

OxymaPure Coupling Reagents: Beyond Solid-Phase Peptide Synthesis

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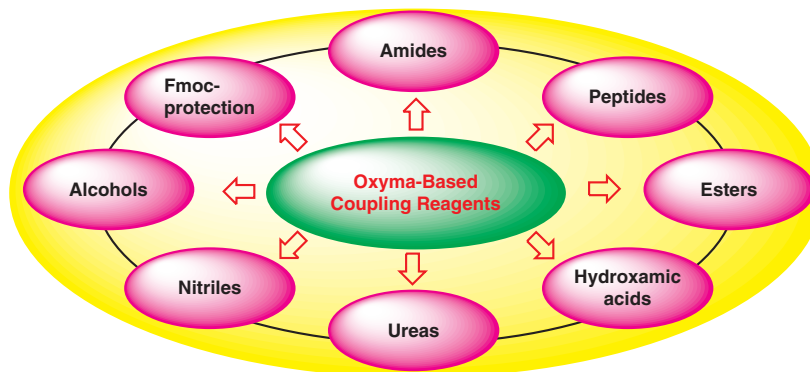
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■■sch 4 is now Table 1 and Fig 6 is now sch 20; subsequent schemes/figures/tables have been renumbered as appropriate■■

Published as part of the Special Topic
Recent Advances in Amide Bond Formation



1 Introduction

Oximes are a class of organic compounds that have prominent structural motifs ($RR'C=NOH$). They are found in numerous drug scaffolds and biologically active compounds, including natural products, pharmaceutical drugs, heterocycles and polymers.^{1–6} Oximes serve as key synthons for the preparation of carbonyl amines, nitriles, amides, thiohydroxamic and thiohydroxamic acid derivatives, nitro compounds, and oxime esters.^{7–14} For example, cyclohexanone oxime is widely used in industry as a key intermediate for the synthesis of caprolactam, which is the precursor of Nylon 6.¹⁵ Oximes have also drawn considerable attention in supramolecular chemistry due to their ability to both accept and donate hydrogen bonds and thus their capacity to form dimers and catemers.^{16,17}

Additives serve to increase coupling efficiency and control epimerization in amide bond formation, with a large number having been developed (Figure 1). In recent years, oximes and their derivatives have attracted increasing interest in the field of peptide chemistry as additives and coupling reagents, respectively. In this context, we reported the excellent performance of OxymaPure [ethyl 2-cyano-2-(hydroxyimino)acetate] (**9**) as a coupling enhancer and racemization suppressant in peptide synthesis.¹⁸ OxymaPure and its derivatives have been used mostly in solid-phase peptide synthesis (SPPS) mode. In 2013, we provided an exten-

Received: 15.07.2020

Accepted after revision: 27.08.2020

Published online:

DOI: 10.1055/s-0040-1706296; Art ID: ss-2020-c0384-st

Abstract OxymaPure [ethyl 2-cyano-2-(hydroxyimino)acetate] is an exceptional reagent with which to suppress racemization and enhance coupling efficiency during amide bond formation. The tremendous popularity of OxymaPure has led to the development of several Oxyma-based reagents. OxymaPure and its derived reagents are widely used in solid- and solution-phase peptide chemistry. This review summarizes the recent developments and applications of OxymaPure and Oxyma-based reagents in peptide chemistry, in particular in solution-phase chemistry. Moreover, the side reaction associated with OxymaPure is also discussed.

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Key words coupling reagent, peptides, racemization, amide bonds, solid-phase synthesis

sive review of OxymaPure and its derived coupling reagents.¹⁹ Since then, this family of reagents has been subjected to a number of modifications, and a wide variety of new OxymaPure-based coupling reagents have been developed. Recently, the American Chemical Society (ACS) Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) described OxymaPure and its aminium derivative COMU, together with TFFH and T3P, as the greenest coupling reagents.²⁰

The present review aims to provide a full appreciation of Oxyma reagents in peptide chemistry, with a particular focus on their use in solution-phase synthesis since their application in solid-phase has already been covered in the aforementioned review.¹⁹ ■■added ref-OK?■■ Special attention will be paid to the applications of the most recent members of this family, as well as some side reactions that can occur under certain conditions.

Biographical Sketches



Srinivasa Rao Manne was born and raised in the small village of Mogalthur in the West Godavari district of Andhra Pradesh, India. He obtained his B.Sc. from Sri YN College, Narasapuram (India) and his M.Sc. (organic chemistry) from V.S.K. College, Bhimavaram (India). He then obtained his Ph.D. from the Indian Institute of

Technology Guwahati under the supervision of Professor Bhubaneswar Mandal. His work involved the applications of the novel coupling reagents Boc-Oxyma, *o*-NosyIOXY and nitrobenzene sulfonic acids in organic synthesis. Currently he is a postdoctoral researcher in the group of Professor Fernando Albericio and Professor Beatriz G.

de la Torre group at the University of KwaZulu-Natal (Durban, South Africa). His research interests are focused on peptide synthesis methodologies utilizing ■■changes OK?■■ peptide coupling reagents and the development of new nitrogen-protecting groups.



Beatriz G. de la Torre obtained her Ph.D. from the University of Barcelona (Spain). After a lengthy ■■change OK?■■ career in Spain, she is presently a Research Professor at KRISP, College of Health Sciences, University of KwaZulu-

Natal (Durban, South Africa). During her career, she has worked extensively on glyco-, nucleo-, and lipo-peptides. Her current scientific interests are focused on the discovery of new antimicrobial peptides, including antituberculosis agents

■■changes OK?■■, peptide-based vaccines, and peptide-based drug-delivery systems. She is also involved in developing green solid-phase peptide synthesis (GSPPS) strategies for both research and industrial purposes.



Ayman El-Faham has been a Professor of Organic Chemistry at the College of Science, King Saud University (Saudi Arabia) since 2011. He received his B.Sc. and M.Sc. degrees from Alexandria University (Egypt) ■■change OK?■■ and his

Ph.D. as a joint project between the University of Massachusetts (USA) and Alexandria University. His major scientific efforts have been concentrated on the development of new coupling reagents, first in the laboratory of Professor Carpino (■■universi-

ty, country?)■■, and since 1993 in collaboration with Professor Albericio (University of KwaZulu-Natal, South Africa). He also has wide-ranging experience of drug discovery using relevant scaffolds. ■■changes OK?■■



Fernando Albericio is a Research Professor at the University of KwaZulu-Natal (South Africa), a full Professor of Organic Chemistry at the University of Barcelona (Spain), and a Visiting Professor at King Saud

University (Saudi Arabia). His major research interests cover practically all aspects of peptide synthetic methodology as well as the synthesis of peptides and small molecules with therapeutic activity (cancer and infec-

tious diseases). He has published more than 950 scientific articles, filed more than 60 patents, and has overseen the graduation of more than 703 ■■please confirm?■■ Ph.D. students.

2 Oxyma-Based Coupling Reagents

2.1 Aminium/Uronium Salts of OxymaPure

Over the years, benzotriazole-based aminium salts such as HATU,^{21,22} HCTU^{23,24} and HBTU^{25,26} have been reported to show high efficiency and good capacity to suppress racemization, and as a result, they have attracted increasing attention for amide bond formation. However, the main disadvantage of these reagents, which are based on benzotriazole scaffolds such as HOBt (1) and HOAt (3), is that they are considered as class 1 explosives, showing autocatalytic decomposition and difficult handling during transport and storage.^{27,28} In 2009, OxymaPure was demonstrated to outperform benzotriazole reagents in terms of yields and lower racemization and, in addition, it did not pose a risk of explosion.¹⁸ The tremendous interest in OxymaPure led to the development of the more efficient Oxyma-based uronium

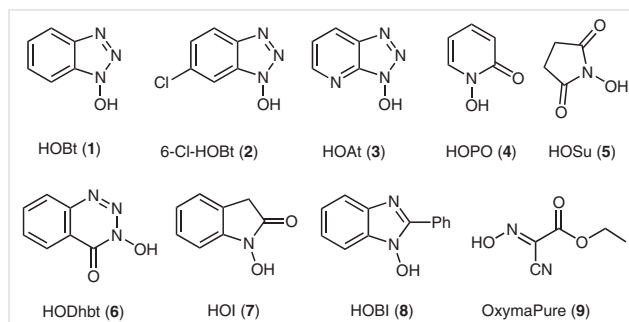
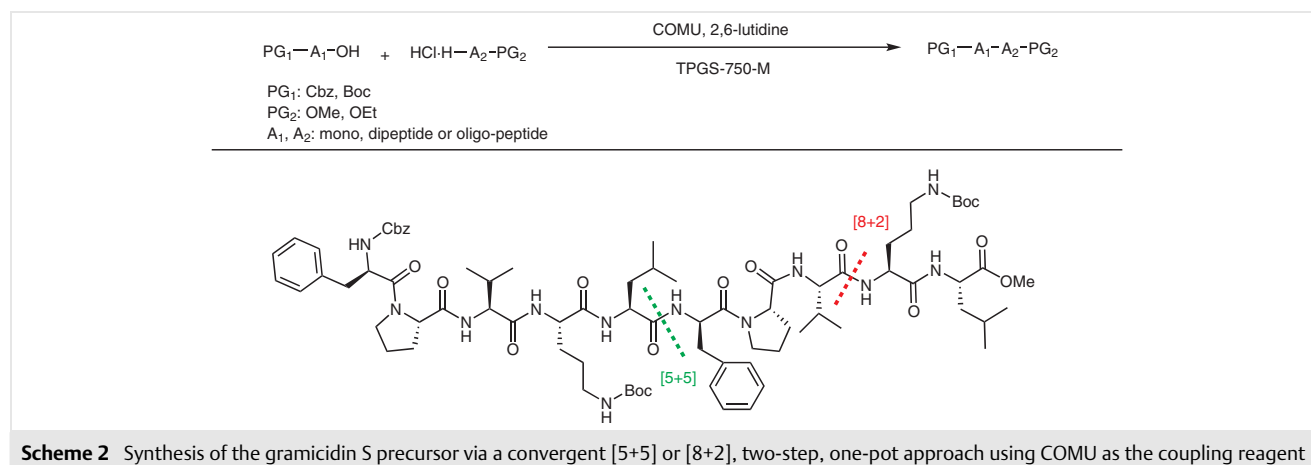
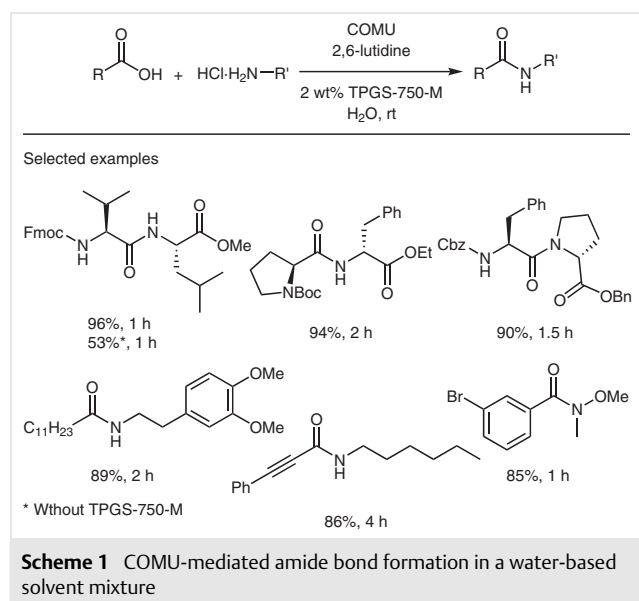


Figure 1 The structures of several additives

salt COMU (10) for amide bond formation (Figure 2).²⁹ This reagent offers unique properties over traditional benzotriazole reagents, such as higher solubility, low epimerization, ease of work-up, and high yields of products.^{30–36}

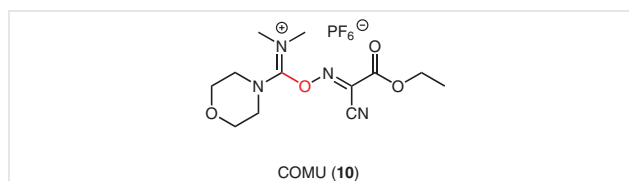


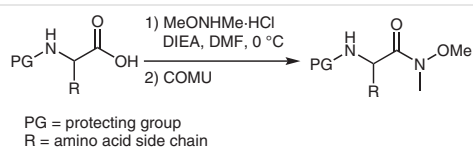
Figure 2 The structure of COMU (10)

However, COMU shows poor hydrolytic stability in DMF due to the presence of a highly reactive C–O bond (shown in red in Figure 2).³⁷ We recently conducted a rigorous study of the hydrolytic stability of COMU in various solvents such as γ -valerolactone (GVL), MeCN, *N*-formylmorpholine (NFM) and DMF.³⁸ After 48 hours, COMU showed 89% and 84% hydrolytic stability in MeCN and GVL, respectively, while only 0% and 3% stability was observed in DMF and NFM, respectively.

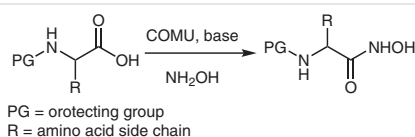
Lipshutz and co-workers developed a convenient and versatile method for amide formation using a combination of COMU and TPGS-750-M in a water-based solvent mixture.³⁹ Here, the surfactant TPGS-750-M played a key role in

the formation of the amide bond. The reaction showed compatibility with common *N*-terminus protecting groups such as Fmoc, Boc, and Cbz, along with various *C*-terminus protecting groups such as alkyl, allyl, and benzyl esters. This method afforded the coupling products in good to excellent yields. Thus, the dipeptide Fmoc-Val-Leu-OEt was formed in excellent yield (96%), but only 53% of product formation was achieved in the absence of the surfactant. The noteworthy feature of this methodology is that it obviates the use of organic solvents, and the aqueous surfactant TPGS-750-M is recyclable, thereby making this protocol greener and environmentally friendly (Scheme 1).

Later, Lipshutz's group extended this efficient protocol using COMU as a coupling reagent to conduct solution-



Scheme 3 Synthesis of Weinreb amides using COMU

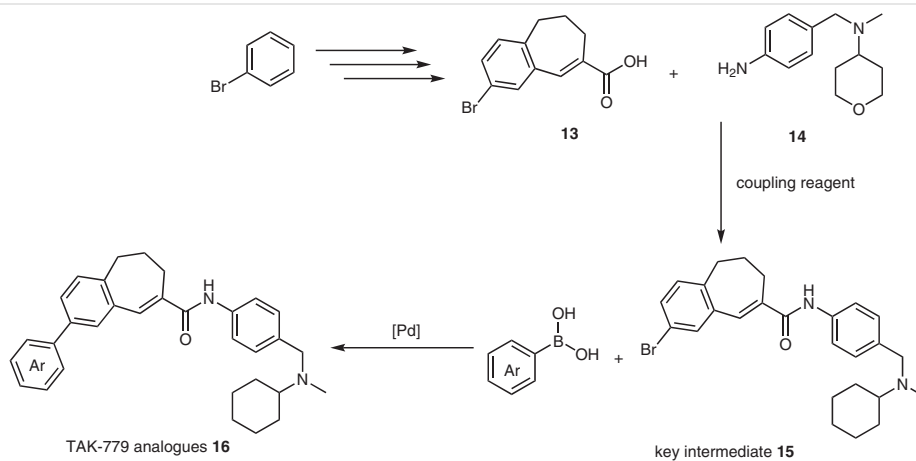


Scheme 4 Synthesis of *N*^α-protected amino/peptide hydroxamic acids

phase peptide synthesis that relied on a tandem deprotection/peptide coupling under mild aqueous micellar conditions using the designer surfactant TPGS-750-M.⁴⁰ This approach is broadly applicable to several types of amino acids with differing polarities and an array of varying substitution patterns on their side chains, including phenyl or alkyl moieties, protected amine or carboxylic acid, and unprotected alcohol and phenolic groups. A segment coupling process was used to extend the polypeptide length to ten amino acid residues without significant loss of efficiency. Also, no epimerization was detected (Scheme 2).

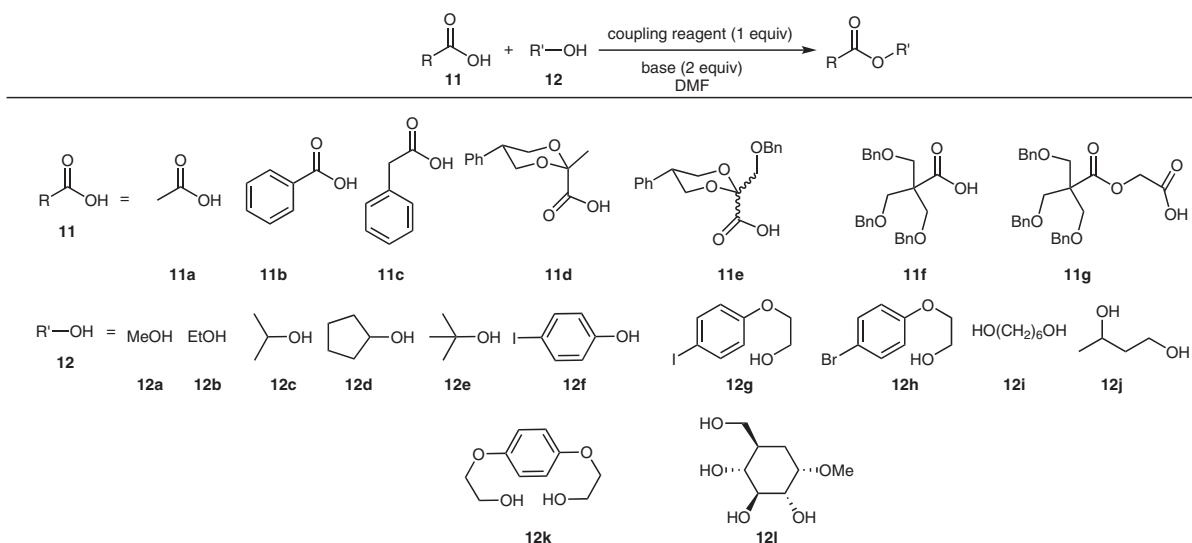
In 2011, Tyrrell et al. reported COMU as a non-hazardous reagent for the conversion of *N*-protected α -amino acids into *N*-methoxy-*N*-methylamines to afford the corresponding Weinreb amides in very good to excellent yields and with minimal racemization.³⁵ The reaction can be monitored visually by the change in color associated with the formation of the product (Scheme 3).

Twibanire and Grindley⁴¹ reported the use of COMU, TB-TU, and TATU to prepare carboxylic acid esters in excellent yields from all types of alcohols at room temperature, under mild conditions in the presence of organic bases and in short reaction times. TBTU and TATU promoted esterification of secondary alcohols faster than COMU in the presence of DBU as the base. Only COMU was effective for the preparation of esters from tertiary alcohols and in the presence of the stronger base 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (Table 1).



Entry	Coupling reagent	Temp	Time	Yield (%) of 15
1	DCC, DMAP	rt	10 h	10
2	EDC, HOBT, NMM	0 °C	15 h	33
3	EDC, HOBT, NMM	reflux	6 h	42
4	EDC, HOBT, NMM	reflux	3 d	58
5	HATU, Et ₃ N	rt	12 h	72
6	COMU, NMM	rt	12 h	77

Scheme 5 Synthesis of TAK-779 analogues 16

Table 1 Synthesis of Carboxylic Acid Esters Using COMU, TBTU, and TATU as Coupling Reagents

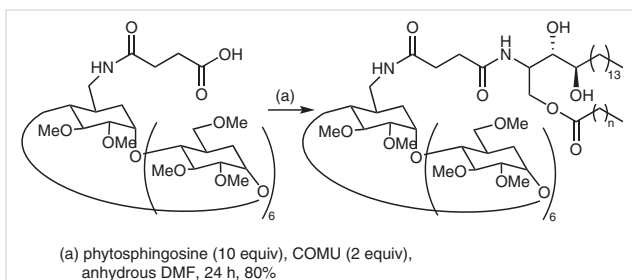
Entry	Acid	Alcohol	Coupling reagent	Base	Time (h)	Yield (%)
1	11b	12f	TBTU	DIEA	0.25	86
2	11b	12f	TATU	DIEA	0.25	96
3	11b	12f	COMU	DIEA	3	79
4	11b	12b	COMU	DBU	2.5	89
5	11b	12g	TBTU	DBU	0.5	81
6	11b	12g	TATU	DIEA	0.5	95
7	11b	12g	COMU	DBU	4.5	74
8	11b	12k	COMU	DBU	5	69
9	11b	12c	TBTU	DBU	4	63
10	11b	12c	COMU	DBU	16	71
11	11b	12c	COMU	MTBD	11	79
12	11b	12d	TBTU	DBU	4	59
13	11b	12d	TATU	DBU	3.5	89
14	11b	12d	COMU	DBU	16	68
15	11b	12e	TBTU	DBU	36	0
16	11b	12e	TATU	DBU	36	0
17	11b	12e	COMU	DBU	36	0
18	11b	12e	TATU	MTBD	36	0
19	11b	12e	COMU	MTBD	16	79
20	11a	12g	COMU	DBU	2	86
21	11c	12f	COMU	DBU	3	81
22	11c	12i	COMU	DBU	4	83
23	11c	12k	COMU	DBU	4	67
24	11d	12h	TBTU	DBU	1	72
25	11d	12g	COMU	DBU	12	73
26	11e	12g	TBTU	DBU	3	60
27	11e	12g	COMU	DBU	14	62
28	11f	12g	COMU	DBU	2	81

■ there are no results for experiments with **12a**, **12j** and **12l**! ■

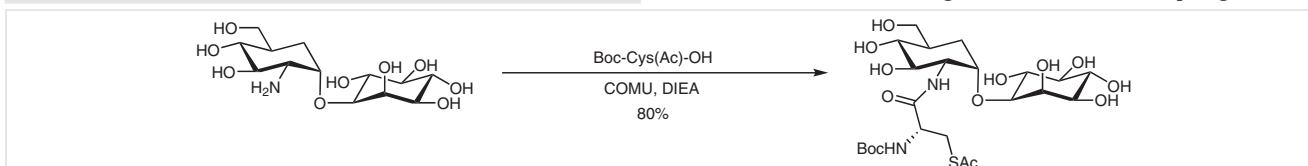
In 2014, Panguluri **■ changes OK? ■** et al.⁴² reported a simple, one-pot protocol under mild conditions for the synthesis of N^{α} -protected amino/peptide hydroxamic acids from the corresponding carboxylic acids. In this protocol, COMU was used as an acid activator in the presence of a base such as DIEA to afford the target products in good yields and without any racemization. They also reported that this strategy was appropriate for the synthesis of simple, bifunctional and sterically hindered α -amino/peptide hydroxamic acids (Scheme 4).

In 2014, Wunsch and co-workers demonstrated the utility of COMU for the synthesis of biologically active TAK-779 analogs, which act similarly to chemokine receptor 5 (CCR5).⁴³ These authors developed a new methodology for the synthesis of TAK-779 analogs using a late-stage diversification strategy. The amide product **15** was a central building unit in the synthesis of these analogs and was obtained by the coupling reaction between acid **13** and aniline **14** using coupling reagents such as DCC, EDC, HATU, and COMU under a range of reaction conditions. Of these reagents, HATU and COMU were found to be effective and gave higher yields of intermediate **15** (Scheme 5).

In 2014, Miao et al. developed a greener synthesis of phytosphingolipidyl β -cyclodextrin derivatives.⁴⁴ In this regard, the key step was the insertion of phytosphingolipidyl **■ phytosphingosine? ■** using a coupling reagent. The traditional reagent DIC/HOBt gave a very poor yield (48%), even when the amount used was increased to 30 equivalents. Alternatively, only 1.5 equivalents of HATU were needed to achieve a high yield of the desired product (90%). However, given the high cost and explosive nature of HATU, this reagent cannot be used on an industrial scale. To overcome this problem, the authors used the less expensive and more efficient coupling reagent COMU and achieved a good yield (80%) of the desired product. **■ changes OK? ■** They reported that this methodology was safe and greener (Scheme 6).



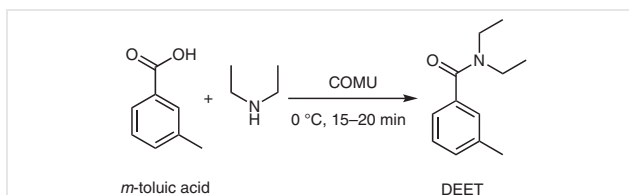
Scheme 6 Application of COMU in the synthesis of cyclodextrin derivatives



Scheme 7 Application of COMU in the synthesis of an intermediate en route to mycothiol **■ changes OK? ■**

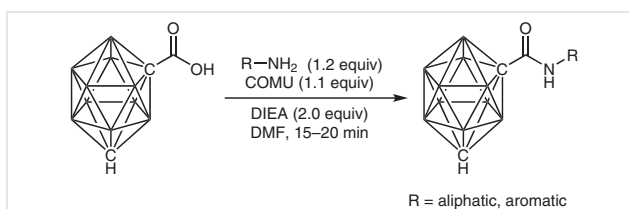
Similarly, Manabe and Ito show the applicability of COMU in the synthesis of mycothiol, which is found in Gram-positive bacteria.⁴⁵ The key intermediate step in this synthesis was insertion of the Cys moiety. HATU gave a very poor yield due to the low solubility of the byproducts, which complicated column purification. However, COMU afforded an excellent yield without any difficulties during the purification process (Scheme 7).

Regarding the safety protocol required when using COMU, in 2015, Withey and Bajic⁴⁶ devised a one-pot, operationally simple, safe and standard protocol to be used by undergraduate students in an organic chemistry laboratory for the preparation of N,N' -diethyl-3-methylbenzamide (DEET) from m -toluic acid using COMU as a non-hazardous coupling reagent. The experiment benefited from short reaction times and no purification was necessary. Students were able to determine the progress of the reaction by simply monitoring the color (Scheme 8).



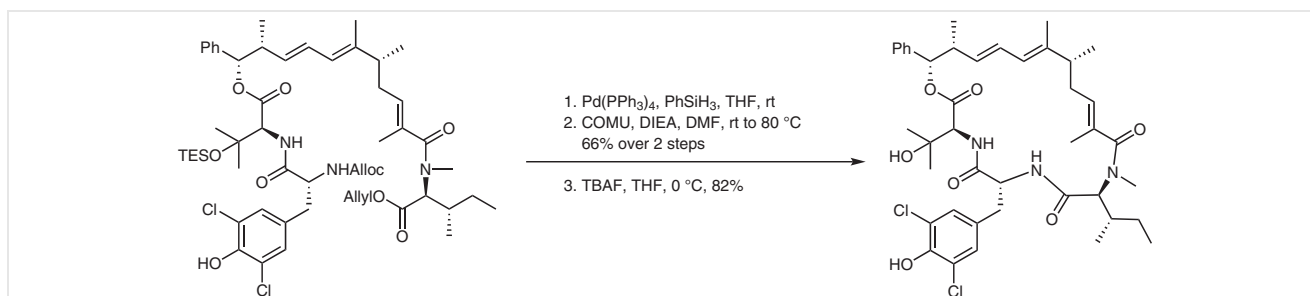
Scheme 8 An undergraduate synthesis of DEET

In 2017, Scholz and Wingen reported promising results using COMU for the synthesis of a carborane.⁴⁷ Amide bond formation in carboranes is unlike that in peptides and organic compounds, and only moderate yields are obtained with other traditional methods (Scheme 9).



Scheme 9 Application of COMU in the synthesis of carborane derivatives

In 2017, Poock and Kalesse⁴⁸ described the total synthesis of nannocystin Ax in an overall yield of 11% starting from a known aldehyde **■ changes OK? ■** building block and in 14 steps. The macrocycle was closed via a macrolactamization reaction using COMU. For this coupling, several



Scheme 10 A macrolactamization reaction using COMU for the synthesis of nannocystin Ax

sets of conditions were tested (e.g., PyBrop, PyClop, Oxyma, EDC·HCl, COMU and DMAP), and it was found that COMU gave the best result (a 66% yield) (Scheme 10).

Similarly, other Oxyma-based uronium salts, namely HOTU (**17**) and TOTU (**18**), have also shown better performance than benzotriazole-based reagents (Figure 3). During the formation of the dipeptide Z-Phg-Pro-NH₂, very low epimerization was observed with COMU and HOTU (0.17% and 0.12%, respectively) compared to HBTU and HATU (8.2% and 3.1%, respectively).

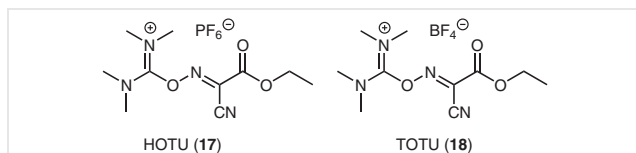
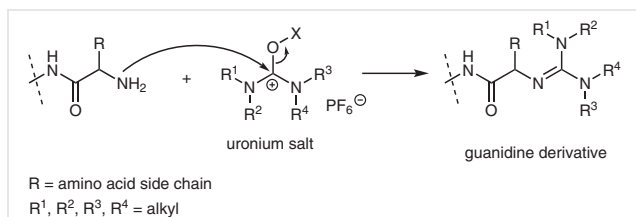


Figure 3 Structures of HOTU and TOTU

2.2 Phosphonium Salts of OxymaPure

The synthesis of sterically hindered or cyclic peptides typically requires longer reaction times and an excess of the coupling reagent. However, the presence of excess uronium/aminium salts as coupling reagents may cause the *N*-terminus of the peptide chain to directly react with the coupling reagent and form an undesired guanidine as a side product (Scheme 11).^{49,50} This reaction leads to the termination of peptide chain growth. On the other hand, the phosphonium salts PyAOP, PyBOP and PyClock have shown similar coupling efficiency.^{49,51} The electrophilic phosphorus does not react with the amine moiety and it prevents the termination of peptide chain growth.



Scheme 11 Guanidine formation

In 2010, our group described the Oxyma-based phosphonium salts PyOxim (PyOxP) (**19**) and PyOxB (**20**) (Figure 4), as efficient alternative coupling reagents to the benzotriazole-based phosphonium salts PyAOP, PyBOP and PyClock.⁵² PyOxim and PyOxB showed greater capacity to suppress racemization than PyAOP, PyBOP and PyClock in a solution-phase coupling reaction. Also, PyOxim and PyOxB showed comparative results to the azabenzotriazole-derivative PyAOP and outperformed the benzotriazole derivatives PyBOP and PyClock during [2+1] segment coupling for the formation of Z-Phe-Val-Pro-NH₂ (Table 2).

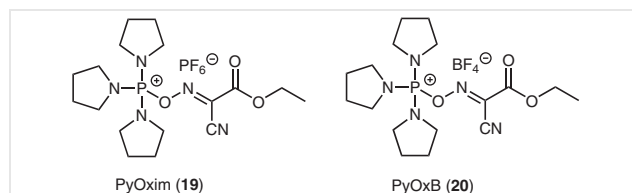
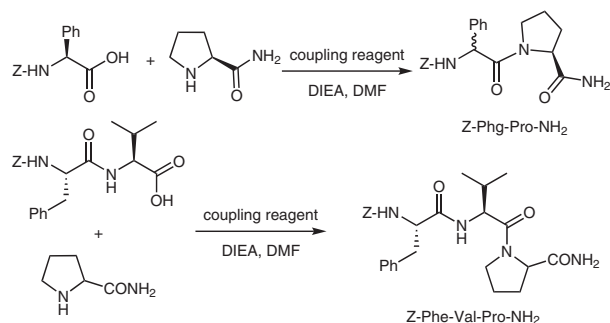


Figure 4 The structures of PyOxim and PyOxB

In addition, PyOxim showed greater performance, not only in linear peptide synthesis, but also in cyclic peptide formation. The high hydrolytic stability of PyOxim enhanced the coupling efficiency during the cyclization of the pentapeptide H-Ala-Ala-NMeAla-Ala-Ala-OH and gave superior results compared with PyBOP, PyAOP, and PyClock (Table 3).

Detin et al.,⁵³ reported the synthesis of 15-mer peptide nucleic acid (PNA) by solid-phase synthesis. The amino-terminal group of PNA was later condensed with bifunctional poly(ethylene oxide) derivatives (PEO, 2 and 5 kDa MW) carrying a Trt-cysteine at one end and a carboxyl group at the other end. The PNA-PEO coupling reaction proved to be sterically hindered, as demonstrated by the large excess of condensing agents necessary to achieve quantitative PNA derivatization. The use of HATU led to only 49.6% and 5.2% conversion yields, in solution- and solid-phase respectively, and to the formation of a non-PEGylated amino-modified PNA as a side product. In contrast, coupling with PyOxim was much more efficient, leading to 100% conversion to the desired conjugate, and without generating undesired side

Table 2 Racemization During the Formation of Z-Phg-Pro-NH₂ and Z-Phe-Val-Pro-NH₂

Entry	Coupling reagent	Racemization (DL%) Z-Phg-Pro-NH ₂	Racemization (LDL%) Z-Phe-Val-Pro-NH ₂
1	PyAOP	2.2	3.0
2	PyBOP	5.8	12.5
3	PyClock	1.6	8.6
4	PyOxim	0.3	5.7
5	PyOxB	0.6	5.3

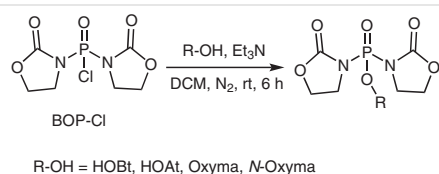
products. The combination of PyOxim-based solution coupling and the optimized purification process was convenient and economical and provided the product in a mixture that could be used for surface functionalization.

Table 3 Cyclization of H-Ala-Ala-NMeAla-Ala-Ala-OH in DMF

Entry	Coupling reagent	Cyclic peptide (%)	Linear peptide ■■OK?■■ (%)	Linear dimer (%)
1	PyAOP	54	10	36
2	PyBOP	43	28	29
3	PyClock	61	15	24
4	PyOxim	70	10	20
5	PyOxB	47	15	38

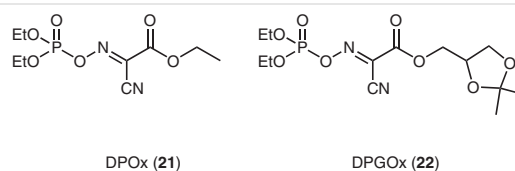
2.3 Oxyma-Based Phosphates

In 2013 ■■2014 in ref 54?■■, our group reported novel Oxyma-based organophosphorus reagents for coupling reactions.⁵⁴ The nucleophilic additives HOBt, HOAt, Oxyma-

**Scheme 12** Synthesis of an organophosphorus reagent

Pure and *N*-Oxyma (carboxamide instead of ethyl ester) reacted with BOP-Cl in the presence of Et₃N, forming the corresponding phosphinic reagent (Scheme 12). Among these reagents, BOP-Oxy showed higher solubility in DMF and MeCN. Also, BOP-Oxy outperformed the other reagents tested in terms of yield and epimerization control in the stepwise solution-phase synthesis of Z-Phg-Pro-NH₂ and the [2+1] segment coupling for the synthesis of Z-Phe-Val-Pro-NH₂ and Z-Gly-Phe-Pro-NH₂. The major advantage of these organophosphorus coupling reagents is that they do not contain any counter anion, such as PF₆ or BH₄, that can hamper the final purification of a peptide.

Recently, Mitachi et al. developed the Oxyma-derived phosphates diethylphosphoryl-Oxyma (DPOx) (**21**) and diethylphosphoryl-glyceroacetone-Oxyma (DPGOx) (**22**) for amide bond formation (Figure 5).⁵⁵ They demonstrated that DPGOx shows relative stability in aprotic solvents such as anhydrous DMF and that it is an effective coupling reagent for *N*-acyl-protected α -amino acids and oligopeptide segment coupling. The hydrolytic stability of diethylphosphoryl-Oxyma derivatives was monitored by ¹H NMR studies. DPOx and DPGOx were hydrolyzed in H₂O (*t*_{1/2} < 3 h) and slowly reacted in DMSO. Also, they were stable in DMF and MeCN over 5 days. Furthermore, diethylphosphoryl-Oxyma derivatives showed better stability in anhydrous DMF in the presence of NaHCO₃ and did not display any measurable decomposition even after 24 hours. The authors found that DPOx and DPGOx were stable in DMF at room temperature and could be stored for more than 30 days under these conditions.

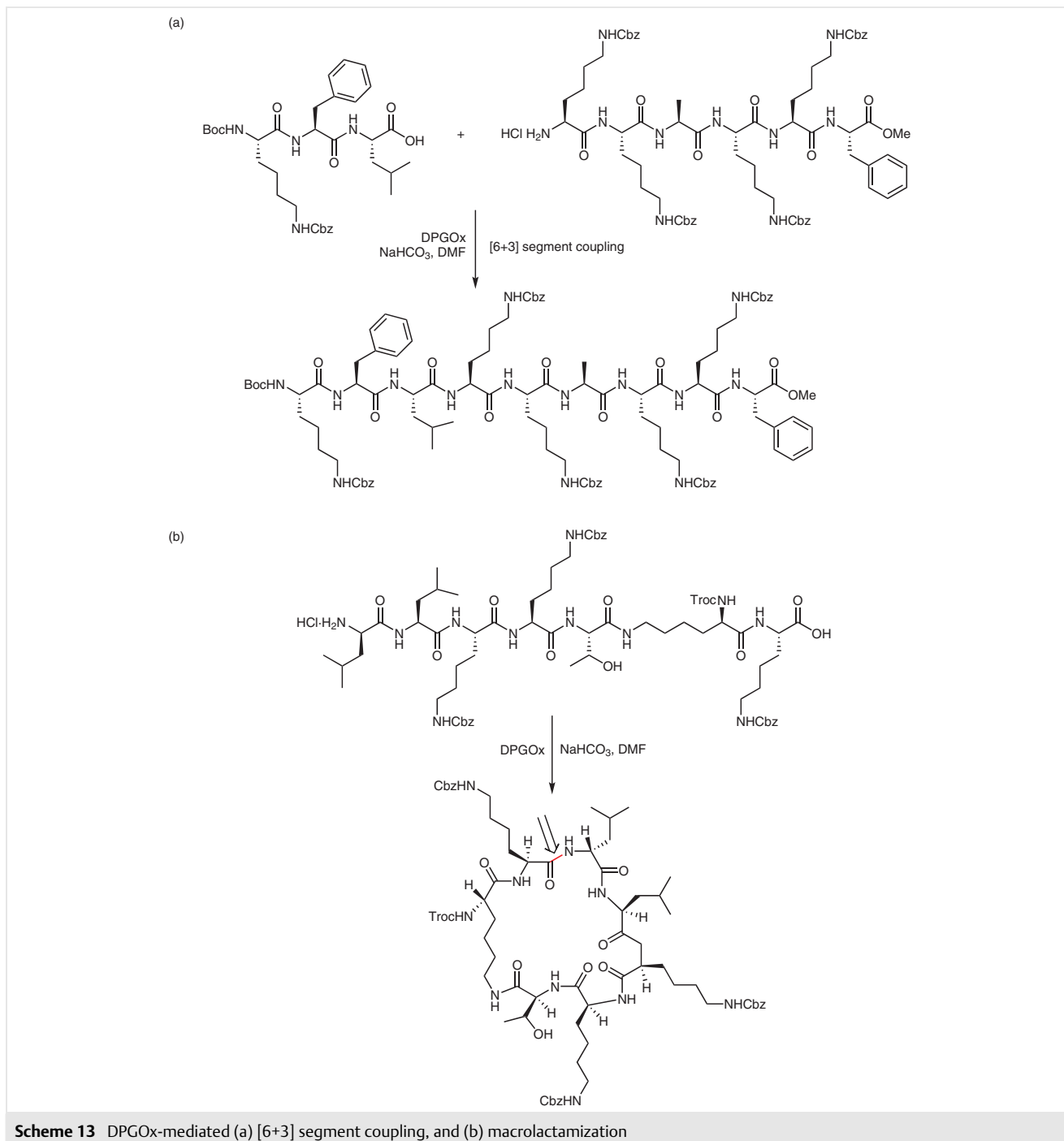
**Figure 5** The structures of DPOx and DPGOx

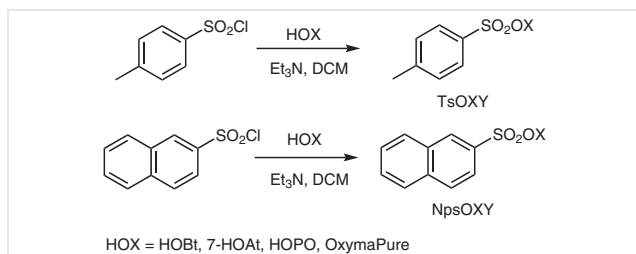
DPGOx allowed for the racemization-free synthesis of *N*-acyl and *N*-formyl dipeptides, pentapeptides, and hexapeptides, with excellent yields. ■■ref. 55?■■ This was the first report of this diethylphosphoryl-Oxyma derivative being used to synthesize *N*-formyl peptides, a process in which it is very difficult to perform the coupling reaction. DPGOx proved efficient for the synthesis of 18-mers of linear oligopeptides, cyclic peptides and complexes of glycopeptides. Also, DPGOx gave an impressive performance in [6+3] and [3+9] segment coupling reactions, the antibacterial peptide fragment being obtained with 92% purity through [6+3] segment coupling reactions. In addition, it was effective for macrolactamizations to form lactams of medium ring size. The reaction rate of the DPGOx-promoted macrolactamizations was much faster than that achieved when using diphenyl phosphoryl azide (DPPA) (Scheme 13).

2.4 Sulfonate Esters of OxymaPure

In 2010, Khattab introduced a new family of Oxyma sulfonate esters, namely TsOXY and NpsOXY, to facilitate coupling reactions (Scheme 14).⁵⁶ These reagents show high efficiency in preactivations within a short period and high stability to the moisture in air. The racemization associated

with the use of these reagents was examined in the synthesis of the dipeptide Z-Phe-Val-OMe and compared with the performance of benzotriazole derivatives. The Oxyma sulfonate esters outperformed these derivatives in terms of preactivation times, yields and racemization suppression (Table 4).



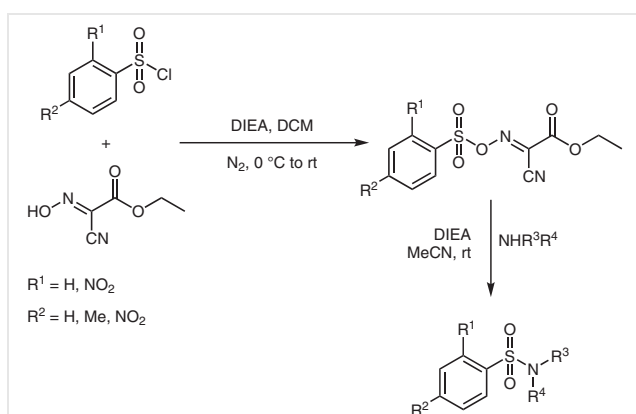


Scheme 14 Synthesis of sulfonate-ester-type coupling reagents
 ■■labeled products–OK?■■

Table 4 Yield and Racemization During the Solution-Phase Synthesis of Z-Phe-Val-OMe

Entry	Coupling reagent	Preactivation time (min)	Yield (%)	DL (%)
1	NpsOAt	120	54.5	6.7
2	NpsOBt	120	69.4	12.9
3	NpsOPO	120	69.8	7.2
4	NpsOxyma	3	92.5	4.8
5	TsOAt	120	45.8	11.0
6	TsOBt	120	52.2	1.4
7	TsOPy	120	63.7	4.1
8	TsOxyma	3	91.5	2.0

In 2013, Mandal and co-workers also prepared various Oxyma sulfonate esters and used them as precursors in the synthesis of sulfonamides.⁵⁷ The main advantages of this protocol were that the synthesis was HCl-free and it worked well with even less nucleophilic anilines (Scheme 15).



Scheme 15 Synthesis of sulfonamides

Furthermore, Mandal reported Oxyma sulfonate esters as efficient promoters for the conversion of aldoximes into nitriles under mild conditions.⁵⁸ The reaction mechanism proposed was through nucleophilic aldoxime attack on ei-

ther the electrophilic center of sulfur (path A) or the electrophilic center of the carbonyl carbon (path B) of the Oxyma sulfonate esters. NMR and X-ray ■■change OK?■■ crystal studies of the intermediates revealed, unexpectedly, that the reaction mechanism was more favorable through the involvement of the OxymaPure-cleaved product of path B (Scheme 16).

Later, in 2014, the same group developed a novel and reliable Oxyma-based coupling reagent, ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosyIOXY), to replace benzotriazole-based reagents.⁵⁹ *o*-NosyIOXY readily activates carboxylic acids to afford amides, peptides, esters, thioesters, hydroxamates, alcohols and heterocyclic compounds.^{60,61} As a salient ■■changes OK?■■ feature of the reagent, after completion of the reaction it produces only the solid byproducts OxymaPure and 2-nitrobenzene sulfonic acid, which can be recovered easily and reused to prepare the same coupling reagent (Scheme 17).

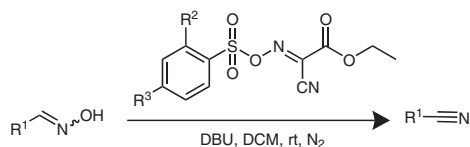
The scope of the application of *o*-NosyIOXY was extended to peptide synthesis. The solution-phase approach to the hydrophobic fragment of the amyloid β -peptide Boc-Val-Val-Ile-Ala-OMe⁶² was achieved in 78% yield using Boc-based peptide synthesis. Furthermore, this approach was extended to SPPS by preparing long-chain peptides. The capacity of *o*-NosyIOXY to suppress racemization was studied in the synthesis of the tripeptide Z-Gly-Phe-Val-OMe. No racemization was observed during the coupling reaction between Z-Gly-Phe-OH and H-Val-OMe. However, other reported reagents afforded good yields but racemization was noted (Table 5).

Table 5 Yield and Racemization During the Formation of Z-Gly-Phe-Val-OMe

Entry	Coupling reagent	Yield (%)	Racemization (%)
1	HBTU	89	5.9
2	HATU	90	1.6
3	HDMB	90	2.9
4	HDMA	90	0.7
5	<i>o</i> -NosyIOXY	91	– ^a

^a No racemization detected.

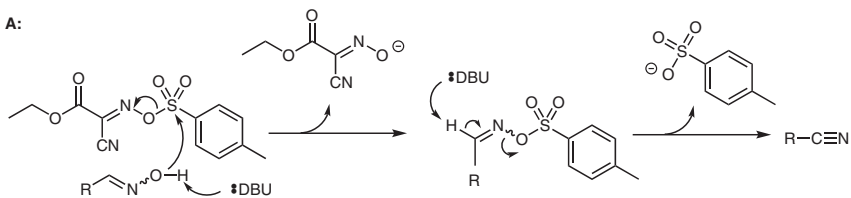
Similarly, another Oxyma-based reagent, namely ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY), was reported by the same group.⁶³ A mild and efficient method for the synthesis of hydroxamic acids directly from carboxylic acids using 4-NBsOXY was described. Also, 4-NBsOXY activated the hydroxamic acids to generate isocyanates via the Lossen rearrangement. Furthermore, these isocyanates reacted with nucleophilic amines and formed the corresponding ureas. This protocol successfully achieved a variety of aliphatic, aromatic and common *N*-



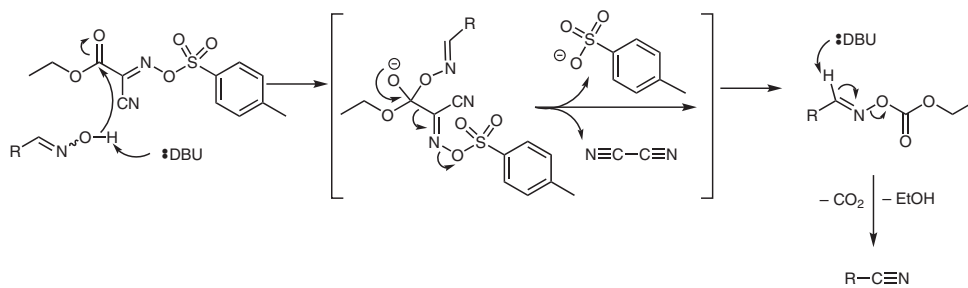
R¹ = alkyl, aryl
 R² = H, NO₂
 R³ = H, Me, NO₂

Plausible reaction mechanisms

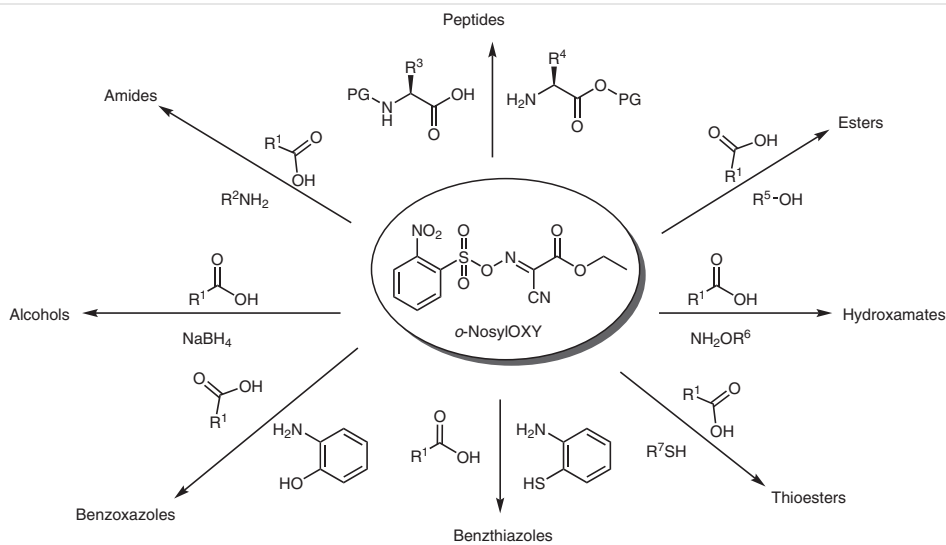
Path A:



Path B:

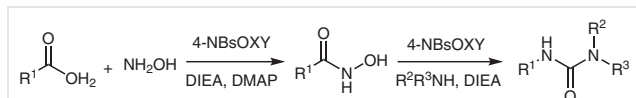


Scheme 16 Synthesis of nitriles from aldoximes using sulfonate esters



Scheme 17 o-nosylOXY-based coupling reactions ■■NBs now Nosyl-OK?■■

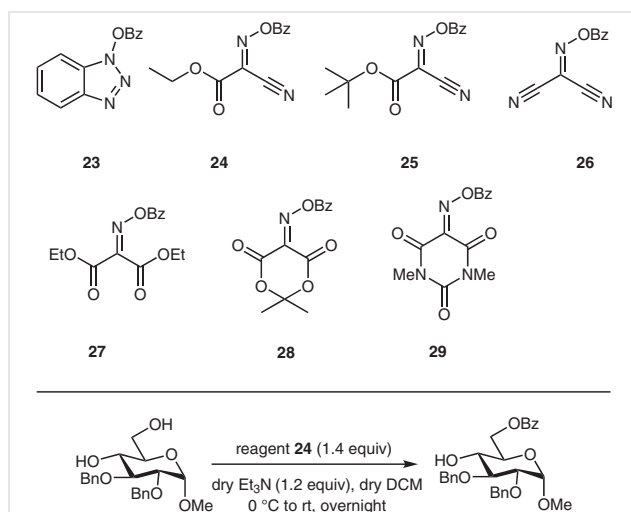
protected amino acids containing hydroxamic acids and peptidyl ureas ■■made plural-OK?■■ without any epimerization (Scheme 18).



Scheme 18 Synthesis of hydroxamic acids and ureas using 4-NBsOXY

2.5 Benzoate Esters of OxymaPure

In 2018, Mandal and co-workers reported (*E*)-ethyl-2-cyano-2-[(2,4,6-trichlorobenzoyl)oxy]imino}acetate (TCBOXY) as an Oxyma-based modified Yamaguchi reagent for acylation.⁶⁴ In this work, the authors reported the first racemization-free synthesis of amides and peptides using a modified Yamaguchi reagent. The reagent TCBOXY alone gave only 30% of the desired product, with the undesired product, namely the amide of 2,4,6-trichlorobenzoic acid, predominating (60%). Surprisingly, TCBOXY produced a high yield of the desired product (91%) in the presence of a catalytic amount of DMAP (Scheme 19). The coupling efficiency of TCBOXY was tested in both solution-phase and solid-phase peptide synthesis. It showed impressive performance during the stepwise coupling solution-phase synthesis of a tetrapeptide, Boc-Val-Val-Ile-Ala-OMe (overall 75% crude yield). Also, the authors used TCBOXY to achieve the racemization-free synthesis of esters and thioesters.

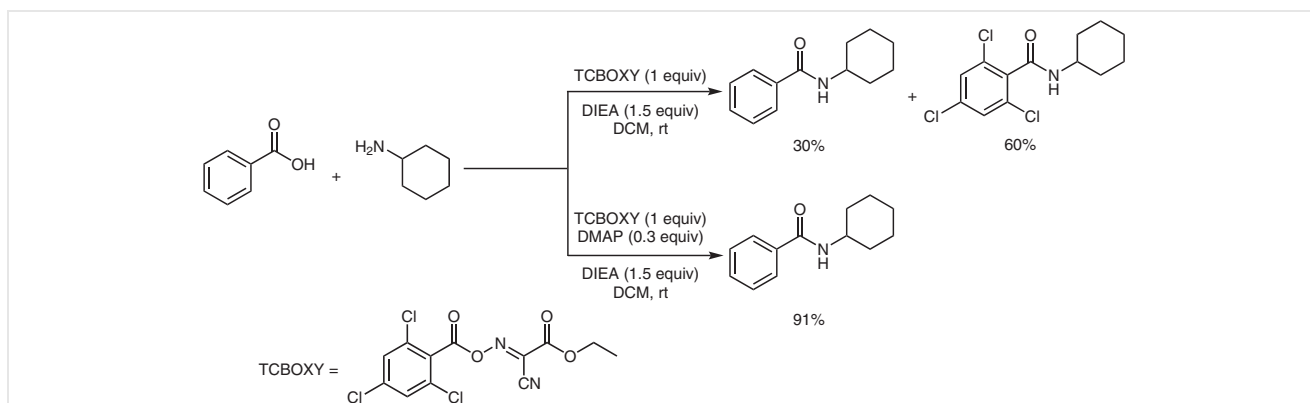


Scheme 20 Structures of benzoylated derivatives **24–29** and the synthesis of a benzoylated carbohydrate ■■changes OK?■■

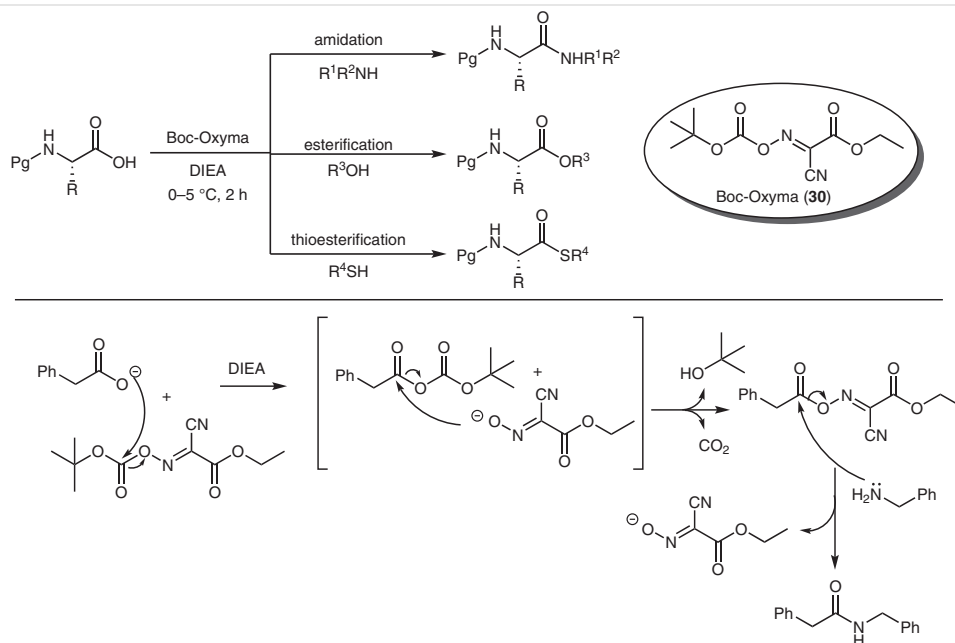
In 2016, Burugupalli et al. reported benzoyl-Oxyma, an efficient reagent for the benzylation of alcohols, as an alternative to HOBt-derived benzoyloxybenzotriazole (BBTZ) (**23**).⁶⁵ The authors synthesized a series of benzoylated oximes **24–29** by changing the electron-withdrawing substituent adjacent to the oxime group (Scheme 20). The oxime-derived reagents **24**, **25** and **26** afforded excellent yields during the benzylation of primary alcohols; these yields were very similar to those obtained with the reagent BBTZ. The other oxime-derived reagents **27**, **28** and **29** did not give satisfactory results. Furthermore, these authors extended the application of benzoyl-Oxyma to the selective acylation of carbohydrate alcohols (Scheme 20).

2.6 Carbonates of OxymaPure Derivatives

In 2013, Mandal and co-workers prepared a novel Oxyma-based reagent, 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma) (**30**), which was successfully tested



Scheme 19 TCBOXY-mediated amide formation

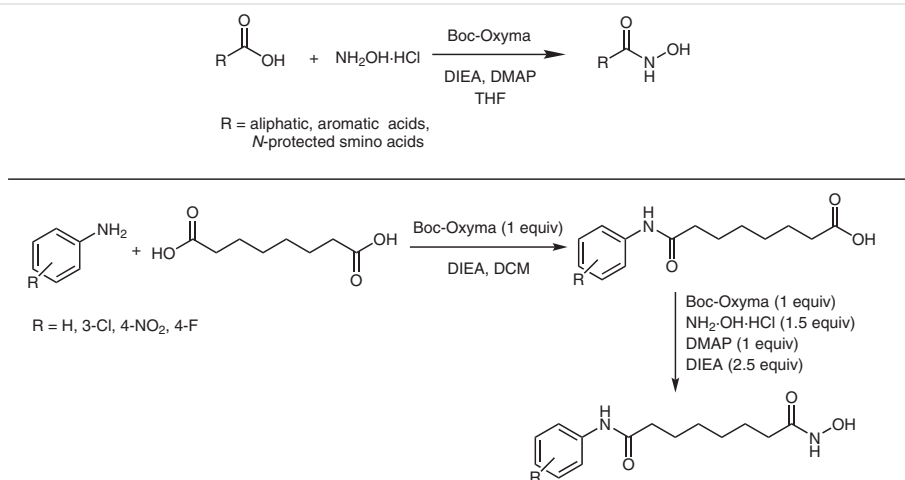


Scheme 21 A plausible reaction mechanism for Boc-Oxyama-mediated amide bond formation ■■(-) now circled negative charge (twice)-OK?■■

in coupling reactions. It proved to be an efficient coupling reagent for the synthesis of amides, peptides, esters and thioesters, without loss of chiral integrity.⁶⁶ On the bases of NMR, IR and X-ray ■■change OK?■■ crystal studies, a plausible reaction mechanism is depicted in Scheme 21. The carboxylate anion reacts with Boc-Oxyama to form a stable Oxyma ester via an anhydride intermediate. Subsequently, the nucleophilic amine reacts with the Oxyma ester and forms the desired amide product. Boc-Oxyama has several notable features: it is easy to prepare, it produces only solid waste OxymaPure as a byproduct, and it can be recovered easily and reused. Also, the protocol does not re-

quire any strong bases during the esterification with secondary and *tert*-butyl alcohols, with the mild base DIEA sufficing (Scheme 21).

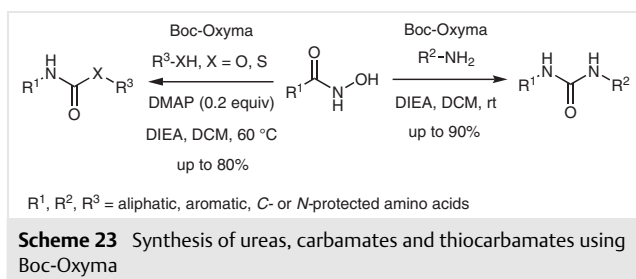
In 2015, further work by Mandal's group used Boc-Oxyama for the synthesis of hydroxamic acids.⁶⁷ This method has been successfully applied for both aromatic and aliphatic carboxylic acids and common *N*-protected amino acids. Also, these authors extended this approach to the synthesis of long-chain peptide hydroxamic acids using the Fmoc-based SPPS protocol. Furthermore, they demonstrated the applicability of this protocol in medicinal chemistry by synthesizing the anticancer agent suberoylanilide hy-



Scheme 22 Synthesis of hydroxamic acids using Boc-Oxyama ■■compd no 13 deleted-OK?■■

droxamic acid^{33,68,69} and its derivatives.⁷⁰ It is notable that both steps were achieved with the same coupling reagent (Scheme 22).

Later, in 2017, the same group reported Boc-Oxyima as an efficient promoter of the conversion of hydroxamic acids into urea derivatives via the Lossen rearrangement.⁷¹ Initially, the hydroxamic acid reacts with Boc-Oxyima in the presence of DIEA at room temperature to give the corresponding isocyanate via the Lossen rearrangement. Further, the isocyanate is subsequently trapped with nucleophilic amines leading to the desired urea derivatives. A wide variety of urea derivatives were synthesized, including simple, dipeptidyl and tripeptidyl ureas, in good to excellent yields. Interestingly, the protocol showed excellent stereoselectivity, and all the final products were obtained without any epimerization. However, this method failed to produce carbamates and thiocarbamates under identical reaction conditions. Mandal also optimized the reaction conditions and found that the best results were obtained in the presence of a catalytic amount of DMAP under reflux conditions (Scheme 23).



In 2010, our group synthesized Fmoc/Alloc-oxime reagents and examined their efficiency for the introduction of the Fmoc/Alloc group.⁷² Most commonly, Fmoc/Alloc-Cl,^{73,74} Fmoc/Alloc-OSu,^{75,76} and Fmoc/Alloc-N₃⁷⁷ reagents were used to synthesize Fmoc/Alloc-protected amino acids. However, these reagents have several drawbacks, for example, highly reactive chlorides may lead to the formation of dipeptide and tripeptide impurities along with the desired *N*-protected amino acids.⁷⁸ The OSu derivatives can lead to the formation of β -alanine or even β -alanine-containing dipeptides through a Lossen rearrangement,⁷⁹ whilst the azide derivatives can be dangerous. Interestingly, the Fmoc-oximes showed less than 0.6% of Fmoc-Gly-Gly-OH dipeptide formation during the preparation of Fmoc-Gly-OH. Of these reagents, Fmoc-cyanopyridyloxime afforded the best results in terms of yield, purity and low dipeptide formation. Similarly, Alloc-cyanopyridyloxime afforded Alloc-Gly-OH in good yield, high purity and with negligible dipeptide formation. The disadvantage of this protocol is that it involves the use of an expensive cyanopyridyloxime, which is difficult to remove from the reaction mixture (Table 6).

Later, in 2017, our group developed another oxime-based derivative, namely Fmoc-Amox (Table 6, entry 6), to tackle the drawbacks associated with Fmoc-cyanopyridyloxime.⁸⁰ Fmoc-Amox provides Fmoc-Gly-OH with high purity and without the formation of any dipeptide impurity. Fmoc-Amox is cheaper than Fmoc-cyanopyridyloxime. In addition, after completion of the reaction, it produces only Amox as a solid byproduct, and this can be removed easily by washing with water. These features make this protocol of high interest from an economic point of view.

Table 6 Introduction of Fmoc Using Fmoc-oximes

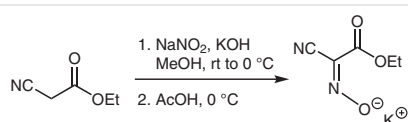
Entry	Oxime	Fmoc-Gly-OH		
		Yield (%)	Purity (%)	
1		82.9	99.7	0.17
2		92.1	99.4	0.57
3		48.5	99.7	0.22
4		91.6	99.9	0.01
5		92.8	99.5	0.41
6		93.0	99.5	0

■ Fmoc missing from the structures in table 6 ■

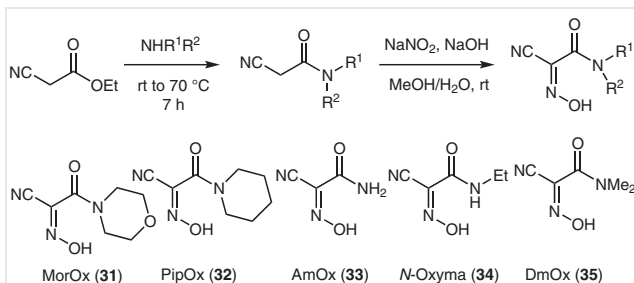
3 OxymaPure Derivatives

Over the years, several modifications have been made to the structure of OxymaPure. The acidity of this compound (pK_a is 4.60)⁸¹ plays a vital role in the reactivity of the additives and the stability of the active esters. However, despite the very low acidity highly acid-sensitive moieties were affected. For example, 2-chlorotritylchloride (CTC) resin, is

highly acid-sensitive and can release prematurely the growing peptide chain.^{82,83} In 2013, our group synthesized the potassium salt, K-Oxyma, of OxymaPure in order to suppress the acidity (Scheme 24).⁸⁴ The thermal stability, coupling efficiency and epimerization control of K-Oxyma resemble those of OxymaPure. In addition, K-Oxyma outperformed OxymaPure in solid-phase elongation with acid-sensitive solid supports. The stepwise solid-phase coupling of myelin basic protein (MBP) 104–118 (H-Gly-Lys-Gly-Arg-Gly-Leu-Ser-Leu-Ser-Arg-Phe-Ser-Trp-Gly-Ala-OH)⁸⁵ on acid-sensitive CTC resin was tested. K-Oxyma not only afforded higher yields than OxymaPure (90% vs 63%) but also gave a higher purity of the desired peptide (91% vs 88%).



Scheme 24 Synthesis of K-Oxyma



Scheme 25 Synthesis of *N*-alkyl-cyanoacetamido oximes

In addition, our group has synthesized a series of *N*-alkyl-cyanoacetamido oximes and examined their additive efficiency with DIC to replace HOSu in couplings that require less activation of the carboxyl group (Scheme 25).⁸⁶ The construction of amide linkages in certain biochemical molecules, peptides and proteins requires stable and less reactive active esters. However, the highly reactive Oxyma active ester and limited reactivity of HOSu esters are restricted. The presence of the carboxamido group confers the *N*-alkyl-cyanoacetamido oximes with high water solu-

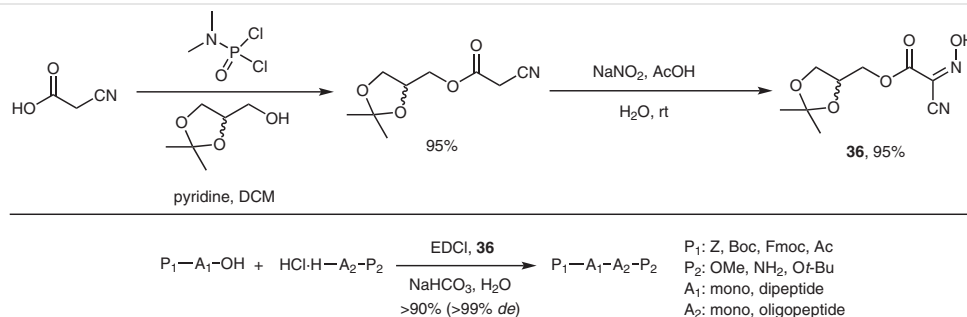
bility and results in **changes OK?** less reactive active esters. The performance of *N*-alkyl-cyanoacetamido oximes was tested during the solution-phase coupling reaction of Z-Phg-OH with H-Pro-NH₂ to form the dipeptide Z-Phg-Pro-NH₂. Remarkably, all the oximes afforded the dipeptide in good yield and with less epimerization than when using HOSu. Of the oximes tested, AmOx and DmOx achieved promising results in terms of optical purity and coupling efficiency (Table 7).

Table 7 Yield and Racemization During the Formation of Z-Phg-Pro-NH₂

Entry	Coupling reagent	Yield (%)	DL (%)
1	DIC/OxymaPure	89.9	1.0
2	DIC/HOSu	70.3	32.7
3	DIC/MorOX	88.4	5.7
4	DIC/PipOx	86.8	10.7
5	DIC/AmOx	81.4	3.0
6	DIC/ <i>N</i> -Oxyma	92.1	3.8
7	DIC/DmOx	93.4	8.3

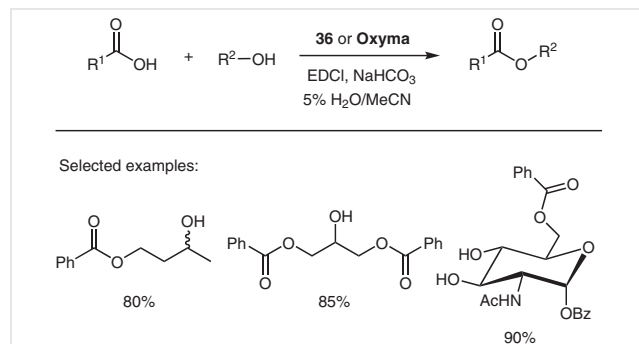
In 2012, Wang et al. reported glyceracetone-Oxyma (**36**) for peptide synthesis in a water-based solvent mixture.⁸⁷ This was the first report of an Oxyma-based additive for aqueous-mediated oligopeptide synthesis. Wang successfully synthesized di, tri and oligopeptides with common *N*-protected amino acids such as Cbz, Boc, Fmoc, and Ac. All the reactions worked well and gave good to excellent yields without any measurable epimerization (Scheme 26).

The same group further extended this methodology for esterification. They achieved selective esterification of primary alcohols with carboxylic acids by using EDCI **EDCI in sch 27?** and NaHCO₃ in the presence of OxymaPure or glyceracetone-Oxyma in 5% H₂O/MeCN as the solvent.⁸⁸ In the presence of secondary alcohols, benzoylated products were obtained selectively at the primary hydroxy group. The authors noted that OxymaPure and glyceracetone-Oxyma afforded equal conversions and yields, but that it was very difficult to separate OxymaPure from the



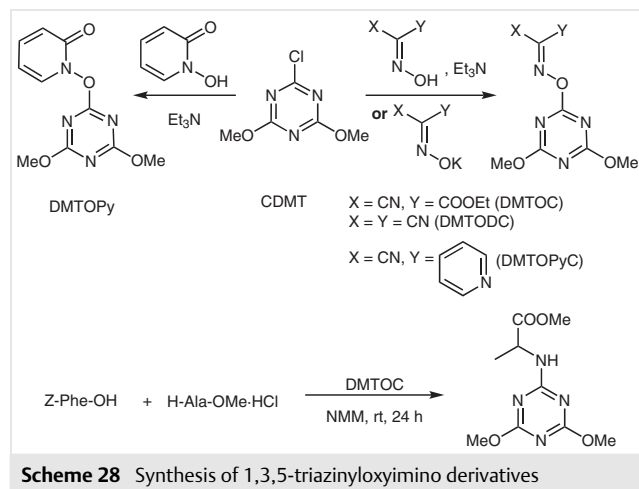
Scheme 26 The preparation of glyceracetone-Oxyma (**36**) and its use in peptide synthesis **changes OK?**

product by column chromatography. In the case of glycerol-acetonide-Oxyma, it was removed straightforwardly by standard acidic or basic work-up (Scheme 27).



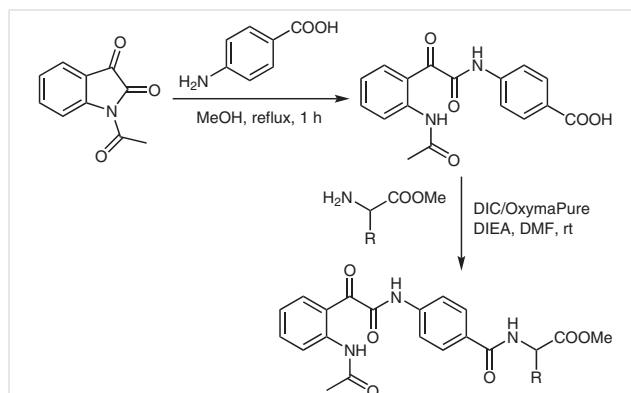
Scheme 27 Selective esterification of primary alcohols

In 2010, our group reported the synthesis and characterization of 1,3,5-triazinyloxyimino derivatives.⁸⁹ These compounds failed to activate the carboxyl group during the formation of peptide bonds but gave the corresponding *N*-triazinyl amino acid derivatives as the major products (Scheme 28).



Scheme 28 Synthesis of 1,3,5-triazinyloxyimino derivatives

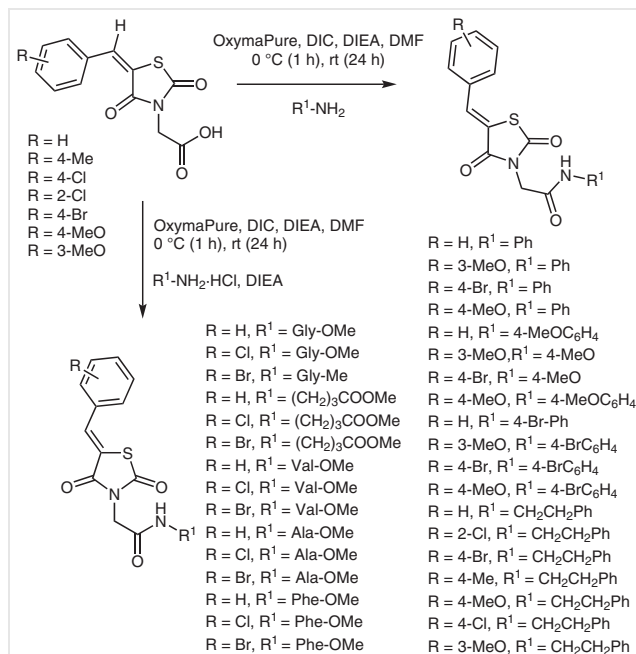
Later, in 2015, we described that the coupling cocktail of DIC/OxymaPure assisted the synthesis of α -ketoamino acid ester 2-[2-(2-acetamidophenyl)-2-oxoacetamido] and 2-[4-[2-(2-acetamidophenyl)-2-oxoacetamido]benzamido] derivatives.⁹⁰ These compounds showed good inhibitory properties and MAO-A **■** *define?* **■** selectivity (Scheme 29).



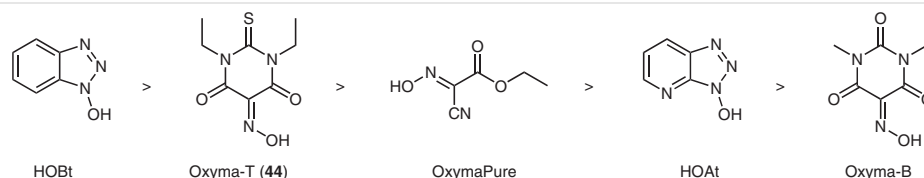
Scheme 29 Synthesis of α -ketoamino acid ester 2-[4-[2-(2-acetamidophenyl)-2-oxoacetamido]benzamido] derivatives

In 2018, Wang et al. reported that Oxyma-assisted click chemistry allowed rapid modification of chitin.⁹¹ The surface modification was achieved without the production of any toxic byproducts or waste organic solvents. This approach emerged as a novel method for the greener production of chitin-based biomaterials.

Very recently, our group disclosed the synthesis of a new series of thiazolidine-2,4-dione carboxamides and amino acid derivatives using DIC/OxymaPure.⁹² The presence of OxymaPure as an additive during the coupling facilitated this reaction, which is not straightforward due to the poor reactivity of the carboxylic moiety, and affords the target products in very good to excellent yields (Scheme 30).



Scheme 30 Synthesis of thiazolidine-2,4-dione carboxamides and amino acid derivatives using OxymaPure/DIC **■** *bottom left, 3rd entry: R¹ = Gly-Me OK, or Gly-OMe? Also, position of R not specified, as it is in top right list* **■** *check E/Z conversion between starting material and products* **■**



Scheme 31 Racemization order during the segment coupling of Z-Phe-Val-OH with H-Pro-NH₂

4 Other Oxime-Based Additives and Coupling Reagents

As shown in this review, the structure of OxymaPure is a remarkable scaffold for the preparation of derivatives that seek to modulate the properties of the additive. In this regard, significant research efforts have been channeled into the development of more efficient oxime-based coupling additives and reagents.

In 2010, our group developed highly reactive uronium salts based on isonitroso Meldrum's acid (HONM) (**37**) for amidation reactions (Figure 6).⁹³ The structure of HONM is similar to that of OxymaPure, except that it has two ester groups adjacent to the *N*-hydroxylamine moiety in a six-membered cyclic structure. The two electron-withdrawing substituents and the geometry enhance the reactivity of HONM compared to OxymaPure. As discussed later, the high reactivity of HONM leads to the formation of an adduct with DIC, and it is restricted to use as an additive with carbodiimide reagents. However, the uronium salts derived from HONM showed higher coupling efficiency than other classical coupling reagents. In this regard, the reactions worked very well and in a very short time, even with less reactive nucleophilic amines such as *p*-chloroaniline.

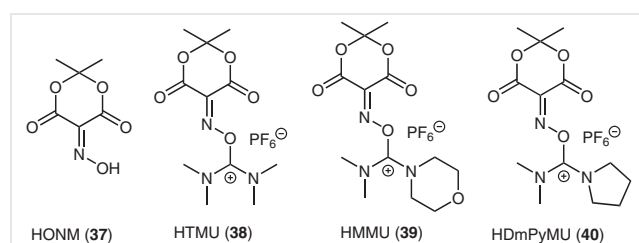


Figure 6 Structures of reagents based on Meldrum's acid

Later, in 2014, we introduced a new oxime-based additive, Oxyma-B (**41**) (Figure 7), which has a similar structure to HONM (based on the structure of barbituric acid) and does not contain any ester moiety.⁹⁴ Oxyma-B showed lower reactivity than HONM, thus allowing acylation with carbodiimide coupling reagents. In addition, it had good solubility in DMF, MeCN, and THF and demonstrated excellent coupling efficiency in both solution- and solid-phase peptide synthesis. Also, Oxyma-B showed greater control of epimerization than OxymaPure and HOAt during the step-

wise and segment synthesis of Z-Phe-Val-Pro-NH₂, Z-Phg-Pro-NH₂, H-Gly-Ser-Phe-NH₂, H-Gly-Cys-Phe-NH₂, H-Gly-His-Phe-NH₂ and H-Gly-Cys(Acm)-Phe-NH₂ peptides.

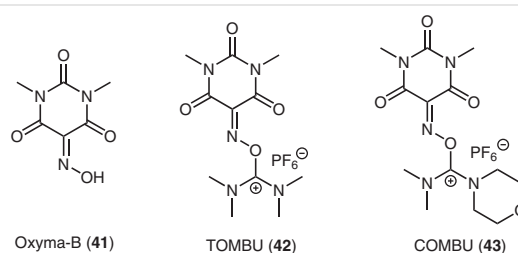
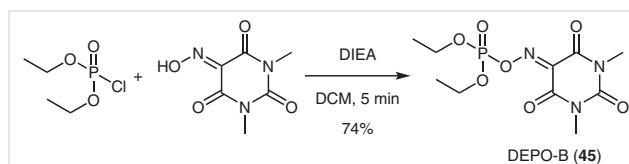


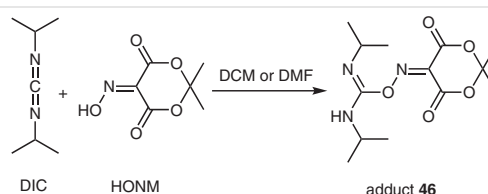
Figure 7 Structures of Oxyma-B-based reagents

Furthermore, our group developed the Oxyma-B-based novel uronium-type coupling reagents TOMBU (**42**) and COMBU (**43**) (Figure 7) for use in peptide bond formation.⁹⁵ These reagents showed higher hydrolytic stability in the solvent DMF than COMU. Also, TOMBU and COMBU outperformed HBTU with respect to coupling yields and optical purity but showed slightly poorer performance than COMU.

In 2016, we reported the novel oxime additive Oxyma-T (**44**), which belongs to a similar family to HONM and Oxyma-B, but is based on the structure of thiobarbituric acid.⁹⁶ Oxyma-T showed greater capacity to prevent epimerization than HOBt, HOAt, OxymaPure, and Oxyma-B in the step-wise assembly of the dipeptide Z-Phg-Pro-NH₂ in solution phase. However, during the segment coupling of Z-Phe-Val-OH with H-Pro-NH₂, it showed less epimerization than



Scheme 32 Synthesis of DEPO-B (**45**)



Scheme 33 The reaction of HONM with DIC

HOBt, but slightly higher epimerization than OxymaPure, HOAt and Oxyma B (Scheme 31). Furthermore, Oxyma-T also afforded a higher yield than HOBt in the solid-phase synthesis of Aib-enkephalin pentapeptide (H-Tyr-Aib-Aib-Phe-Leu-NH₂, 43% and 18%, respectively), but a very poor yield compared to HOAt and OxymaPure (55% and 71%, respectively).

Recently, our group described diethylphosphoryl-Oxyma-B ■■change OK?■■ (DEPO-B) (**45**) as a new Oxyma-B-based coupling reagent for peptide bond formation.⁹⁷ DEPO-B was easily synthesized by the reaction of Oxyma-B and diethyl chlorophosphate in the presence of a base in DCM (Scheme 32), and was used directly in subsequent reactions without any purification. In the presence of DIEA, the reaction afforded a good yield (74%), but gave a very poor yield (31%) with Et₃N. DEPO-B showed high solubility and good hydrolytic stability in DMF. Indeed, even after 13 days, 85% of the reagent was observed in this solvent. Hence, DEPO-B has emerged as a suitable reagent for the preparation of stock solutions and for use in an automatic peptide synthesizer.

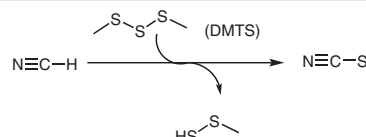
5 Side Reactions Using OxymaPure Derivatives

No reaction of termination through a transamidation—via the reaction of an emaino ■■■?■■■ with an ethyl ester—has been described for OxymaPure derivatives, even when using microwave-assisted heating.^{34,98} However, these derivatives can react with DIC. This effect is more pronounced when the oxime is more reactive, which is the case for the oxime derived from Meldrum's acid.⁹³ HONM can react directly with DIC and form the corresponding adduct **46** (Scheme 33). In this case, the reaction is significant and leads to the inactivation of DIC and therefore very poor coupling yields. The corresponding uronium salts of this oxime derivative give much better results.

A similar but less severe reaction has been described by Kolis and co-workers at Eli Lilly⁹⁹ when using OxymaPure in combination with DIC. In this case, the formation of hydrogen cyanide (HCN) was observed. The authors noted that the formation of HCN was exacerbated when excess amounts of DIC and OxymaPure are used relative to the

amino acid. However, this side reaction ■■changes OK?■■ has also been observed with substoichiometric amounts of DIC and OxymaPure with respect to the protected amino acid (0.5:0.5:1) (Scheme 34).

Very recently, Pawlas, Rasmussen and co-workers¹⁰⁰ showed that the addition of dimethyl trisulfide (DMTS) during the coupling greatly minimizes the side reaction without penalizing the coupling reaction. DMTS scavenges HCN only and does not react with other components such as DIC and OxymaPure (Scheme 35).



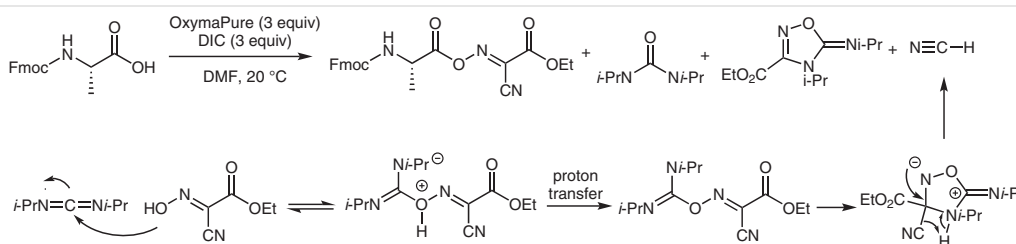
Scheme 35 HCN scavenging by DMTS

6 Conclusion

This review summarizes the recent developments and applications of OxymaPure and Oxyma-based reagents in peptide chemistry, including relevant reaction mechanisms. Oxyma-based reagents such as aminium/uronium salts, phosphonium salts, phosphates, sulfonate esters, benzoate esters and carbonates of OxymaPure have shown excellent coupling efficiency in amide bond formation, as well as in biologically active peptides and molecules. Furthermore, several modifications have been made to the structure of OxymaPure and a wide variety of oxime-based additives and reagents have been developed. In all cases, the OxymaPure derivatives have outperformed their HOBt counterparts. In summary, it can be concluded that OxymaPure reagents have broad applicability beyond solid-phase peptide synthesis.

7 List of Abbreviations

Alloc: allyloxycarbonyl
 BBTZ: benzoyloxybenzotriazole
 Boc: *t*-Butyloxycarbonyl
 Boc-Oxyma: 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate



Scheme 34 Reaction of OxymaPure with DIC

BOP: benzotriazol-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate
 BOP-Cl: *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
 Cbz, Z: benzyloxycarbonyl
 CDMT: 2-chloro-4,6-dimethoxy-1,3,5-triazine
 6-Cl-HOBt: 6-chloro-1-hydroxybenzotriazole
 COMU: 1-[1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)-dimethylamino-morpholinomethylene]methanaminium hexafluorophosphate
 CTC: 2-chlorotriethylchloride
 DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
 DCC: *N,N'*-dicyclohexylcarbodiimide
 DCM: dichloromethane
 DCMT: 2,4-dichloro-6-methoxy-1,3,5-triazine
 DEET: *N,N'*-diethyl-3-methylbenzamide
 DIC: *N,N'*-diisopropylcarbodiimide
 DIEA: diisopropylethylamine
 DMAP: *N,N*-dimethylaminopyridine
 DMTS: dimethyl trisulfide
 DPGOx: diethylphosphoryl-glyceroacetone-Oxyma
 DPOx: diethylphosphoryl-Oxyma
 DPPA: diphenyl phosphoryl azide
 Fmoc: 9-fluorenylmethyloxycarbonyl
 GVL: γ -valerolactone
 HATTU: *S*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate ■■check abbreviation, should 'S' be 'O'?■■
 HATU: *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
 HBMTU: *O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-trimethylenuronium hexafluorophosphate
 HBTU: *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
 HCTU: *N*-[(1*H*-6-chlorobenzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
 HDMA: 1-[(dimethylamino)(morpholino)methylene]-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate-3-oxide
 HDMB: 1-[(dimethylamino)(morpholino)methylene]-1*H*-benzotriazolium hexafluorophosphate-3-oxide
 HOAt: 1-hydroxy-7-azabenzotriazole
 HOBI: *N*-hydroxy-2-phenylbenzimidazole
 HOBt: 1-hydroxybenzotriazole
 HODhbt: 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
 HOI: *N*-hydroxyindolin-2-one
 HONM: isonitroso Meldrum's acid
 HOPy: 1-hydroxy-2-pyridinone
 HOSu: *N*-hydroxysuccinimide
 HOTU: *O*-[cyano(ethoxycarbonyl)methyleneamino]-

N,N,N',N'-tetramethyluronium hexafluorophosphate
 MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
 4-NBsOXY (*p*-NBsOXY): 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate
 NFM: *N*-formylmorpholine
 NMM: *N*-methylmorpholine
o-NosylOXY: ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate
 OxymaPure: ethyl 2-cyano-2-(hydroxyimino)acetate
 PyAOP: [(7-azabenzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
 PyBOP: benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate
 PyBroP: bromotri(pyrrolidino)phosphonium hexafluorophosphate
 PyCloP: chlorotri(pyrrolidino)phosphonium hexafluorophosphate
 PyClock ■■change OK?■■: (6-chloro-benzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate
 PyOxB: *O*-[(cyano(ethoxycarbonyl)methylidene)amino]yloxytripyrrolidinophosphonium tetrafluoroborate
 PyOxim (PyOxP): *O*-[(cyano(ethoxycarbonyl)methylidene)amino]yloxytripyrrolidinophosphonium hexafluorophosphate
 SAHA: suberoylanilide hydroxamic acid
 SPPS: solid-phase peptide synthesis
 TATU: *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
 TBTU: *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
 TCBOXY: (*E*)-ethyl-2-cyano-2-[(2,4,6-trichlorobenzoyl)oxy]imino)acetate
 TFFH: tetramethylfluoroformamidiniumhexafluorophosphate
 TOTU: *O*-[cyano(ethoxycarbonyl)methyleneamino]-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
 Trt: trityl
 T3P: propane phosphonic acid anhydride

Funding Information

We are grateful to the American Chemical Society (ACS) Green Chemistry Institute (GCI) (Pharmaceutical Roundtable Ignition Grant) for funding S.R.M. In addition, the work in laboratory of the authors was funded in part by the following: the South African Agency for Science and Technology Advancement, The National Research Foundation (NRF) (Blue Sky's Research Programme, Grant No. 120386) and the University of KwaZulu-Natal (South Africa); the Ministerio de Ciencia e Innovación (Spanish Ministry of Science, Innovation) (RTI2018-093831-B-100), the Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2017 SGR 1439) and the Ministerio de Economía y Competitividad; and the International Scientific Partnership Program ISPP at King Saud University (ISPP# 0061).■■changes OK?■■

Acknowledgment

Special thanks go to Mr. Yoav Luxembourg for encouraging our work on coupling reagents.

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