMR and ^{13}C NMR.
[b] Isolated yields.
Source: Reproduced with permission from Reference 36.

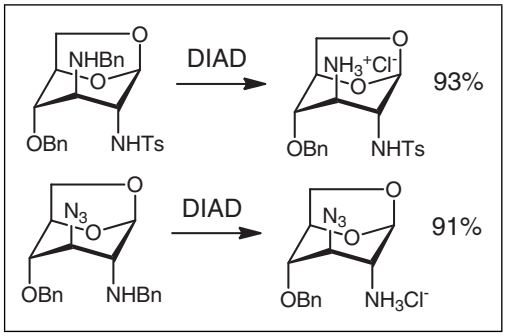


FIGURE 1.21 Selective N-debenzylation of benzylamines by DIAD according to Kroutil et al. [37].

Kroutil and collaborators [37] developed conditions enabling chemoselective cleavage of benzylamines in the presence of such functionalities as azide, *O*-benzyl, and *N*-tosyl using diisopropyl azidodicarboxylate (DIAD). Figure 1.21 shows some examples of this high-yielding methodology.

Spencer et al. [38] compared the rate of hydrogenation of benzyl ethers containing different substituents in the aromatic ring. The differences are significant. For example, the reaction of the compound with the benzyl group containing trifluoromethyl group in the para position is about five times slower than the reaction of a compound with unsubstituted benzyl group. Introduction of *t*-butyl group into the para position of the benzyl ether increases the rate of hydrogenation about 25 times. The researchers found that the naphthylmethyl (NAP) group is exceptionally selective. Figure 1.22 shows the carbohydrate examples.

It is worth adding that the NAP group can be introduced either using NAP bromide [38, 39] or by forming the cyclic naphthyl acetal followed by hydrogenation

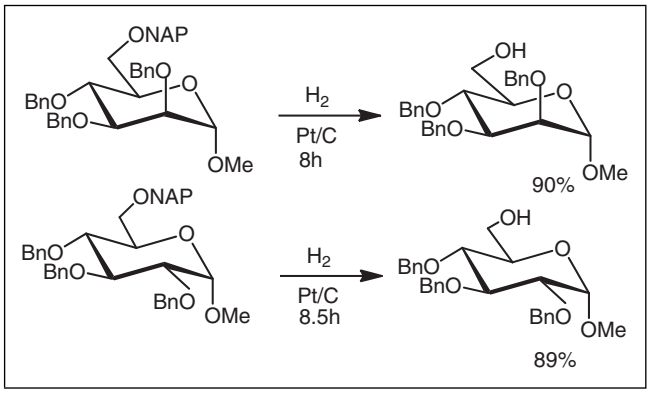


FIGURE 1.22 Selective removal of the NAP group in the presence of benzyl ethers according to Spencer et al. [38].

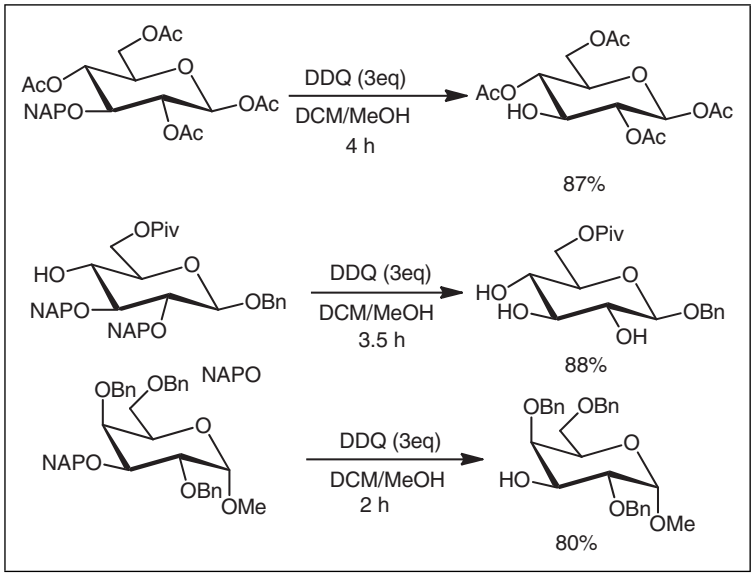


FIGURE 1.23 Selective removal of NAP groups in the presence of benzyl ethers using DDQ according to Matta et al. [39].

[40]. Interestingly, the NAP group can be cleaved also at room temperature using entirely different conditions than Spencer and coworkers. Matta et al. [39] developed a method based on DDQ. Figure 1.23 shows the conditions and yields. Recently, Boons et al. [41] took advantage of this approach when synthesizing an unusual phosphoglycopeptide derived from α-dystroglycan. Yields were equally high.

Kovensky and coworkers [42] demonstrated quantitative yields of the allyl group removal from the anomeric position of allyl galactopyranosiduronic acid derivatives. The authors employ a two-step procedure consisting of DABCO and $(Ph_3P)_3RhCl$ followed by mercuric-assisted cleavage. Their work is an excellent example of difficulties one often encounters when employing a specific reactant to a novel structure. It turned out that standard literature procedures lead to mixtures consisting of the starting material, the desired product, and a significant amount of the allyl group oxidation product. Most alternatives did not offer any improvement. Eventually, the researchers developed a very successful method as shown in Figure 1.24.

Recently, Finnish and Hungarian scientists [43] have shown the effectiveness of utilizing flow chemistry to deprotection of benzyl/benzylidene protected carbohydrates. While the required conditions (that were not optimized) include a relatively high pressure of hydrogen (40 bar) and elevated temperature (80°C), the method offers excellent yields and does not affect such protecting groups as acetates and silyl ethers. Figure 1.25 shows the results. The presented yields are isolated yields.

Das and collaborators [44] developed a method enabling an effective and mild removal of a trityl group in the presence of various protecting groups. The method employs silica-supported sodium hydrogen sulfate. Figure 1.26 shows the results.

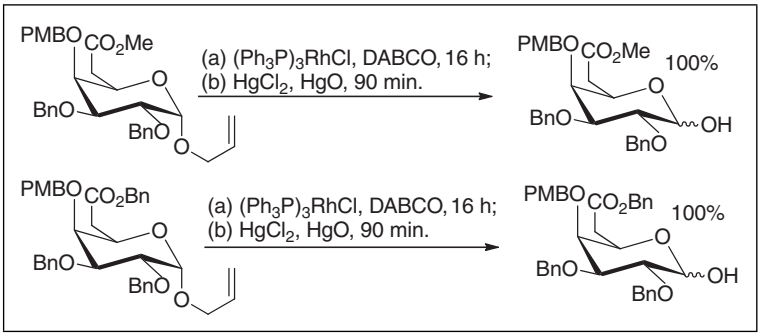


FIGURE 1.24 Barbier et al.'s [42] two-step method to remove the allyl group from allyl galactopyranosiduronic acid derivatives using DABCO and $(Ph_3P)_3RhCl$ followed by mercuric-assisted cleavage.

Sharma et al. [45] describe a novel, zirconium chloride-based methodology enabling a highly selective deprotection of *t*-butyldimethylsilyl (TBS) ethers in the presence of *t*-butyldiphenylsilyl (TPS) ethers. Figure 1.27 shows the only carbohydrate example from the paper. Other examples are equally impressive. While the difference between the TPS and TBS ethers seems to be very minute, one can accomplish a spectacular selectivity in deprotection of these species. However, without

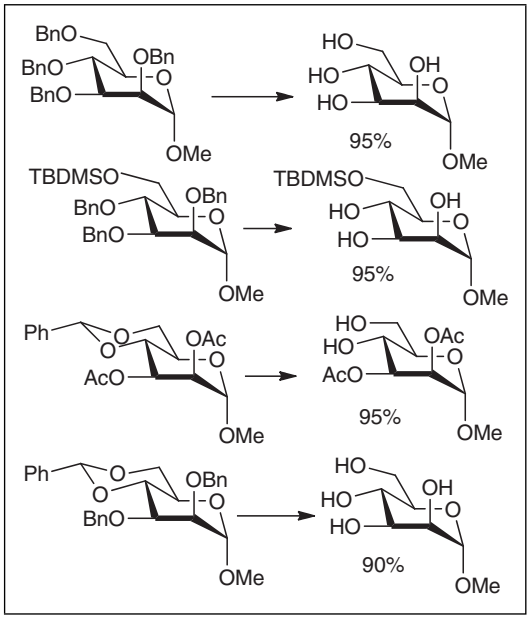


FIGURE 1.25 Application of flow chemistry to deprotection of benzyl-/benzylidene-protected carbohydrates [43].

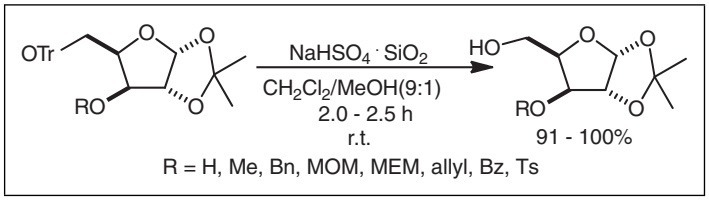


FIGURE 1.26 Chemoselective deprotection of trityl ethers using silica-supported sodium hydrogen sulfate developed by Das et al. [44].

appropriate experiments, it is impossible to say whether similar selectivity is achievable when, for example, one of the hydrogen atoms in a *t*-butyl group is replaced with a large macromolecular unit.

Another accomplishment in deprotection of silyl ethers has been developed by Chen, Le, Lin, and coworkers [46] who deprotect primary silyl ethers in the presence of the secondary ones and other protecting groups such as benzyl ethers. The methodology requires that the silyl ethers are treated with a catalytic amount of CBr_4 in methanol under photochemical reaction conditions. Selected results are shown in Figure 1.28.

Pale and coworkers [47] developed a new type of a protecting group-bis (4-methoxy-phenyl) methyl group. The relevant ethers are formed (in acetonitrile) and deprotected (in ethanol) in the presence of Cu(II) bromide. The yields are high. Figure 1.29 shows the carbohydrate deprotection (decoupling) example. It is worth noting that the size of the protecting group suggests that it may be equally effective when large substituent is attached to one of the methoxyphenyl groups.

Sridhar and Chandrasekaran [48] developed a novel protecting group for amines and alcohols, propargyloxycarbonyl (Poc) group. It can be easily removed under neutral conditions using tetrathiomolybdate MoS_4^{2-} in acetonitrile at room temperature.

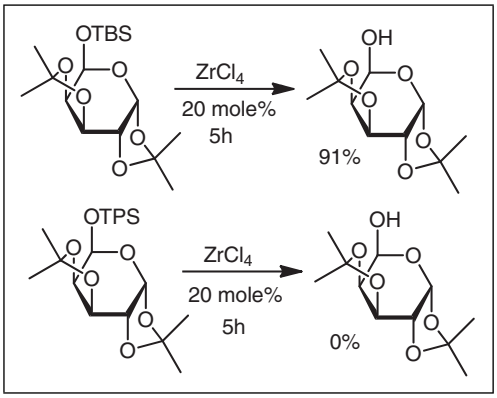


FIGURE 1.27 Sharma et al.'s deprotection of *t*-butyldimethylsilyl ethers in the presence of *t*-butyldiphenylsilyl ethers.

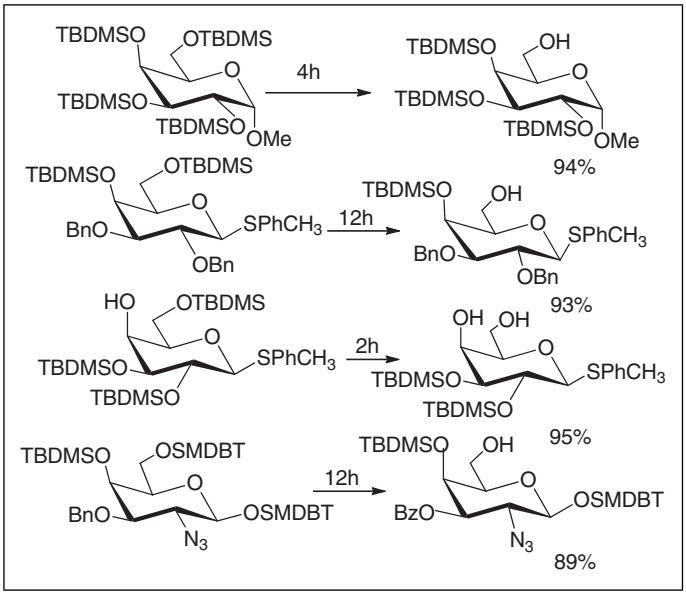


FIGURE 1.28 Chen, Lee, Lin, and coworkers' selective deprotection of secondary silyl ethers.

Such groups as benzylidene acetals, benzyl ethers, acetyl and levulinoyl esters, and allyl and benzyl carbonates are left untouched. Importantly, the new protective group (Poc) is compatible with acidic, basic, and also glycosylation conditions. While all the examples relate to the gluco configuration, there are no reasons to believe that other configurations would not give similar results. Figure 1.30 shows a few examples of Poc deprotection.

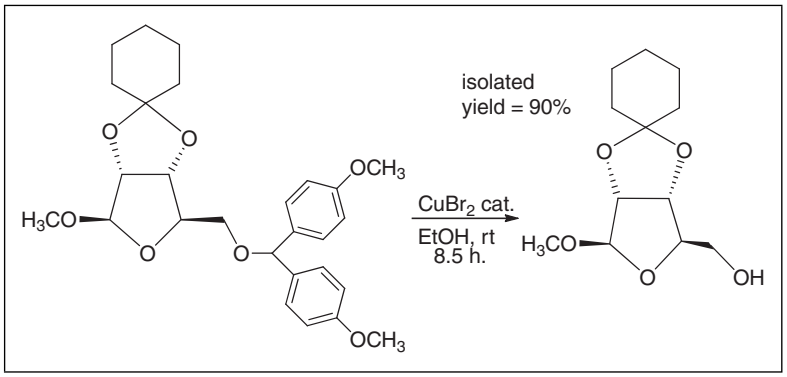


FIGURE 1.29 Deprotection of a new protecting group-bis (4-methoxyphenyl) methyl group developed by Pale and coworkers [47].

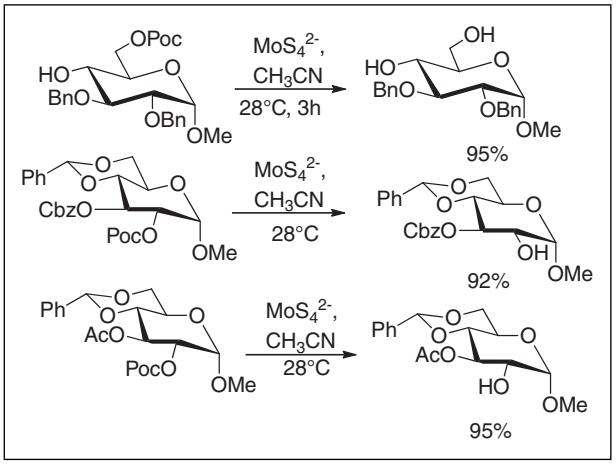


FIGURE 1.30 High-yielding removal of propargyloxycarbonyl (Poc) group developed by Sridhar and Chandrasekaran [48].

1.6 CONCLUSION

We hope that the present review convincingly shows click chemistry to be an exceptionally useful methodology not only applicable to coupling larger molecular units but also when such coupling must be later somehow reversed. The proposed strategy of using sacrificial units is simple and should become the approach of choice when the units must be later decoupled. The review shows that there are several excellent click reactions and some of them such as azide alkyne addition or thiol addition to unsaturated systems have been applied very successfully to the synthesis of various large molecules including macromolecular units containing carbohydrates. Nevertheless, the field of decoupling is much less often visited, and thus, there is an acute need for novel methods of decoupling. In addition, we hope that future availability of a variety of sacrificial units will encourage chemists to take advantage of them. It will enable much better assessment of what the limitations of specific decoupling methods are. The area of research that should strongly benefit from such knowledge is the sequencing of complex, natural polysaccharides.

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