RSC Advances

PAPER

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2026, **16**, 24659

New benzotriazole–sulfonate coupling reagents and applications

Sayanta Roy and Bhubaneswar Mandal *

Received 22nd April 2026
Accepted 28th April 2026

DOI: 10.1039/d6ra03443h

rsc.li/rsc-advances

Amide and ester bond formation is crucial in medicinal chemistry and relies heavily on coupling reagents in both academic and industry. We report the development of new cost-effective recyclable benzotriazole–sulfonate coupling reagents in a straightforward, rapid, and easy manner. The reagents efficiently activate carboxylic acids to form amides, esters, thioesters, and peptides, with excellent yields and high chirality retention. The reagent enables drug modifications and transformations, including aldoxime-to-nitrile and carboxylic acid-to-ketone conversions. The use of green solvents effectively minimizes the environmental impact.

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

1 Introduction

Peptide therapeutics have garnered considerable interest, with many peptide-based drugs now approved for commercial use.[1] Amide and ester functionalities are also widespread in pharmaceuticals and fine chemicals.[2,3] Coupling reagents play a vital role in their synthesis, but their industrial production generates large amounts of toxic waste (Fig. 1A). One promising strategy to minimize waste generation involves the use of recyclable reagents. Recently, a novel recyclable NDTP-based coupling reagent was reported, enabling rapid and sustainable amide and peptide synthesis without epimerization.[4] Chiba *et al.* developed an electrochemical peptide-coupling method in which oxidized triphenylphosphine cations activate carboxylic acids to form amides, allowing for efficient phosphine reagent recycling.[5] Similarly, the Saito group introduced a greener peptide-coupling protocol that uses a recyclable bicyclic benziodazolone reagent, which also serves as a base and can be electrochemically regenerated from its iodine(I) form.[6] Recently, we reported a new Oxyma-sulfonate-based recyclable coupling reagent for sustainable amidation and esterification.[7] Recycling solvents and reagents significantly reduced the environmental impact. Replacing hazardous solvents with greener ones, another effective route to enhancing the sustainability of chemical synthesis. For instance, North *et al.* replaced hazardous DMF with the polar aprotic propylene carbonate solvent, yielding peptides with comparable purity and efficiency.[8] Cebri *et al.* demonstrated green solvent mixtures of Cyrene, sulfolane, or anisole with dimethyl or diethyl carbonate can effectively replace DMF in Fmoc solid-phase peptide synthesis.[9] Pawlas *et al.* reported green solid-phase peptide synthesis (SPPS) using a recyclable EtOAc/DMSO mixture solvent.[10] In peptide synthesis, hydroxybenzotriazole (HOBt) is widely used as a racemization suppressor.[11] Many uronium and phosphonium reagents incorporate HOBt derivatives;[12] however, their non-recyclable nature and the reliance on hazardous solvents (DMF, DCM, NMP) increase environmental risks.[13] Very few benzotriazole–sulfonate coupling reagents have been reported in the literature; these are either inefficient in peptide synthesis or insufficiently explored in other organic transformations.[14–20] We envisioned the development of a five-member heterocycle containing recyclable coupling reagents that operate efficiently in green solvents, eliminating hazardous DMF and enabling sustainable, diverse organic

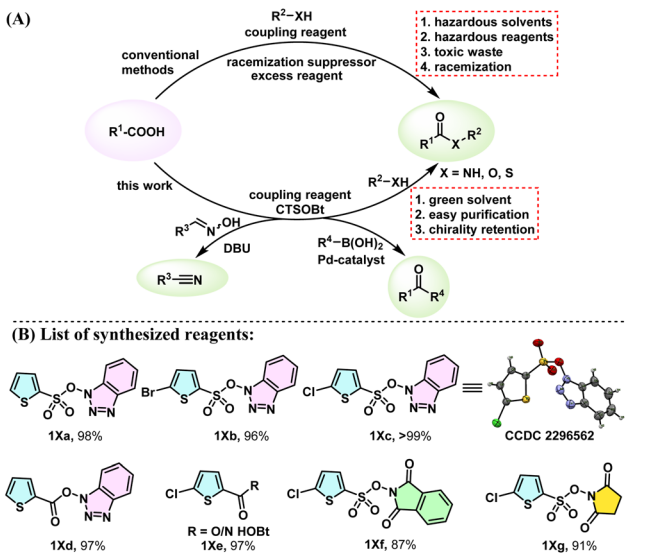


Fig. 1 (A) Coupling reagents in organic transformations, (B) synthesized heterocyclic reagents.

Department of Chemistry, Laboratory of Peptide and Amyloid Research, Indian Institute of Technology Guwahati, Assam-781039, India. E-mail: bmandal@iitg.ac.in; Tel: +91 361 258 2319

© 2026 The Author(s). Published by the Royal Society of Chemistry

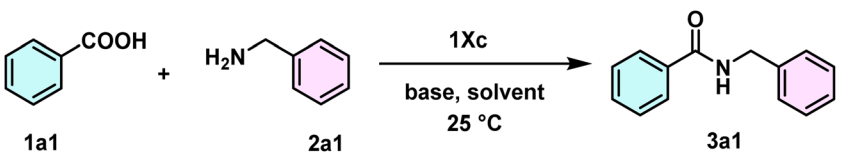
Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

transformations. We also envisioned that the presence of a heteroatom in the five-membered ring may facilitate interaction with the acid group. This interaction could keep the acid in close proximity to the coupling reagent, thereby enabling facile and efficient activation of the acid group upon reaction and promoting efficient amidation, esterification, and other organic transformations.

2 Results and discussion

Herein, we designed and synthesized several heterocyclic coupling reagents by reacting various thiophene sulfonyl or carbonyl chloride derivatives with other heterocycles such as HOBt, *N*-hydroxyphthalimide, or *N*-hydroxysuccinimide (Fig. 1B). The reagents were synthesized in good yields in a rapid, straightforward procedure. We then evaluated their efficiency in amidation. The reaction of benzoic acid (0.5 mmol) and benzylamine (0.5 mmol) in the presence of **1Xa** (0.5 mmol), DIPEA (0.6 mmol) in DCM (1 mL) offered amide **3a1** in 73% yield. Other reagents, except **1Xf** and **1Xg**, afforded the product in varying yields, with **1Xc** providing the highest yield (83%, entry 3, Table S1). Therefore, **1Xc** was used for subsequent reactions. HOBt can react at either O- or N-positions; the crystal structure of **1Xc** (CCDC 2296562) confirmed an O-substituted structure. Its synthesis in other solvents also gave excellent yields (Table S2). The large-scale synthesis of **1Xc** offered >99% yield (entry 7, Table S2). Amidation with **1Xc** was optimized in other solvents (THF, EtOAc, ACN, DMSO, DMF, $CHCl_3$, acetone, and acetone/H_2O) and bases (DIPEA, Et_3N, DBU). The highest yield of **3a1** (98%) was achieved in acetone with DIPEA within 30 min (entry 8, Table 1), and these conditions were considered as optimized. Using the optimized conditions, we explored the scope of amides, esters, thioesters, and peptides in solution (Table 2). Under optimized conditions, aromatic acids with electron-donating or withdrawing groups reacted efficiently with various amines, including benzylic, electron-deficient aromatic, and aliphatic amines, to afford the corresponding amides (**3a1–3a9**) in excellent yields (91–98%). C- and N-terminal protected amino acids, even with rigid side chains, gave amides (**3a10–3a15**) in excellent yields. Heterocyclic and long-chain aliphatic acids afforded amides (**3a16**, **3a17**) in good yields (96% and 89%). We further explored the synthesis of esters and thioesters. Aromatic acids with electron-donating and electron-withdrawing groups reacted efficiently with benzylic and poorly nucleophilic aromatic alcohols, affording the desired esters (**3a18–3a22**, **3a21** (CCDC 2307268)) in good yields. The slightly lower yields are likely due to the weaker nucleophilicity of alcohols compared to amines. Long-chain, heterocyclic, and Fmoc-amino acids gave esters (**3a24–3a27**) in good yields (84–96%) with aromatic/aliphatic alcohols. Acetonide-protected carbohydrate acceptors gave esters (**3a28**, **3a29**) satisfactorily, and Boc-amino acids afforded thioesters (**3a30**, **3a31**) in good yields. Interestingly, C- and N-protected amino acids under optimized conditions afforded excellent peptide formation. Boc-, Fmoc-, and Cbz-protected amino acids bearing aromatic, sterically hindered, or protected side chains offered excellent peptides (**3a32–3a44**) yields. We also successfully synthesized tripeptides (**3a45**, **3a46**) and a tetrapeptide (**3a47**) with satisfactory yields. The protocol's practical applicability was demonstrated by modifying various drug molecules. Ciprofibrate and the NSAIDs reacted efficiently with amines, alcohols, and thiols to give amide, ester, and thioester derivatives (**3a48–3a58**) in good to excellent yields. Febuxostat and gemfibrozil reacted with aromatic alcohol and cyclic aliphatic

Table 1 Optimization of reaction conditions



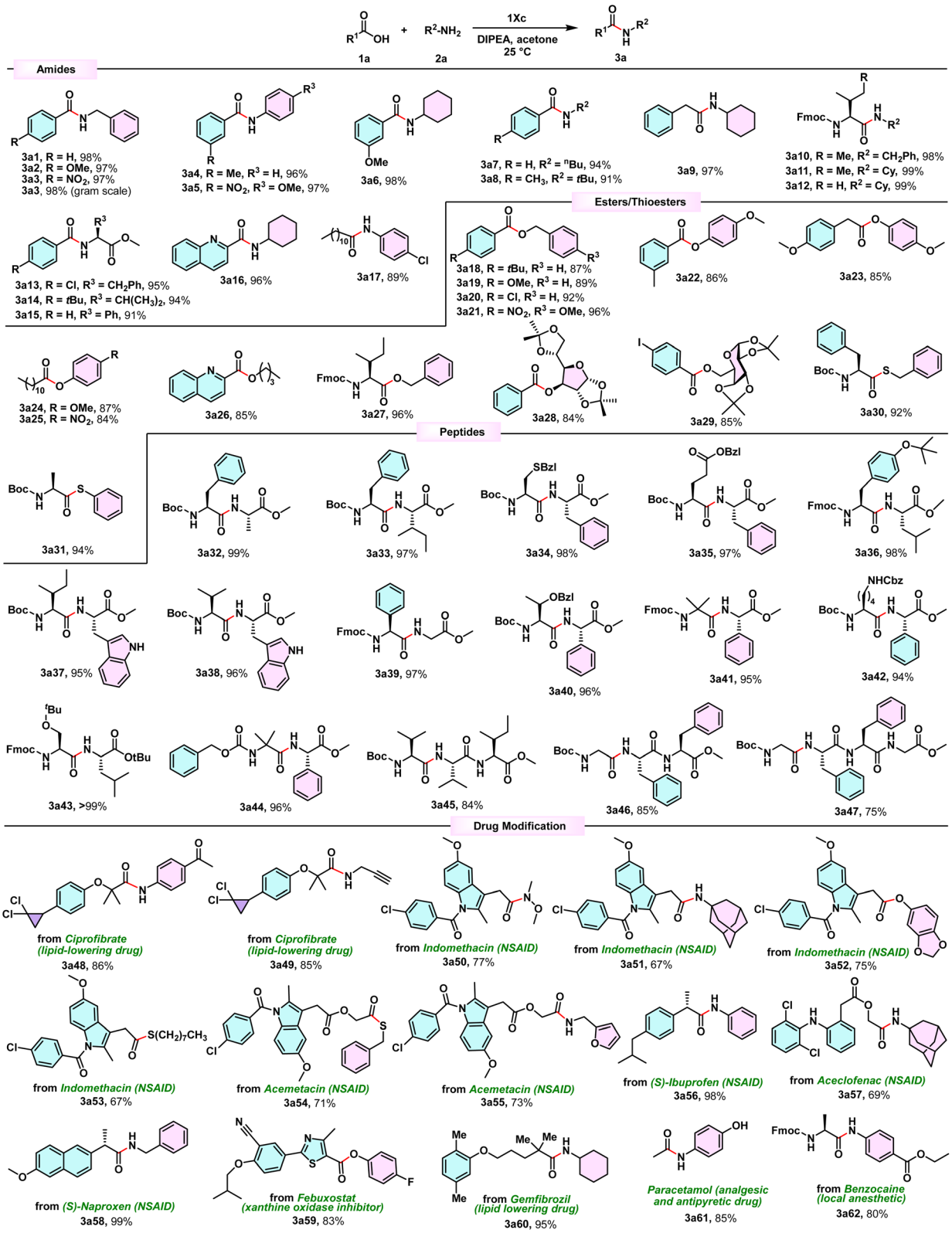
Entry	Solvent	Base	Time[c]	Yield[d] (%)
1[a]	DCM	DIPEA	12 h	83
2[a]	THF	DIPEA	2 h	64
3[a]	EtOAc	DIPEA	1.3 h	91
4[a]	ACN	DIPEA	35 min	88
5[a]	DMSO	DIPEA	3 h	50
6[a]	DMF	DIPEA	15 min	90
7[a]	$CHCl_3$	DIPEA	1.4 h	89
8[a]	Acetone	DIPEA	30 min	98
9[b]	Acetone/H_2O (1 : 1)	DIPEA	1 h 30 min	85
10[b]	Acetone/H_2O (1 : 4)	DIPEA	5 h	85
11[a]	Acetone	Et_3N	45 min	85
12[a]	Acetone	DBU	50 min	79

[a] Reaction conditions: **1a1** (0.5 mmol), **2a1** (0.5 mmol), **1Xc** (0.5 mmol), base (0.6 mmol), solvent (1 mL), 25 °C. [b] 50 °C. [c] Time after adding amine. [d] Isolated yields.

© 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

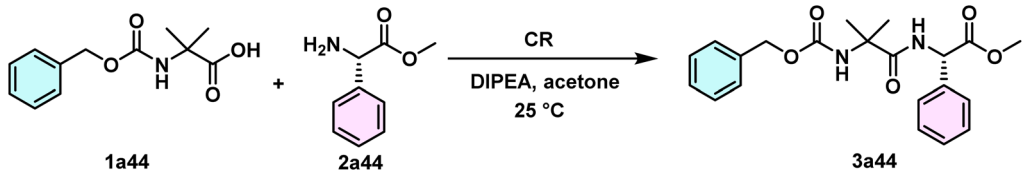
Table 2 Scope of amides, esters, thioesters, and peptides[a]



[a] Reaction conditions: **1a1** (0.5 mmol, 1 equiv.), **2a1** (0.5 mmol, 1 equiv.), **1Xc** (0.5 mmol, 1 equiv.), DIPEA (0.6 mmol, 1.2 equiv.), acetone (1 mL), 25 °C, isolated yield.

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 3 Comparative yields and racemization/epimerization during peptide **3a44** synthesis[a]

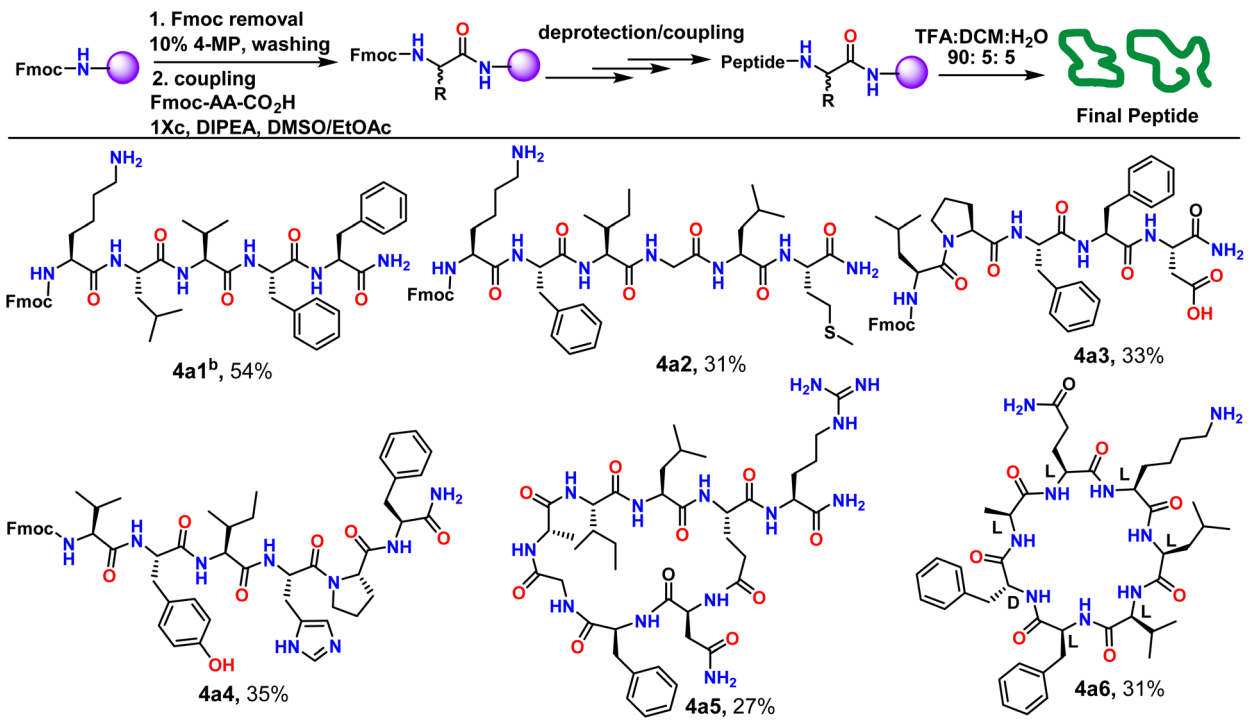


Entry[a]	Coupling reagents (CR)	Yield[c]	ee[d]
1	BOP	84%	95%
2	HBTU	69%	98%
3	HATU	68%	95%
4	DCC	63%	90%
5[b]	EDC HCl/Oxyma	67%	79%
6	COMU	78%	96%
7	1Xc	96%	>99%

[a] Reaction conditions: **1a44** (0.5 mmol, 1 equiv.), **2a44** (0.5 mmol, 1 equiv.), CR (0.5 mmol, 1 equiv.), DIPEA (0.6 mmol, 1.2 equiv.), acetone (1 mL), 25 °C. [b] DIPEA (1.1 mmol, 2.2 equiv.). [c] Isolated yield. [d] Determined by HPLC.

amine to afford modified drugs (**3a59**, **3a60**) satisfactorily. Paracetamol was also synthesised successfully (**3a61**), and benzocaine reacted smoothly with Fmoc amino acid, offering **3a62** in good yield. Upon synthesizing dipeptide **3a44** using several literature-reported coupling reagents, we compared the coupling efficiency and epimerization/racemization suppressing capacity with reagent **1Xc**. Reagent **1Xc** delivered the peptide yield superior to that obtained after the reaction with literature-reported reagents and provided excellent chiral retention (entry

Table 4 Scope of solid phase synthesized peptides[a]



[a] Reaction conditions: Rink amide resin (0.14 mmol, loading 0.7 mmol g^{-1}), amino acids (0.28 mmol, 2 equiv.), **1Xc** (0.35 mmol, 2.5 equiv.), DIPEA (0.7 mmol, 5 equiv.), solvent (2 mL): DMSO/EtOAc (1 : 9), Fmoc cleave: 10% 4-methylpiperidine (4 MP), coupling time: 3 h. [b] Yield in DMSO/acetone (1 : 19). AA = amino acid. Isolated yield.

© 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

7, Table 3). The same dipeptide system has previously been used in the literature to study racemization/epimerization.[21,22]

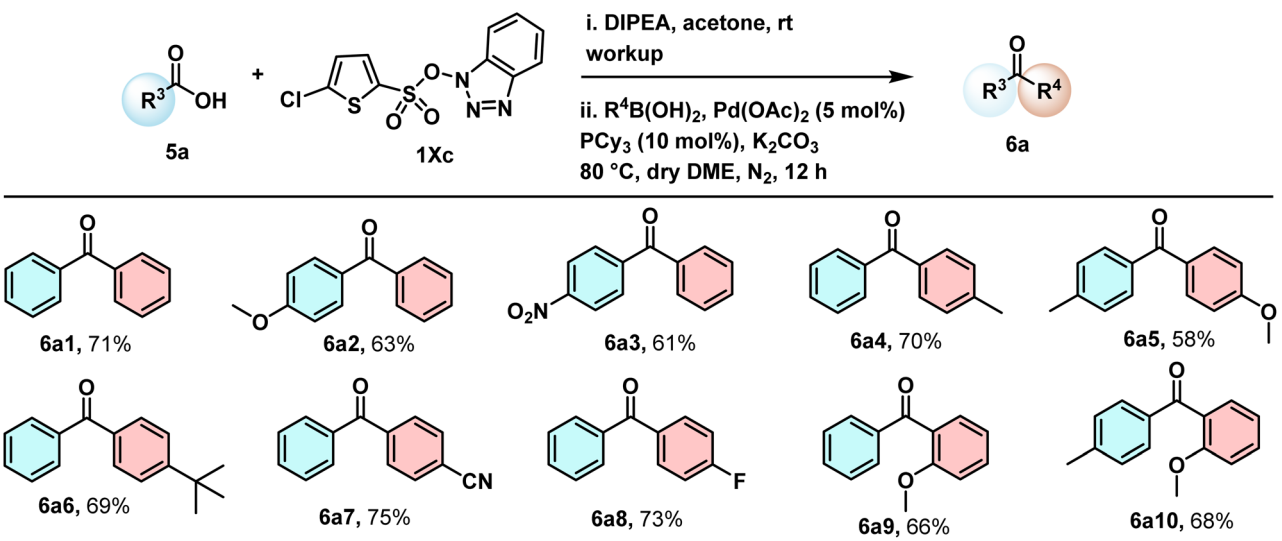
The application of reagent **1Xc** was extended in solid-phase peptide synthesis (Table 4). Although peptide synthesis is well-established, long-chain peptide synthesis remains challenging. Here, we aimed to replace the hazardous solvent DMF with a greener alternative. Initially, Fmoc-KLVFF-NH_2 (**4a1**),[23] an amyloid beta fragment peptide, was synthesized on Rink amide MBHA resin in acetone, affording peptide **4a1** in 41% yield. Binary solvent mixtures DMSO/EtOAc (1 : 9) and DMSO/acetone (1 : 19) were tested, yielding peptide **4a1** in 53% and 54%, respectively (Table S3). DMSO/acetone (1 : 19) was neglected due to poor resin swelling, and DMSO/EtOAc (1 : 9) was considered as the optimized solvent. We also synthesized eledoisin-related peptide **4a2** (31%) and the Soto peptide LPFFD **4a3** (33%), with satisfactory yields.[24,25] The hexapeptide VYIHPF (**4a4**), a fragment of the tissue hormone Angiotensin II,[26] was obtained in 35% yield. Cyclic peptide Cy-NFGAILER-NH_2 (**4a5**) was obtained *via* side-chain-to-tail cyclization in 27% yield.[27] Similarly, the head-to-tail cyclic peptide Cy-KLVFfAE (**4a6**), an inhibitor of $A\beta_{40}$ aggregation,[28] was synthesised successfully.

We further explored the application of **1Xc** by synthesizing ketones from aromatic carboxylic acids (Table 5) and nitriles from aromatic aldoximes (Table 6A). Ketones are widely found in natural products and pharmaceuticals.[29] Activated carboxylic esters offer carbonyl retention in Suzuki–Miyaura reactions.[30] Initially, benzoic acid was treated with reagent **1Xc** in acetone to generate an intermediate, which was subsequently extracted with ethyl acetate (EtOAc) and concentrated. This intermediate then underwent a palladium-catalyzed reaction with phenylboronic acid using $Pd(OAc)_2/PCy_3$, K_2CO_3, dioxane at 80 °C, yielding desired ketone **6a1** in 33% isolated yield (entry 1, Table S4). The reaction was optimized by varying solvents, bases, ligands, and catalysts. With 5 mol% $Pd(OAc)_2$ and 10 mol% PCy_3, using K_2CO_3 (2 equiv.) in dimethoxyethane (DME) at 80 °C, the yield of ketone **6a1** increased to 71% (entry 5, Table S4), which was identified as the optimized conditions. Under optimized conditions, diverse aromatic acids and aryl boronic acids coupled smoothly to give the desired ketones (**6a2–6a10**) in good yields (58–75%).

Furthermore, we replaced the coupling reagent with our **1Xc** reagent to test the conversion of aromatic aldoximes to nitriles under previously reported conditions.[31] Remarkably, aromatic aldoximes bearing either electron-donating or electron-withdrawing groups furnished the desired nitriles (**8a1–8a4**) in excellent yields, demonstrating the broad applicability of our reagent.

Polymer-supported coupling reagents have attracted considerable attention owing to their ease of recovery, ability to minimize racemization/epimerization, and simplified isolation of final products.[32] Here, we also synthesised a polymer-supported coupling reagent (**1Xp**, Table 6B) and characterised it using IR and EDX analysis (Table 6C–F). In IR analysis, the disappearance of the 3421 cm^{-1} peak (O–H stretching) and the appearance of 1398 cm^{-1} (SO_3-ester) peak suggested the successful synthesis of the coupling reagent. This result was further supported by EDX analysis. In EDX, the presence of both the S and Cl atom %, along with the C, N, and O atom %, confirmed the successful synthesis of the coupling reagent (**1Xp**), which was missing in the EDX of commercial polymeric HOBt (P-HOBt). The amidation of 4-methoxybenzoic acid with cyclohexylamine using **1Xp** was examined in acetone in the presence of DIPEA and in binary solvent systems (DMSO/EtOAc 1 : 9 and DMSO/acetone 1 : 19). The DMSO/acetone (1 : 19)

Table 5 Scope of ketones[a]

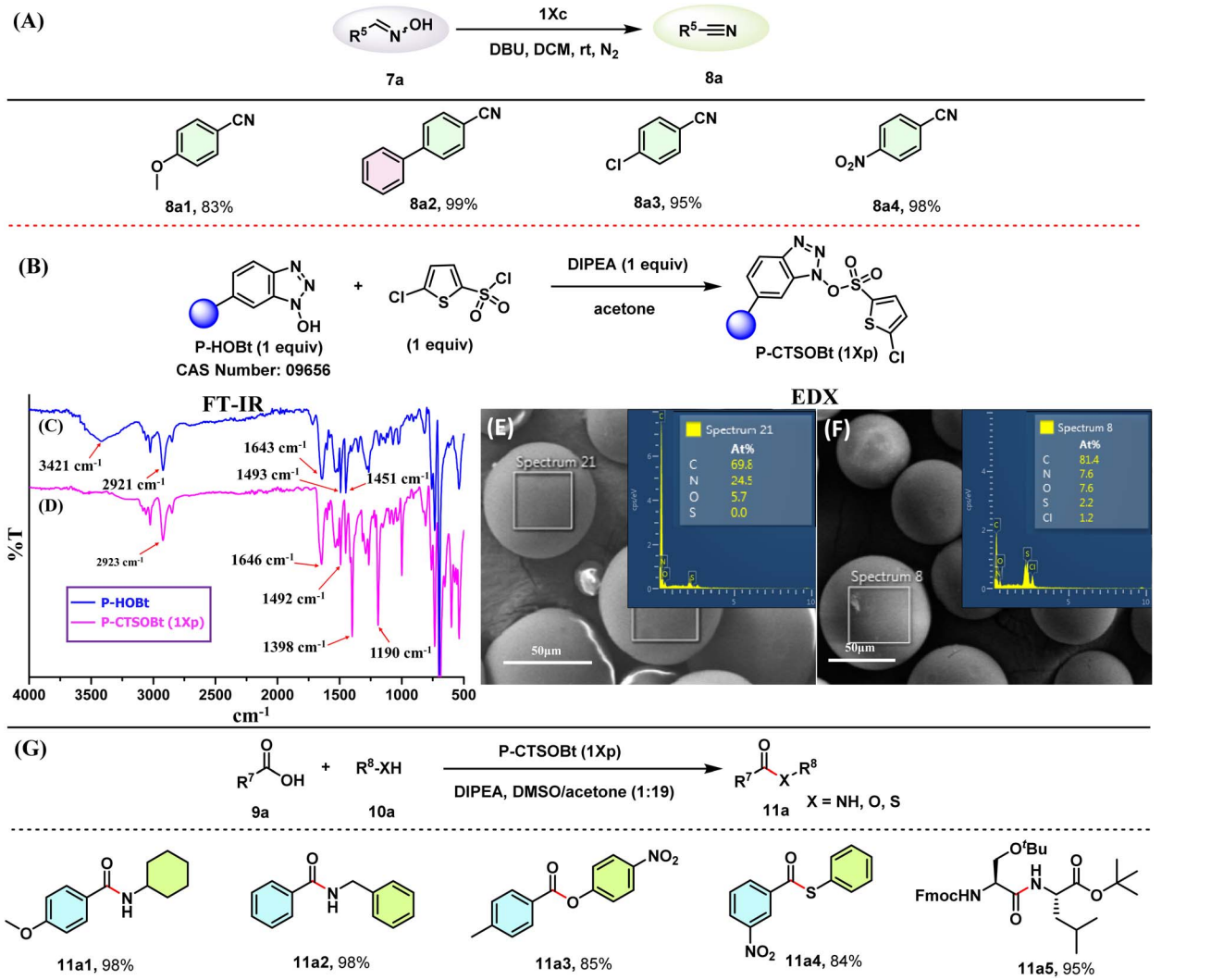


[a] Reaction conditions: Step-i. **5a** (0.2 mmol), **1Xc** (0.2 mmol, 1 equiv.), DIPEA (0.2 mmol, 1 equiv.), acetone (1 mL); Step-ii. $R^4B(OH)_2$ (0.3 mmol, 1.5 equiv.), $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), K_2CO_3 (0.4 mmol, 2 equiv.), DME (1 mL), 80 °C, N_2, isolated yield.

© 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 6 Scope of nitriles and synthesis of polymeric coupling reagent, applications[a]



[a] Reaction conditions: (A) **7a** (0.4 mmol, 1 equiv.), **1Xc** (0.4 mmol, 1 equiv.), DBU (0.8 mmol, 2 equiv.), DCM (1 mL), rt, N_2, 2 h, isolated yield. (B) Polymer-bound HOBt resin (200 mg, 0.2 mmol, 1 mmol g^{-1}), DIPEA (0.2 mmol) and 5-chlorothiophene-2-sulfonyl chloride (0.2 mmol), acetone (1.5 mL). FT-IR of (C) P-HOBt, (D) P-CTSOBt (**1Xp**); EDX of (E) P-HOBt, (F) P-CTSOBt (**1Xp**). (G) **1Xp**: 0.2 mmol (loading: 1 mmol g^{-1}), **9a** (0.2 mmol, 1 equiv.), **10a** (0.2 mmol, 1 equiv.), DIPEA (0.24 mmol, 1.2 equiv.), solvent (1 mL): DMSO/acetone (1 : 19), 25 °C, 1–6 h (after adding R^8-XH), isolated yield.

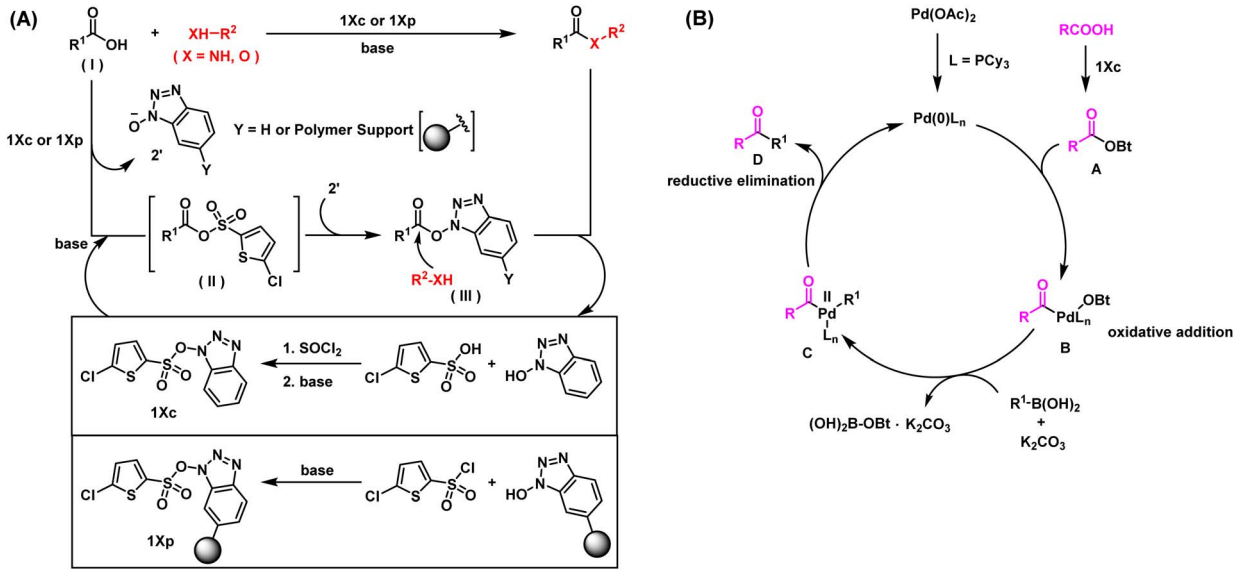
mixture afforded amide **11a1** in 98% yield (Table S5). Using this solvent system, examples of amides, esters, thioesters, and peptides (**11a2–11a5**) were synthesised from aromatic, aliphatic, and amino acids, providing excellent yields (84–98%, Table 6G). Upon completion of the reaction, the polymer-supported HOBt could be conveniently recovered by washing with solvent and reused multiple times without a decrease in reactivity.

A plausible mechanistic pathway for the synthesis of amides, esters, thioesters, and peptides using **1Xc** or **1Xp** is depicted in Scheme 1A. Initially, DIPEA facilitates the generation of the carboxylate nucleophile. The nucleophilic attack of the carboxylate nucleophile on the sulfonyl center of **1Xc** or **1Xp** forms the mixed anhydride (II) with elimination of OBt^- (2′). Subsequent nucleophilic attack of OBt^- (2′) on the carbonyl carbon of intermediate (II) affords the activated intermediate (III). Finally, nucleophiles (*e.g.*, amines, alcohols, thiols, or amino acids) attack intermediate (III) to produce the desired amides, esters, thioesters, or peptides.

The recovered mixture of byproducts (5-chlorothiophene-2-sulfonic acid (SA) and HOBt) can be treated with $SOCl_2$ at 70 °C in toluene, using a catalytic amount of DMF, to regenerate the corresponding sulfonyl chloride. Then, the addition of base can lead to the formation of coupling reagent **1Xc**. We recycled 51% of the coupling reagent **1Xc**, and using this recycled reagent, the reaction between benzoic acid and benzylamine afforded 95% of amide **3a1**. In the case of **1Xp**, the recovered P-HOBt can

© 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 1 (A) Plausible mechanism for amidation/esterification and recyclability of coupling reagents **1Xc** or **1Xp**; (B) Plausible mechanism for ketone synthesis.

directly react with 5-chlorothiophene-2-sulfonyl chloride in the presence of a base to form **1Xp**.

A plausible mechanism for the synthesis of ketones is also proposed in Scheme 1B. Initially, $Pd(OAc)_2$ and the ligand (PCy_3) react to generate an *in situ* Pd(0) complex. This complex undergoes oxidative addition with acyl-OBt (A), forming intermediate B. Base-assisted transmetalation with the boronic acid then produces intermediate C. Finally, reductive elimination affords the desired ketone product D, regenerating the Pd(0) catalyst.

3 Conclusion

In conclusion, we have designed and synthesized new benzotriazole–sulfonate coupling reagents that enable the sustainable synthesis of amides, esters, thioesters, nitriles, ketones, and peptides with excellent yields and chirality retention. The use of recyclable coupling reagents (**1Xc** and polymer-supported **1Xp**), green solvents, and broad substrate scope in diverse organic transformations highlights the wide applicability and practicality of this protocol. We believe these new coupling reagents will find wider applications in many other organic transformations.

Author contributions

S. R.: conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing – review and editing. B. M.: conceptualization, supervision, writing – review and editing, and funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

CCDC 2296562 (**1Xc**) and 2307268 (**3a21**) contain the supplementary crystallographic data for this article.[33a,b]

Supplementary information (SI): detailed experimental procedures and complete characterization data for all new compounds. See DOI: https://doi.org/10.1039/d6ra03443h.

Acknowledgements

We thank CIF, and Department of Chemistry, IIT Guwahati, for NMR, SC-XRD, and other instrumental facilities; and SERB, Govt. of India, for financial support (Grant Number: CRG/2023/004467).

References

1 G. Rossino, et al., Peptides as Therapeutic Agents: Challenges and Opportunities in the Green Transition Era, *Molecules*, 2023, **28**, 7165.
2 G. Li and M. Szostak, Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature, *Nat. Commun.*, 2018, **9**, 4165.
3 B. Liu, F. Hu and B.-F. Shi, Recent Advances on Ester Synthesis *via* Transition-Metal Catalyzed C–H Functionalization, *ACS Catal.*, 2015, **5**, 1863–1881.
4 Y. Li, et al., NDTP Mediated Direct Rapid Amide and Peptide Synthesis without Epimerization, *Org. Lett.*, 2022, **24**, 1169–1174.
5 S. Nagahara, et al., Biphasic electrochemical peptide synthesis, *Chem. Sci.*, 2021, **12**, 12911–12917.
6 D. Uehara, et al., Peptide coupling using recyclable bicyclic benziodazolone, *Chem. Commun.*, 2024, **60**, 956–959.

Open Access Article. Published on 11 May 2026. Downloaded on 6/9/2026 6:58:53 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

7 S. Roy and B. Mandal, A New Green Oxyma-Sulfonate Coupling Reagent for Sustainable Organic Transformations, *ACS Sustain. Chem. Eng.*, 2025, **13**, 5531–5545.
8 S. B. Lawrenson, R. Arav and M. North, The greening of peptide synthesis, *Green Chem.*, 2017, **19**, 1685–1691.
9 L. Ferrazzano, et al., Green Solvent Mixtures for Solid-Phase Peptide Synthesis: A Dimethylformamide-Free Highly Efficient Synthesis of Pharmaceutical-Grade Peptides, *ACS Sustain. Chem. Eng.*, 2019, **7**, 12867–12877.
10 J. Pawlas and J. H. Rasmussen, ReGreen SPPS: enabling circular chemistry in environmentally sensible solid-phase peptide synthesis, *Green Chem.*, 2019, **21**, 5990–5998.
11 G. Windridge and E. C. Jorgensen, 1-Hydroxybenzotriazole as a racemization-suppressing reagent for the incorporation of im-benzyl-L-histidine into peptides, *J. Am. Chem. Soc.*, 1971, **93**, 6318–6319.
12 A. El-Faham and F. Albericio, Peptide Coupling Reagents, More than a Letter Soup, *Chem. Rev.*, 2011, **111**, 6557–6602.
13 S. Jadhav, et al., Replacing DMF in solid-phase peptide synthesis: varying the composition of green binary solvent mixtures as a tool to mitigate common side-reactions, *Green Chem.*, 2021, **23**, 3312–3321.
14 N. B. Palakurthy and B. Mandal, Sulfonamide synthesis using N-hydroxybenzotriazole sulfonate: an alternative to pentafluorophenyl (PFP) and trichlorophenyl (TCP) esters of sulfonic acids, *Tetrahedron Lett.*, 2011, **52**, 7132–7134.
15 L. A. Carpino, J. Xia, C. Zhang and A. El-Faham, Organophosphorus and Nitro-Substituted Sulfonate Esters of 1-Hydroxy-7-azabenzotriazole as Highly Efficient Fast-Acting Peptide Coupling Reagents, *J. Org. Chem.*, 2004, **69**, 62–71.
16 B. Devadas, B. Kundu, A. Srivastava and K. B. Mathur, 6-Nitro-1-β-napthalenesulfonyloxybenzotriazole : A novel coupling reagent for peptide synthesis, *Tetrahedron Lett.*, 1993, **34**, 6455–6458.
17 M. Furukawa, N. Hokama and T. Okawara, 1-(2-Nitrobenzenesulfonyloxy)-6-nitrobenzotriazole: A New Reagent for Coupling in Peptide Synthesis, *Synthesis*, 1983, 42–44.
18 K. G. Devine and C. B. Reese, Highly reactive condensing agents for the synthesis of oligonucleotides by the phosphotriester approach, *Tetrahedron Lett.*, 1986, **27**, 5529–5532.
19 M. K. Singh and M. K. Lakshman, A Simple Synthesis of Nitriles from Aldoximes, *J. Org. Chem.*, 2009, **74**, 3079–3084.
20 N. B. Palakurthy, D. Dev, S. Paikaray, S. Chaudhury and B. Mandal, Synthesis of O-benzyl hydroxamates employing the sulfonate esters of N-hydroxybenzotriazole, *RSC Adv.*, 2014, **4**, 7952–7958.
21 C. M. Gabriel, et al., Amide and Peptide Bond Formation in Water at Room Temperature, *Org. Lett.*, 2015, **17**, 3968–3971.
22 D. Petkova, N. Borlinghaus, S. Sharma, J. Kaschel, T. Lindner, J. Klee, A. Jolit, V. Haller, S. Heitz, K. Britze, J. Dietrich, W. M. Braje and S. Handa, Hydrophobic Pockets of HPMC Enable Extremely Short Reaction Times in Water, *ACS Sustain. Chem. Eng.*, 2020, **8**, 12612–12617.
23 T. A. Enache, A.-M. Chiorcea-Paquim and A. M. Oliveira-Brett, Amyloid Beta Peptide VHHQ, KLVFF, and IIGLMVGGVV Domains Involved in Fibrilization: AFM and Electrochemical Characterization, *Anal. Chem.*, 2018, **90**, 2285–2292.
24 G. A. Cottrell and M. E. Welsh, Effects of Synthetic Eledoisin and Bradykinin on Certain Invertebrate Preparations and the Isolated Frog Heart, *Nature*, 1966, **212**, 838–839.
25 Ü. Murvai, et al., Effect of the beta-sheet-breaker peptide LPFFD on oriented network of amyloid β25-35 fibrils, *J. Mol. Recogn.*, 2011, **24**, 453–460.
26 E. C. Jorgensen and W. Patton, Angiotensin II analogs. II. Cyclo-(-Val-Tyr-Ile-His-Pro-Phe-), *J. Med. Chem.*, 1969, **12**, 935–936.
27 W. Hoffmann, et al., NFGAIL Amyloid Oligomers: The Onset of Beta-Sheet Formation and the Mechanism for Fibril Formation, *J. Am. Chem. Soc.*, 2018, **140**, 244–249.
28 S. Kalita, et al., Copper chelating cyclic peptidomimetic inhibits Aβ fibrillogenesis, *RSC Med. Chem.*, 2022, **13**, 761–774.
29 R. Ruzi, K. Liu, C. Zhu and J. Xie, Upgrading ketone synthesis direct from carboxylic acids and organohalides, *Nat. Commun.*, 2020, **11**, 3312.
30 L. J. Gooßen and K. Ghosh, A new practical ketone synthesis directly from carboxylic acids: first application of coupling reagents in palladium catalysis, *Chem. Commun.*, 2001, 2084–2085, DOI: 10.1039/B106779F.
31 D. Dev, et al., An unexpected involvement of ethyl-2-cyano-2-(hydroxyimino) acetate cleaved product in the promotion of the synthesis of nitriles from aldoximes: a mechanistic perception, *Tetrahedron Lett.*, 2013, **54**, 4397–4400.
32 R. Chinchilla, et al., Polymer-bound TBTU as a new solid-supported reagent for peptide synthesis, *Tetrahedron Lett.*, 2000, **41**, 2463–2466.
33 (*a*) CCDC 2296562: Experimental Crystal Structure Determination, 2026, DOI: 10.5517/ccdc.csd.cc2h2rn0; (*b*) CCDC 2307268: Experimental Crystal Structure Determination, 2026, DOI: 10.5517/ccdc.csd.cc2hfx0w.

© 2026 The Author(s). Published by the Royal Society of Chemistry