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Synthetic exploration of electrophilic xanthylation via powerful *N*-xanthylphthalimides†

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Organic xanthates are broadly applied as synthetic intermediates and bioactive molecules in synthetic chemistry. Electrophilic xanthylation represents a promising approach but has rarely been explored mainly due to the lack of powerful electrophilic reagents. Herein, synthetic exploration of electrophilic xanthylation via powerful *N*-xanthylphthalimides was investigated. This strategy might provide a new avenue to less-concerned but meaningful electrophilic xanthylation in organic synthesis. With the help of these powerful reagents, electrophilic xanthylation of a wide range of substrates including aryl/alkenyl boronic acids, β -keto esters, 2-oxindole, and alkyl amines, as well as previously inaccessible phenols (first report) was achieved under mild reaction conditions. Notably, this simple electrophilic xanthylation of alkyl amine substrates will occur in the desulfuration reaction, consistent with the previously reported methods. Similarly, xanthamide and thioxanthate groups could also be transformed into desired nucleophiles via this electrophilic reagent strategy. The broad substrate scope, excellent functional group compatibility and late-stage functionalization of bioactive or functional molecules made them very attractive as general reagents which will allow rapid incorporation of SC(S)R (R = OEt, Oalkyl, NEt₂ and SEt) into the target molecules.

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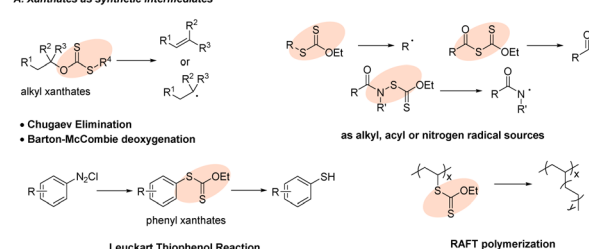
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1 Introduction

Organic sulfur compounds have become the focus of research interest due to their presence in myriad natural products,¹ organic synthesis,^{2,3} biological processes⁴ and materials science.⁵ Xanthates and their analogues, a special class of sulfur-containing compounds with the S–C(S) linkage,⁶ have gained extensive importance because of their potential applications in the area of synthetic intermediates and bioactive molecules (Fig. 1). As an important functional group in synthetic chemistry, the first encounter with xanthates could generate (Z)-olefins through the famous Chugaev elimination (Fig. 1A)⁷ at a high temperature, which perhaps serve as key intermediates in the manufacture of viscose from cellulose.⁸ Besides, the well-developed Barton–McCombie deoxygenation⁹ serving as a convenient source of alkyl radicals¹⁰ had a profound impact on the modification of carbohydrates in

organic synthesis. Most importantly, organic xanthates could be also utilized as alkyl, acyl or nitrogen radical sources¹¹ for further diverse or multifunctional transformations. Moreover, the extensive application of aryl xanthates is the famous Leuckart thiophenol reaction *via* nucleophilic xanthylation with diazonium salts (Fig. 1A).¹² Furthermore, in the field of materials science, the RAFT polymerization process (Fig. 1A)¹³ can introduce xanthate groups into long-chain alkyl groups, which can thus avoid the disadvantage of chain termination in

A. Xanthates as synthetic intermediates



B. Xanthates and its analogues as bioactive molecules

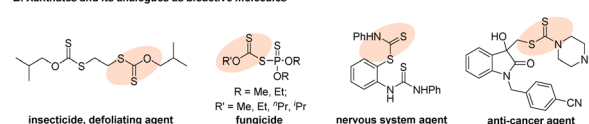


Fig. 1 Xanthates and its analogues as synthetic intermediates and bioactive molecules.

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traditional polymerization reactions and make the free radical polymerization more controllable, providing a new method for the functional improvement of polymer materials. Additionally, xanthate units and their analogues are present prominently in agrochemicals (Fig. 1B, insecticide and fungicide)^{14a,b} and pharmaceuticals (nervous system agent and anti-cancer agent),^{14c,d} which has attracted increasing interest from both academia and the pharmaceutical industry. Therefore, development of new and valuable strategies for the efficient synthesis of organic xanthates from numerous substrates has been attracting continuous interest from the synthetic community.

The conventional approach for the construction of xanthylated compounds typically involves metal-free nucleophilic substitution of electrophiles¹⁵ or a copper-mediated xanthylation of aryl halides with potassium ethylxanthate,¹⁶ well developed by Zard, Sekar, Melchiorre and others (Scheme 1A). As an alternative strategy, recent radical xanthylations using xanthylated synthons as radical acceptors or donor sources have emerged.^{17–19} In 2022, a facile, efficient, and practical protocol that enables the preparation of aryl xanthates from functionalized dibenzothiophenium salts and sodium ethylxanthogenate *via* a photoactivated electron donor–acceptor (EDA) complex was first established by Wang and his coworkers.¹⁸ Notably, Alexanian^{19a,b} recently reported a direct C–H radical xanthylation or decarboxylative radical xanthylation

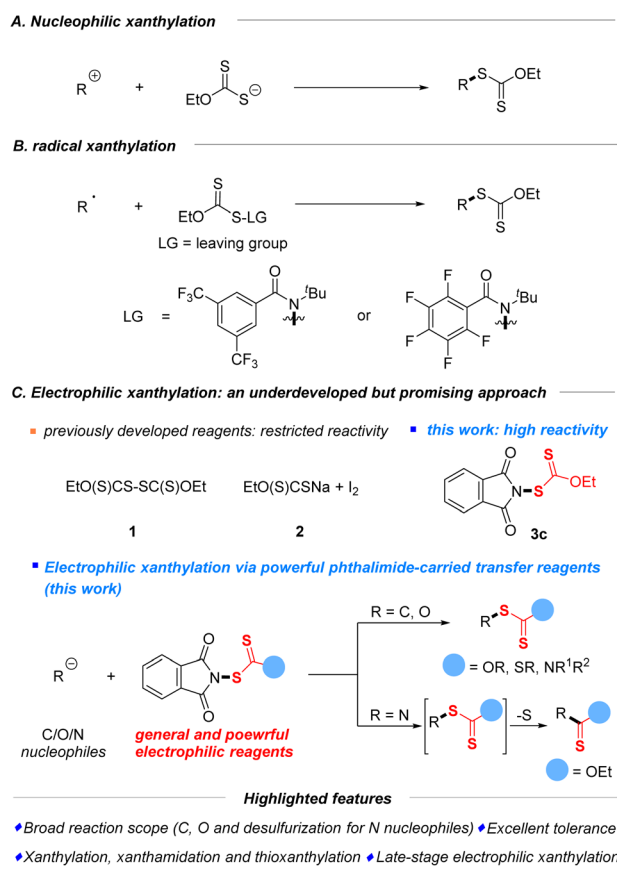
by distinctive reagent *N*-ethylxanthylamides under redox-neutral conditions to unlock a wide array of conversions of hydrocarbons (Scheme 1B).

Considering that structurally diverse organic molecules especially lead compounds of drugs are typically electron-rich, electrophilic xanthylation represents an attractive strategy that will be widely applied in the future of drug research and development (R&D), but it has rarely been explored due to the scarcity of general and powerful electrophilic reagents. So far, only two electrophilic reagents (EtO(S)CS–SC(S)OEt (**1**) and EtO(S)CSNa/I₂ (**2**)) have been reported for electrophilic substitutions of methylene compounds (**1**) and special amines (**2**).²⁰ Our further electrophilic attempts disclosed that these previously developed reagents (Scheme 1C, 1–2) have restricted reactivity for common C/N/O nucleophiles (boronic acids, keto esters, alkyl amines, and phenols, please see the ESI† for more details). Therefore, the search for a practical and efficient synthetic auxiliary that can conveniently play the role of xanthyl group transfer, as a general and powerful electrophilic xanthylating reagent, is of high demand and scientific interest. Inspired by the successful development of electrophilic phthalimide-based reagents,^{21,22} which probably benefits from the cleavage of the weak “N–S” bond, we wished to consider whether *N*-xanthylphthalimides could serve as broadly applicable reagents that enable electrophilic xanthylation of various nucleophiles. The reactivities of electrophilic xanthyl reagents were then demonstrated by xanthylation of a wide range of substrates, including C and N common nucleophiles as well as the first report of O nucleophiles in good to excellent yields with superb functional group compatibility under mild conditions (Scheme 1C). Notably, this simple electrophilic xanthylation of amine substrates will occur in the desulfuration reaction to give important and valuable thiocarbamates. Especially, the late-stage direct xanthylation of bioactive or functional molecules made this electrophilic xanthyl reagent very attractive to allow rapid incorporation of SC(S)OEt into target electron-rich molecules during the search for new drugs.

2 Results and discussion

2.1. Preparation of electrophilic ethylxanthyl reagents with amide or sulfonamide skeletons

N-Ethylxanthyl phthalimide **3c** was originally synthesized in 16% yield by De Greef in 2006,²³ but its synthetic applications are unexplored. As an air and moisture-stable solid, it can be simply and rapidly synthesized from commercially available phthalimide and potassium ethylxanthate in 71% yield *via* a modified synthesis protocol, as shown in Fig. 2. X-ray crystallographic analysis of **3c**²⁴ shows that the N (1)–S (1) bond length is 1.683 Å, which is longer than the comparable bonds in a crystal of previously developed *N*-difluoromethylthiophthalimide and *N*-trifluoromethylthio succinimide (1.681 Å and 1.676 Å, respectively) (please see the ESI† for more details). These data reveal that reagent **3c** is likely to be a potential electrophilic reagent. Similarly, ethylxanthyl reagents based on other amide or sulfonamide skeletons (succinimide **3a**, 5,5-



Scheme 1 Synthetic strategies for xanthylation.



Development of amide or sulfonamide-based electrophilic ethyl xanthate reagents:

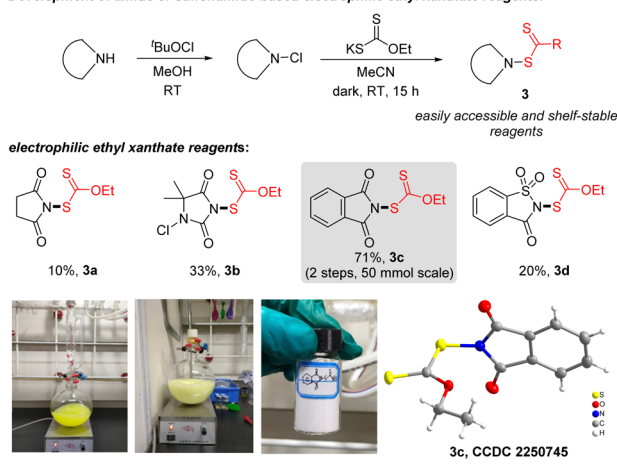


Fig. 2 Two-step scalable preparation of *N*-ethylxanthylphthalimide **3c** and its analogues.

dimethylhydantoin **3b**, and saccharin **3d**) could also be prepared in acceptable yields (10–33%) *via* this strategy.

2.2. Xanthylation of aryl/alkenyl boronic acids

With these xanthyl reagents **3a–3d** based on the amide or sulfonamide skeleton in hand, radical aliphatic C–H xanthylations were investigated and failed to give xanthylated hydrocarbons, indicating that the current *N*-xanthyl reagents, developed by De Greef and our group, are significantly different from Alexanian's *N*-xanthyl amides.^{19a,b} Thus, we are trying to determine whether they can achieve electrophilic xanthylation that has received little attention but represents a meaningful strategy. Thus, we chose easily available, bench-stable aryl boronic acids as the precursors of aryl nucleophiles to investigate Chan–Lam-type xanthylation with electrophilic reagents **1–3d** (Table 1A). The initial attempt had proved that EtO(S)CS–SC(S)OEt (**1**) or EtO(S)CSNa/I₂ (**2**) has no reactivity for the cross-coupling of 4-biphenyl boronic acid. Further explorations with the mixing of **4ap** and *N*-ethylxanthyl succinimide (**3a**) or *N*-ethylxanthyl saccharin (**3d**) in the presence of CuBr at 60 °C failed to deliver the xanthyl group to the aromatic ring, while unsuccessful conversion also occurred if the commercially available 5,5-dimethylhydantoin auxiliary (**3b**) was used. Surprisingly, the phthalimide skeleton (**3c**) was masked as the excellent leaving group in promoting the envisioned electrophilic transformation and could afford the desired ethylxanthyl-substituted **5ap** in 86% yield. Subsequently, systematic investigations were conducted to obtain the optimal conditions of the reaction by choosing **3c** as the model xanthyl reagent (Table 1B). A range of Cu(I) or Cu(II) catalysts (CuCl, CuBr, CuI and Cu(OAc)₂) were screened, but no enhancement in the yield was detected (entries 2–3). Surprisingly, a reaction in the presence of cheap CuSO₄ using 2,2'-bipyridine as the ligand in MeCN at 60 °C for 15 h provided a 97% yield of EtOC(S)S-derived product **5ap** (entry 1). Notably, this Chan–Lam-type xanthylation can be

Table 1 Reaction optimization^{a,b}

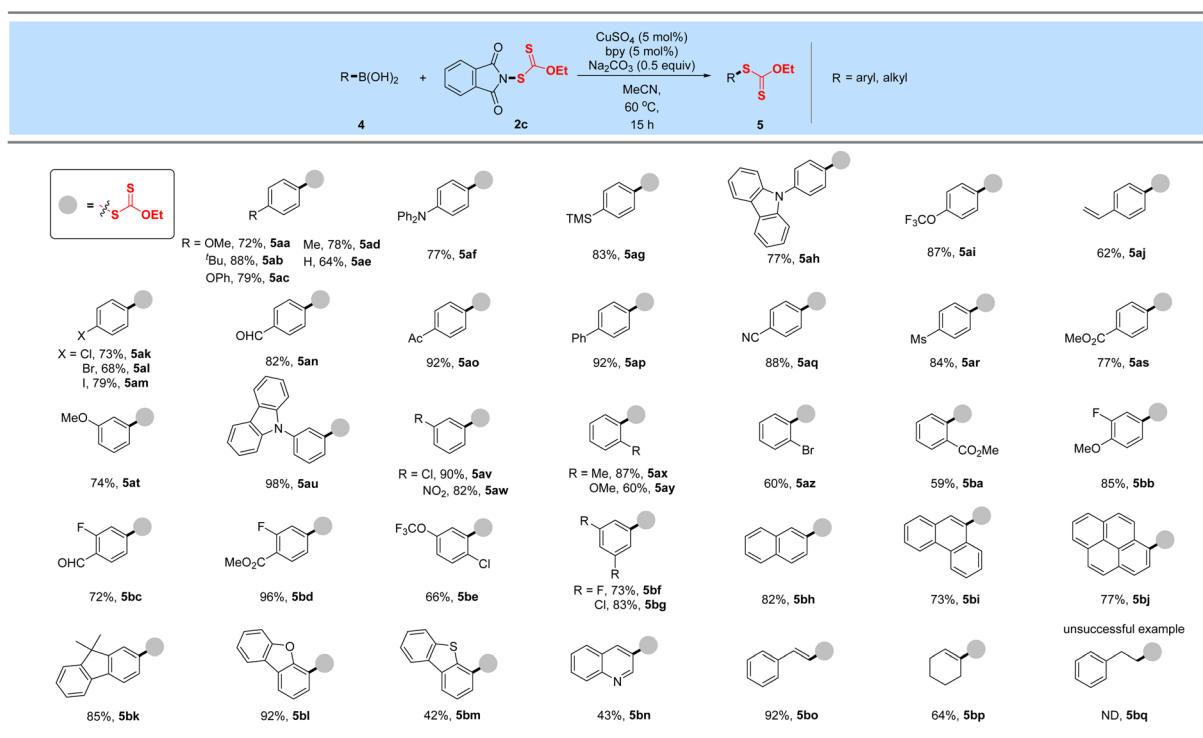
A. Our initial attempts on electrophilic xanthylating reagent						
	4ap	1-3d	CuBr (5 mol%) L ₁ (5 mol%) Na ₂ CO ₃ (0.5 equiv.)	MeCN, 60 °C, 15 h		5ap
Reagent [SC(S)OEt]	1	2	3a	3b	3c	3d
Yield (5ap)	ND	ND	ND	ND	86%	ND
B. Systematic optimization						
	4ap	3c	CuSO ₄ (5 mol%) L ₁ (5 mol%) Na ₂ CO ₃ (0.5 equiv.)	MeCN, 60 °C, 15 h		5ap
Entry	Variations from standard conditions				Yield (5ap , %)	
1	none				97	
2	CuCl, CuBr or CuI instead of CuSO ₄				76–87	
3	Cu(OAc) ₂ instead of CuSO ₄				47	
4	CuSO ₄ ·5H ₂ O instead of CuSO ₄				87	
5	L ₂ or L ₃ instead of L ₁				66–69	
6	L ₄ instead of L ₁				34	
7	Li ₂ CO ₃ instead of Na ₂ CO ₃				66	
8	K ₂ CO ₃ , Cs ₂ CO ₃ or ^t BuOK instead of Na ₂ CO ₃				18–24	
9	DCM instead of MeCN				70	
10	toluene instead of MeCN				41	
11	DMF instead of MeCN				ND	
12	THF or DME instead of MeCN				55–68	
13	RT instead of 60 °C				78	
14	air instead of Ar				33	

^a Standard conditions: 4-biphenylboronic acid (0.10 mmol), reagent **3c** (0.12 mmol, 1.2 equiv.), CuSO₄ (5 mol%), bpy (5 mol%) and Na₂CO₃ (0.5 equiv.) in MeCN (1.0 mL) at 60 °C for 15 h. ^b Yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

catalyzed by a hydrated copper catalyst (CuSO₄·5H₂O), albeit the yield decreases slightly (entry 4). Control experiments showed that simple 2,2'-bipyridine is the most effective ligand for copper catalysts to promote this conversion, while other bidentate nitrogen ligands such as 4,4'-di-*tert*-butyl-2,2'-bipyridine (L₂), *o*-phenanthroline (L₃), and *N,N'*-dimethyl-1,2-ethanediamine (L₄) gave unsatisfactory results (entries 5–6). Considering that the base plays an important role in the transmetalation process of cross coupling,²⁵ a series of strong and weak bases including Li₂CO₃, Na₂CO₃, K₂CO₃, Cs₂CO₃ and ^tBuOK were investigated, and Na₂CO₃ was found to be the optimal base (entries 1, 7–8). Additionally, the effect of solvent on this coupling reaction was also explored (entries 9–12): DCM, toluene, and ether solvent (THF and DME) could afford the target product **5ap** in 41–70% yields, while no target product was observed if DMF was employed which might be attributed to the coordination effect between DMF and the copper catalyst. As anticipated, this xanthate coupling reaction can be carried out at room temperature with a slightly reduced yield (78%, entry 13). By contrast, only 33% yield of the desired product was detected when it was conducted in air instead of an argon atmosphere (entry 14).

After obtaining the optimal conditions, the boronic acid scope of this Chan–Lam-type coupling was explored in Table 2. Overall, a variety of aryl boronic acids with electron-donating or



Table 2 Xanthylation of aryl/alkenyl boronic acids^{a,b}

^a Reaction conditions: aryl or alkenyl boronic acid (**4**, 0.50 mmol), reagent **3c** (0.6 mmol, 1.2 equiv.), $CuSO_4$ (5 mol%), bpy (5 mol%) and Na_2CO_3 (0.5 equiv.) in MeCN (3.0 mL) at 60 °C for 15 h. ^b Isolated yields.

-withdrawing substituted groups at the *para*, *meta*, and *ortho*-positions proceeded smoothly to deliver a set of corresponding xanthylated products in good to excellent yields (59–98%), which displays excellent reactivity and functional group compatibility over the traditional nucleophilic aromatic xanthylation. Many functional groups including methoxy, *tert*-butyl, phenoxy, trimethylsilyl, methyl, trifluoromethoxy, alkenyl, chlorine, bromine, iodine, aldehyde, acetyl, ester, methanesulfonyl, cyano and nitro were all tolerated (**5aa–5bg**). Diphenylamine (**5af**) and carbazole (**5ah**, **5au**) groups widely used in the field of functional materials can be compatible with this system to afford 77–98% yields of ethyl arylxanthates. This transformation also proceeded smoothly for disubstituted aryl boronic acids bearing methoxy, trifluoromethoxy, fluorine, chlorine, aldehyde or ester substituents and gave desired products in good to excellent yields after simple column chromatography purification (**5bb–5bg**). These outcomes implied that the vast change in electronic properties of aryl boronic acids did not shut down the occurrence of the reaction. In particular, reserved bromide (**5al** and **5az**), iodine (**5am**) and unprotected vinyl substituents (**5aj**) were compatible in this coupling, thus allowing subsequent functional-group orthogonal transformations. Besides, boronic acids from the 9,9-dimethyl-9H-fluorene (**5bk**) and polybenzo skeleton (naphthalene, phenanthrene or pyrene, **5bh–5bj**) were further tested and could be well tolerated in this developed xanthylation, which provide modification methods of these meaningful molecules

in fluorescence chemistry. Encouragingly, this simple copper-catalyzed coupling protocol can be applied to structurally diverse heteroaromatic boronic acids such as benzofuran, benzothiophene and quinoline, delivering the desired Chan-Lam-type coupling products in 92%, 42% and 43% yields, respectively (**5bl–5bn**). Additionally, satisfactory yields could be obtained when styryl boronic acid and cyclohexenyl boronic acid were used as model substrates in this strategy (**5bo–5bp**). In accordance with the general trend of reactivity, alkyl boronic acid was tested but failed to achieve the desired xanthyl coupling (**5bq**).

2.3. Xanthylation of other nucleophiles

As a supplement to the traditional synthesis of α -xanthylation of 1,3-carbonyl compounds under strong base conditions,^{20b,c} our attempt of *N*-ethylxanthyl phthalimide **3c** with soft nucleophile β -keto esters was conducted under mild conditions to expand the synthesis of Csp³-xanthates, as shown in Table 3. With the assistance of K_2CO_3 , a range of β -keto esters including methyl, *tert*-butyl and adamantane esters, could be well compatible in this protocol (**6aa–6aj**). Moreover, this transformation proceeded smoothly to afford the α -xanthyl products from indanone substrates with electron-withdrawing (F, Cl, Br, **6aa**, **6ac–6ad**, **6af**) or electron-donating (Me, OMe, **6ab**, **6ae**, **6ag**) functional groups at different positions of phenyl rings. Notably, the *N*-Boc-3-phenyl-2-oxindole substrate derived from dye isatin was



also tolerated and afforded the xanthylated product in a satisfactory yield for this transformation (**6ak**). Unfortunately, the reactions of **3c** with additional 1,3-dicarbonyls such as cyclic and acyclic diketones, diesters, and dinitrile with or without substituents at the α position as well as a ketone or its silyl enol ether failed under our standard or revised conditions.

With the successful development of methods for the formation of C-xanthates, we next sought to investigate the electrophilic xanthylation of heteroatomic nucleophiles, which is an attractive yet rarely reported issue in xanthate chemistry. Electrophilic coupling with weakly nucleophilic phenols to obtain O-xanthate products was first reported by us. As summarized in the bottom of Table 3, phenol substrates were smoothly converted to the corresponding O-xanthates in 68–97% yields with the aid of Cs_2CO_3 , bearing multiple functional groups including methoxyl, *tert*-butyl, methylthio, phenoxy, benzyl, halides, ester and cyano at different positions of phenyl rings (**7aa–7ao**). Polysubstituted halophenols could successfully deliver the corresponding products in acceptable yields (**7ap–7aq**). Similarly, 2-naphthol could be also expediently xanthylated under these mild reaction conditions (**7ar**). However, aliphatic alcohols are not applicable to obtain corresponding O-xanthate products (**7as–7at**). Encouraged by the superior performance of *N*-ethylxanthyl phthalimide **3c** of phenols, coupling with amine substrates to obtain *N*-xanthylamines, which could display the potential fungicidal activity,^{20d} was further explored. Surprisingly, it was found that the reaction of alkyl amines with powerful reagent **3c** could successfully generate moderate to high yields of structurally diverse thiocarbamates with different rotamers *via* desulfuration

of *N*-xanthylamines (Table 4), which is indirectly proved by control experiments (Scheme 2, and see the ESI† for more details) and consistent with the occurrence of the desulfuration phenomenon in previous literature.^{20a,ef} Electron-rich and electron-deficient benzylamines bearing different halogens, trifluoromethyl, cyano, methoxy and *tert*-butyl were all tolerated in the reaction with **3c** to deliver the corresponding thiocarbamate products (**8aa–8ag**) in high yields. As expected, electrophilic xanthylation of long-chain alkyl amines (phenylethylamine and cetylamine, **8ah–8ai**) and even cycloalkyl amines (1-indamine and 4-amino-1-boc-piperidine, **8aj–8ak**) can occur smoothly for the desulfuration conversion. Notably, heterocyclic amines including furfurylamine, thiophene-2-ethanamine and tryptamine could be coupled to afford the desired *N*-C(S)OEt products in this system (**8al–8an**). In addition to the primary alkyl amines, the reaction of secondary alkyl amines 4-phenylpiperidine and di-*n*-propylamine with **3c** also proceeded in high to excellent yields under standard conditions (**8ao–8ap**). Additionally, *tert*-butylamine with a large steric hindrance can also successfully deliver the corresponding target product (**8aq**). Furthermore, when we extended this system to the substrates of aromatic amines or amide salts from 2-pyrrolidinone or substituted benzamide, the corresponding *N*-xanthylamides or thiocarbamates cannot be obtained (**8ar–8at**).

2.4. Applications of xanthyl-derived reagents

Phthalimide, an efficient amide transfer framework, can also be used in the synthesis of xanthyl-derived reagents, which can also be efficiently coupled with various C and O nucleophiles

Table 3 Xanthylation of other C and O nucleophiles^{a,d}

$$\text{Nu} + \text{3c} \longrightarrow \text{Nu-S-C(=S)-OEt} \quad \text{6-7}$$

$$\text{Nu} = \text{C/O} \quad \text{6-7}$$

$$\text{Nu} = \text{C/O} \quad \text{6-7}$$

other C nucleophiles^b

$$\text{F} \quad \text{63\%, 6aa}$$

$$\text{Me} \quad \text{96\%, 6ab}$$

$$\text{R} = \text{Cl, 84\%, 6ac}$$

$$\text{Br, 75\%, 6ad}$$

$$\text{OMe, 88\%, 6ae}$$

$$\text{Br} \quad \text{58\%, 6af}$$

$$\text{MeO} \quad \text{97\%, 6ag}$$

$$\text{85\%, 6ah}$$

$$\text{80\%, 6ai}$$

$$\text{CO}_2\text{Ad} \quad \text{87\%, 6aj}$$

$$\text{Ph} \quad \text{57\%, 6ak}$$

$$\text{R} = \text{CO}_2\text{Et or CN, R}' = \text{H or Bn, ND, 6al-6ao}$$

$$\text{ND, 6ap}$$

$$\text{ND, 6aq}$$

$$\text{R} = \text{H or Bn, ND 6ar-6as}$$

$$\text{ketone or silyl enol ether ND, 6at-6au^c}$$

O nucleophiles^c

$$\text{R} = \text{OMe, 85\%, 7aa}$$

$$\text{tBu, 89\%, 7ab}$$

$$\text{SMe, 97\%, 7ac}$$

$$\text{OPh, 80\%, 7ad}$$

$$\text{H, 90\%, 7ae}$$

$$\text{Ph} \quad \text{93\%, 7af}$$

$$\text{X} = \text{Cl, 93\%, 7ag}$$

$$\text{Br, 94\%, 7ah}$$

$$\text{95\%, 7ai}$$

$$\text{93\%, 7aj}$$

$$\text{86\%, 7ak}$$

$$\text{R} = \text{OMe, 86\%, 7al}$$

$$\text{I, 95\%, 7am}$$

$$\text{Bn} \quad \text{92\%, 7an}$$

$$\text{Br} \quad \text{90\%, 7ao}$$

$$\text{Cl} \quad \text{91\%, 7ap}$$

$$\text{MeO} \quad \text{87\%, 7aq}$$

$$\text{68\%, 7ar}$$

$$\text{ND, 7as}$$

$$\text{ND, 7at}$$

$$\text{unsuccessful examples}$$

^a Reaction conditions: other C nucleophile (0.50 mmol), reagent **3c** (0.6 mmol, 1.2 equiv.) and K_2CO_3 (1.1 equiv.) in DCE (3.0 mL) at 80 °C for 16 h.

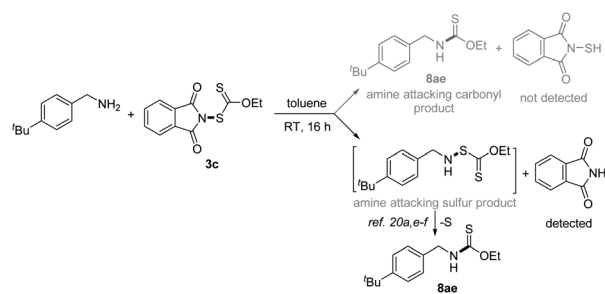
^b Ketone (1.05 equiv. NaH as the base) or its silyl enol ether (w/o K_2CO_3 (1.1 equiv.)) was used. ^c O nucleophile (0.50 mmol), reagent **3c** (0.7 mmol, 1.4 equiv.) and Cs_2CO_3 (1.1 equiv.) in DCE (3.0 mL) at 80 °C for 16 h. ^d Isolated yields.



Table 4 Xanthylation of N nucleophiles^{a,b}

unsuccessful examples

^a Reaction conditions: amine or amide salt (0.50 mmol) and reagent **3c** (0.6 mmol, 1.2 equiv.) in toluene (3.0 mL) at RT for 16 h. ^b Isolated yields. The ratio of the thiocarbamate product means the rotamer ratio.



Scheme 2 Control experiments.

(4-biphenyl boronic acid, 4-bromoindanone methyl ester and *para*-chlorophenol) to give manifold xanthate products in excellent yields under the corresponding conditions (**9aa–9ad**, **10aa–10ad**, and **11aa–11ad**, Table 5). These diverse xanthyl reagents could tolerate multiple functional groups such as halogen, alkenyl, aromatic ring and thiophene heterocycle during their preparations and synthetic transformations. More specifically, this strategy could also be employed for the transfer of electrophilic xanthamide and thioxanthate groups, incorporating –SC(S)R (R = NEt₂ and SEt) into corresponding organic molecules in satisfactory yields (**9ae**, **10af**, **11af**), which

Table 5 Applications of xanthyl-derived reagents^{a,d}

3, xanthyl-derived reagents 9-11, xanthates, xanthamides, thioxanthates

xanthates ($R = \text{Oalkyl}$)

xanthamides ($R = \text{NEt}_2$)

thioxanthates ($R = \text{SEt}$)

9^a Nu = 81%, 9aa

Nu = 72%, 9ab

Nu = 82%, 9ac

Nu = 79%, 9ad

10^b 79%, 10aa

96%, 10ab

63%, 10ac

85%, 10ad

11^c 83%, 11aa

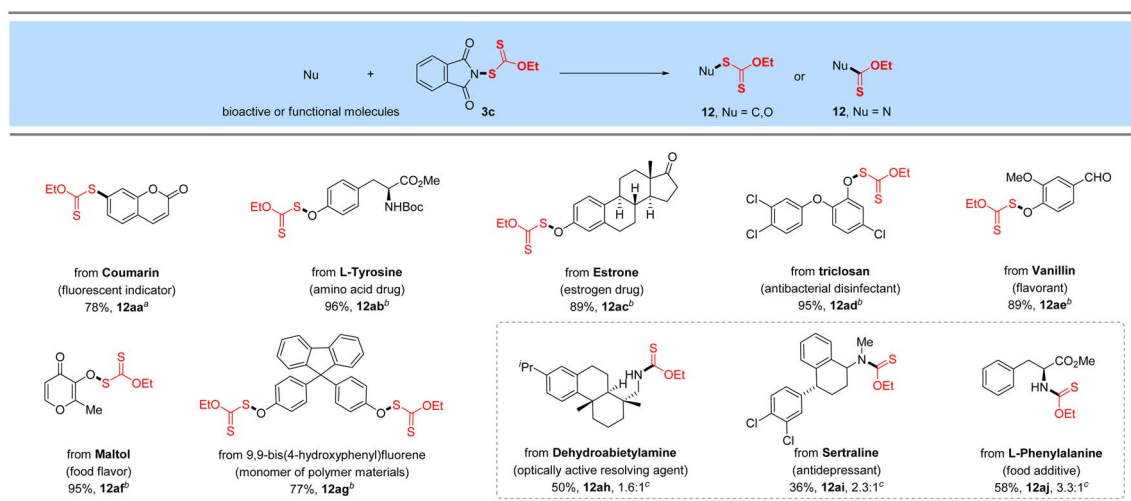
97%, 11ab

81%, 11ac

97%, 11ad

^a Reaction conditions: 4-biphenyl boronic acid (0.50 mmol), reagent **3** (0.6 mmol, 1.2 equiv.), CuSO₄ (5 mol%), bpy (5 mol%) and Na₂CO₃ (0.5 equiv) in MeCN (3.0 mL) at 60 °C for 15 h. ^b 4-Bromoindanone methyl ester (0.50 mmol, 1.2 equiv.) and K₂CO₃ (1.1 equiv.) in DCE (3.0 mL) at 80 °C for 16 h. ^c 4-Chlorophenol (0.50 mmol), reagent **3** (0.7 mmol, 1.4 equiv.) and Cs₂CO₃ (1.1 equiv.) in DCE (3.0 mL) at 80 °C for 16 h. ^d Isolated yields.



Table 6 Late-stage xanthylation of bioactive or functional molecules^{a,d}

^a Reaction conditions: aryl boronic acid (0.50 mmol), reagent **3c** (0.6 mmol, 1.2 equiv.), CuSO₄ (5 mol%), bpy (5 mol%) and Na₂CO₃ (0.5 equiv.) in MeCN (3.0 mL) at 60 °C for 15 h. ^b Phenol (0.50 mmol), reagent **3c** (0.7 mmol, 1.4 equiv.) and Cs₂CO₃ (1.1 equiv.) in DCE (3.0 mL) at 80 °C for 16 h. ^c Alkyl amine (0.50 mmol) and reagent **3c** (0.6 mmol, 1.2 equiv.) in toluene (3.0 mL) at RT for 16 h. The ratio of the thiocarbamate product means the rotamer ratio. ^d Isolated yields.

would provide a novel electrophilic alternative to the traditional synthesis of xanthamide- or thioxanthate-containing compounds.²⁶

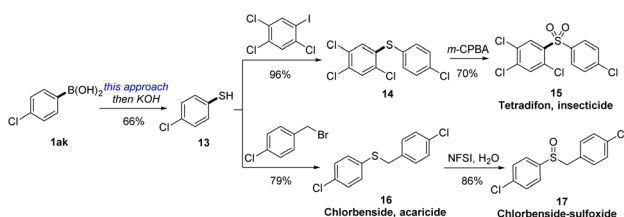
2.5. Late-stage xanthylation of bioactive or functional molecules

The promising functional group tolerance and high efficiency of this protocol enabled its application to the late-stage xanthylation of structurally complicated bioactive, functional molecules or druglike scaffolds (Table 6). For instance, boronic acid substrate derived from fluorescent indicator 7-hydroxycoumarin reacted smoothly with *N*-xanthylphthalimide **3c** catalyzed by cheap CuSO₄ (**12aa**). Besides, a 96% yield of the target *O*-xanthate was successfully obtained for the *N*-protected amino acid drug *L*-tyrosine (**12ab**). Moreover, the bioactive phenol substrate estrone drug was tested as a superior candidate under the standard reaction conditions and furnished the *O*-SC(S)OEt product in 89% yield (**12ac**). As a broad-spectrum antibacterial disinfectant against *Staphylococcus*, *Escherichia coli* and *Candida albicans*, phenol-derived triclosan could be decorated with the –SC(S)OEt linkage in an excellent yield (95%, **12ad**) through our developed electrophilic ethylxanthyl reagent **3c**. Likewise, natural or

synthetic food flavoring agents such as vanillin and maltol successfully underwent the reaction with 89–95% yields of target O–S coupling products **12ae–12af**, which shows good compatibility with activated carbon–carbon double bonds. Finally, 9,9-bis(4-hydroxyphenyl)fluorene as a monomer of polymer materials, was investigated and converted to the corresponding xanthyl product in 77% yield under the optimized conditions (**12ag**), displaying its potential applications in the field of functional materials. It is noteworthy that dehydroabietylamine (optically active resolving agent) and an antidepressant sertraline were coupled with reagent **3c** to yield the corresponding desulfurating thiocarbamates (**12ah–12ai**) in 36–50% yields. As expected, modification of esterified amino acid *L*-phenylalanine can also produce the desired *N*-C(S)OEt product (**12aj**).

2.6. Synthetic applications

To highlight the practical utility of this protocol in synthesis, we then unlock the synthesis of two important thioether-containing bioactive insecticides (Scheme 3). Thus, treating 4-chlorophenylboric acid with ethyl xanthyl reagent **3c** by this electrophilic xanthylation approach and thiolysis under alkaline conditions could generate 4-chlorothiophenol. After cross coupling with 2,4,5-trichloro-1-iodobenzene and excessive oxidation by *m*-CPBA, a famous insecticide tetradifon (**15**)²⁷ was synthesized in 44% overall yield. Likewise, we then applied this strategy in the synthesis of an acaricide chlorbenside (**16**), which could also be selectively converted into the sulfoxide derivative (**17**) by NFSI *via* a controllable oxidation.²⁸



Scheme 3 Synthesis of bioactive tetradifon and chlorbenside-sulfoxide.

3 Conclusions

In summary, a highly desirable and remarkable electrophilic xanthylation *via* easily accessible and shelf-stable xanthylating



reagent *N*-xanthylphthalimides has been developed. The present protocol might provide a new avenue to the xanthate derivatives in an unmet electrophilic manner in organic synthesis. These xanthylating reagents are effective and powerful for the direct transfer of the –SC(S)OR groups to a rich portfolio of substrates, including Cu-catalyzed Cham–Lam-type xanthylation with organoboronic acids, and electrophilic xanthylation of β -keto esters, 2-oxindole, alkyl amines, as well as previously inaccessible phenols (first report) under metal-free conditions. Notably, this simple electrophilic xanthylation of alkyl amines reported by us also occurs in the desulfuration reaction, providing a novel synthesis method to access valuable *O*-ethylthiocarbamates. Additionally, we also report the introduction of xanthamide and thioxanthate groups into organic molecules *via* this electrophilic reagent strategy. Highlighted features of mild conditions, broad substrate scope, and excellent tolerance, as well as late-stage functionalization of biologically active or functional molecules and further application to the synthesis of bioactive drugs made them very attractive as general reagents which will allow rapid incorporation of SC(S)R (R = OEt, Oalkyl, NEt₂ and SEt) into densely functionalized drug-like molecules. Expanding the synthetic application of these electrophilic reagents is underway and will be reported shortly.

Data availability

All experimental data in this manuscript are available in the ESI.†

Author contributions

S. W., L. Y., F. L., Y. Z. and D. Z. conceived and designed the experiments. S. W., L. Y., F. L. and Y. Z. performed the experiments and analyzed the data. X.-R. L. performed the single crystal diffraction studies. Q. W., and D. Z. co-wrote the paper. Q. W. assisted in editing the manuscript and approved its contents. D. Z. directed the project. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) C. Jacob, *Nat. Prod. Rep.*, 2006, **23**, 851–863; (b) K. L. Dunbar, D. H. Scharf, A. Litomska and C. Hertweck, *Chem. Rev.*, 2017, **117**, 5521–5577; (c) N. Wang, P. Saidhareddy and X. Jiang, *Nat. Prod. Rep.*, 2020, **37**, 246–275.
- (a) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842; (b) M. H. Feng, B. Q. Tang, H. L. Steven and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200–1216; (c) P. Devendar and G. Yang, *Top. Curr. Chem.*, 2017, **375**, 82; (d) S. Huang, M. Wang and X. Jiang, *Chem. Soc. Rev.*, 2022, **51**, 8351–8377.
- (a) V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.*, 2004, **37**, 611–620; (b) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.*, 2007, **107**, 5133–5209; (c) Y. Li and M.-H. Xu, *Chem. Commun.*, 2014, **50**, 3771–3782; (d) S. Otocka, M. Kwiatkowska, L. Madalińska and P. Kiełbasiński, *Chem. Rev.*, 2017, **117**, 4147–4181.
- (a) G. A. Benavides, G. L. Squadrito, R. W. Mills, H. D. Patel, T. S. Isbell, R. P. Patel, V. M. Darley-Usmar, J. E. Doeller and D. W. Kraus, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 17977–17982; (b) J. A. Cebollada, P. Kosuri, J. A. R. Pardo and J. M. Fernández, *Nat. Chem.*, 2011, **3**, 882–887; (c) M. Wang and X. Jiang, *Topics Curr. Chem.*, 2018, **376**, 1–40.
- (a) K. Takimiya, S. Shinamura, I. Osaka and E. Miyazaki, *Adv. Mater.*, 2011, **23**, 4347–4370; (b) X. Li, Y. Zhu, J. Shao, B. Wang, S. Zhang, Y. Shao, X. Jin, X. Yao, R. Fang and X. Shao, *Angew. Chem., Int. Ed.*, 2014, **53**, 535–538; (c) H. Iino, T. Usui and J. Hanna, *Nat. Commun.*, 2015, **6**, 6828; (d) D. A. Boyd, *Angew. Chem., Int. Ed.*, 2016, **55**, 15486–15502.
- (a) P. Delduc, C. Tailhan and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1988, 308–310; (b) S. Z. Zard, *Angew. Chem., Int. Ed.*, 1997, **36**, 672–685.
- (a) L. Chugaev, *Chem. Ber.*, 1899, **32**, 3332–3335; (b) H. R. Nace, *Org. React.*, 1962, **12**, 57–100; (c) K. Lee and D. L. Boger, *J. Am. Chem. Soc.*, 2014, **136**, 3312–3317; (d) D. H. Dethe and B. D. Dherange, *J. Org. Chem.*, 2018, **83**, 3392–3396; (e) F. S. Karimi, A. Seif and E. Zahedi, *ChemistrySelect*, 2022, **7**, e202202169.
- S. R. Rao, *Xanthates and Related Compounds*, Marcel Dekker Inc., New York, 1971, ch. 9.
- (a) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, **16**, 1574–1585; (b) D. H. R. Barton, S. I. Parekh and C.-L. Tse, *Tetrahedron Lett.*, 1993, **34**, 2733–2736; (c) D. H. R. Barton, *Half a Century of Free Radical Chemistry*, Cambridge University Press, Cambridge, 1993; (d) H. S. Park, H. Y. Lee and Y. H. Kim, *Org. Lett.*, 2005, **7**, 3187–3190; (e) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10596–10612; (f) S. Koshino, E. Kwon and Y. Hayashi, *Eur. J. Org. Chem.*, 2018, 5629–5638; (g) F. W. Friesse and A. Studer, *Angew. Chem., Int. Ed.*, 2019, **58**, 9561–9564; (h) M. Konya, K. Shimoyama, S. Arima, T. Fukuda, R. Uchida, H. Tomoda and T. Nagamitsu, *Org. Lett.*, 2020, **22**, 5131–5134.
- (a) W. Hartwig, *Tetrahedron*, 1983, **39**, 2609–2645; (b) D. Crich and L. Quintero, *Chem. Rev.*, 1989, **89**, 1413–1432; (c) Q. Huang, J. Michalland and S. Z. Zard, *Angew. Chem., Int. Ed.*, 2019, **58**, 16936–16942.

- (a) C. Jacob, *Nat. Prod. Rep.*, 2006, **23**, 851–863; (b) K. L. Dunbar, D. H. Scharf, A. Litomska and C. Hertweck,



- 11 (a) F. Gagosz, C. Moutrille and S. Z. Zard, *Org. Lett.*, 2002, **4**, 2707–2709; (b) B. Quiclet-Sire, N. D. My Tran and S. Z. Zard, *Org. Lett.*, 2012, **14**, 5514–5517; (c) L. Debien and S. Z. Zard, *J. Am. Chem. Soc.*, 2013, **135**, 3808–3811; (d) K. K. K. Goh, S. Kim and S. Z. Zard, *Org. Lett.*, 2013, **15**, 4818–4821; (e) L. Qin and S. Z. Zard, *Org. Lett.*, 2015, **17**, 1577–1580; (f) L. Anthore, S. Li, L. V. White and S. Z. Zard, *Org. Lett.*, 2015, **17**, 5320–5323; (g) B. Quiclet-Sire and S. Z. Zard, *Synlett*, 2016, **27**, 680–701; (h) C. G. Na and E. J. Alexanian, *Angew. Chem., Int. Ed.*, 2018, **57**, 13106–13109; (i) A. M. Carestia, D. Ravelli and E. J. Alexanian, *Chem. Sci.*, 2018, **9**, 5360–5365; (j) S. K. Ayer and J. L. Roizen, *J. Org. Chem.*, 2019, **84**, 3508–3523; (k) B. Schweitzer-Chaput, M. A. Horwitz, E. de Pedro Beato and P. Melchiorre, *Nat. Chem.*, 2019, **11**, 129–135; (l) D. Spinnato, B. Schweitzer-Chaput, G. Goti, M. Ošeka and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2020, **59**, 9485–9490; (m) X. Chen and S. Z. Zard, *Org. Lett.*, 2020, **22**, 3628–3632; (n) E. de Pedro Beato, D. Mazzarella, M. Balletti and P. Melchiorre, *Chem. Sci.*, 2020, **11**, 6312–6324; (o) V. S. Dorokhov and S. Z. Zard, *Org. Lett.*, 2021, **23**, 2164–2168; (p) J. Li, J. Li, X. Ji, R. He, Y. Liu, Z. Chen, Y. Huang, Q. Liu and Y. Li, *Org. Lett.*, 2021, **23**, 7412–7417; (q) V. S. Dorokhov, B. Quiclet-Sire and S. Z. Zard, *Org. Lett.*, 2022, **24**, 2878–2882; (r) J. Michalland, N. Casaretto and S. Z. Zard, *Angew. Chem., Int. Ed.*, 2022, **61**, e202113333; (s) B. Bieszczad and S. Z. Zard, *Org. Lett.*, 2022, **24**, 6973–6977; (t) T. Zhou, H. Chen, Y. Liu, H. Wang, Q. Yan, W. Wang and F. Chen, *J. Org. Chem.*, 2022, **87**, 15582–15597.
- 12 R. Leuckart, *J. Prakt. Chem.*, 1890, **41**, 179–224.
- 13 (a) R. T. A. Mayadunne, E. Rizzardo, J. Chiefari, Y. K. Chong, G. Moad and S. H. Thang, *Macromolecules*, 1999, **32**, 6977–6980; (b) G. Moad, E. Rizzardo and S. H. Thang, *Polymer*, 2008, **49**, 1079–1131; (c) S. Binauld, L. Delafresnaye, B. Charleux, F. D'Agosto and M. Lansalot, *Macromolecules*, 2014, **47**, 3461–3472; (d) C. Dommange, F. D'Agosto and V. Monteil, *Angew. Chem., Int. Ed.*, 2014, **53**, 6683–6686; (e) S. Allison-Logan, F. Karimi, Y. Sun, T. G. McKenzie, M. D. Nothling, G. Bryant and G. G. Qiao, *ACS Macro Lett.*, 2019, **8**, 1291–1295; (f) R. Li and Z. An, *Angew. Chem., Int. Ed.*, 2020, **59**, 22258–22264; (g) P. G. Georgiou, H. L. Marton, A. N. Baker, T. R. Congdon, T. F. Whale and M. I. Gibson, *J. Am. Chem. Soc.*, 2021, **143**, 7449–7461; (h) X. Zhang, Y. Jiang, Q. Ma, S. Hu and S. Liao, *J. Am. Chem. Soc.*, 2021, **143**, 6357–6362; (i) P. Das Karmakar and S. Pal, *Polym. Chem.*, 2022, **13**, 1394–1400; (j) X. Zhang, Z. Yang, Y. Jiang and S. Liao, *J. Am. Chem. Soc.*, 2022, **144**, 679–684.
- 14 (a) R. H. Jones and S. L. Giolito, *US Pat.* 2743209A, 1956; (b) R. J. Venkateswara, V. Yenamandra and R. K. Vijaya, *WO Pat.* 02079179 A1, 2002; (c) S. M. Sondhi, R. P. Verma, N. Singhal, R. Shukla, R. Raghubir and M. P. Dubey, *Indian Drugs*, 1999, **36**, 50–54; (d) S. Bhandari, A. R. Katore, D. M. Bajaj, P. Sharma, V. Talla and N. Shankaraiah, *ChemistrySelect*, 2018, **3**, 6766–6774.
- 15 (a) L. Degani and R. Fochi, *Synthesis*, 1978, 365–368; (b) Y. Lu, C.-M. Li, Z. Wang, J. Chen, M. L. Mohler, W. Li, J. T. Dalton and D. D. Miller, *J. Med. Chem.*, 2011, **54**, 4678–4693; (c) A. Coluccia, S. Passacantilli, V. Famigliini, M. Sabatino, A. Patsilnakos, R. Ragno, C. Mazzocchi, L. Sisinni, A. Okuno, O. Takikawa, R. Silvestri and G. La Regina, *J. Med. Chem.*, 2016, **59**, 9760–9773; (d) Y. Li, X. Luo, Y. Shao and L. Chen, *J. Org. Chem.*, 2018, **83**, 8768–8774; (e) Z. Zhu, X. Tang, J. Cen, J. Li, W. Wu and H. Jiang, *Chem. Commun.*, 2018, **54**, 3767–3770; (f) G. Huang, J. Li, J. Li, J. Li, M. Sun, P. Zhou, L. Chen, Y. Huang, S. Jiang and Y. Li, *J. Org. Chem.*, 2020, **85**, 13037–13049; (g) E. Badali, H. Rahimzadeh, A. Sharifi, A. Habibi and A. Z. Halimehjani, *Org. Biomol. Chem.*, 2020, **18**, 4983–4987; (h) N. Sundaravelu, A. Nandy and G. Sekar, *Org. Lett.*, 2021, **23**, 3115–3119; (i) X. Zeng and S. Z. Zard, *Org. Lett.*, 2022, **24**, 5245–5248; (j) J. Li, Y. Liu, Z. Chen, J. Li, X. Ji, L. Chen, Y. Huang, Q. Liu and Y. Li, *J. Org. Chem.*, 2022, **87**, 3555–3566; (k) A. Nandy and G. Sekar, *J. Org. Chem.*, 2022, **87**, 7536–7546; (l) S. Mondal, E. M. Di Tommaso and B. Olofsson, *Angew. Chem., Int. Ed.*, 2023, e202216296; (m) D. I. Bugaenko, A. A. Volkov, V. V. Andreychev and A. V. Karchava, *Org. Lett.*, 2023, **25**, 272–276.
- 16 (a) V. K. Akkilagunta and R. R. Kakulapati, *J. Org. Chem.*, 2011, **76**, 6819–6824; (b) D. J. C. Prasad and G. Sekar, *Org. Lett.*, 2011, **13**, 1008–1011; (c) S. Sangeetha, P. Muthupandi and G. Sekar, *Org. Lett.*, 2015, **17**, 6006–6009; (d) S. Sangeetha and G. Sekar, *Org. Lett.*, 2017, **19**, 1670–1673; (e) M. Soleiman-Beigi and Z. Arzhegar, *Synlett*, 2018, **29**, 986–992; (f) X. Zhao, Q. Li, J. Xu, D. Wang, D. Zhang-Negrierie and Y. Du, *Org. Lett.*, 2018, **20**, 5933–5937; (g) N. Sundaravelu and G. Sekar, *Org. Lett.*, 2019, **21**, 6648–6652; (h) S. Sangeetha and G. Sekar, *Chem. Commun.*, 2020, **56**, 10906–10909; (i) N. Sundaravelu, T. Singha, A. Nandy and G. Sekar, *Chem. Commun.*, 2021, **57**, 4512–4515; (j) Y. Zhang, W. Lai, L. Zhang, X. Gao, G. Qiu and H. Zhou, *Org. Biomol. Chem.*, 2021, **19**, 1827–1834.
- 17 (a) G. Bouhadir, N. Legrand, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron Lett.*, 1999, **40**, 277–280; (b) Y. Kwak, R. Nicolaÿ and K. Matyjaszewski, *Macromolecules*, 2009, **42**, 3738–3742; (c) S. S. Ashirbaev, V. V. Levin, M. I. Struchkova and A. D. Dilman, *J. Fluorine Chem.*, 2016, **191**, 143–148; (d) R. He, Y. Liu, Y. Feng, L. Chen, Y. Huang, F. Xie and Y. Li, *Org. Lett.*, 2022, **24**, 3167–3172.
- 18 M. Zhang, B. Wang, Y. Cao, Y. Liu, Z. Wang and Q. Wang, *Org. Lett.*, 2022, **24**, 8895–8900.
- 19 (a) W. L. Czaplinski, C. G. Na and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 13854–13857; (b) C. G. Na, D. Ravelli and E. J. Alexanian, *J. Am. Chem. Soc.*, 2020, **142**, 44–49; (c) J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin and G. Liu, *Nature*, 2019, **574**, 516–521.
- 20 (a) F. A. Bolth, R. D. Chrozier and L. E. Strow, *US Pat.* 3907854, 1975; (b) S. Matsui, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1853–1865; (c) V. Maslak, Ž. Čeković and R. N. Saičić, *Synlett*, 1998, 1435–1437; (d) O. V. Bakbardina, I. Y. Pukhnyarskaya, M. A. Gazalieva, S. D. Fazylov and E. M. Makarov, *Russ. J. Appl. Chem.*, 2006, **79**, 1726–1728; (e) M. M. Milosavljević, A. D. Marinković, S. Petrović and M. Sovrlić, *Chem. Ind. Chem. Eng. Q.*, 2009, **15**, 257–262; (f) M. M. Milosavljević, M. Sovrlić, A. D. Marinković and



- D. D. Milenković, *Monatsh. Chem.*, 2010, **141**, 749–755; (g) P.-E. Dufils, G. David, B. Boutevin, G. Woodward, G. Otter, A. Guinaudeau, S. Mazières and M. Destarac, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 1997–2007.
- 21 (a) M. Li, X.-S. Xue and J.-P. Cheng, *Acc. Chem. Res.*, 2020, **53**, 182–197; (b) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, **52**, 12856–12859; (c) D. Zhu, Y. Gu, L. Lu and Q. Shen, *J. Am. Chem. Soc.*, 2015, **137**, 10547–10553; (d) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner and H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847–2854; (e) F. Shen, P. Zhang, L. Lu and Q. Shen, *Org. Lett.*, 2017, **19**, 1032–1035.
- 22 (a) M. Watanabe, K. Shirai and T. Kumamoto, *Chem. Lett.*, 1975, **8**, 855–858; (b) J. Klose, C. B. Reese and Q. Song, *Tetrahedron*, 1997, **53**, 14411–14416; (c) S. E. Denmark, D. J. P. Kornfilt and T. Vogler, *J. Am. Chem. Soc.*, 2011, **133**, 15308–15311; (d) J. Qiu, D. Wu, P. G. Karmaker, H. Yin and F.-X. Chen, *Org. Lett.*, 2018, **20**, 1600–1603; (e) W.-C. Gao, Y.-Z. Shang, H.-H. Chang, X. Li, W.-L. Wei, X.-Z. Yu and R. Zhou, *Org. Lett.*, 2019, **21**, 6021–6024; (f) J. Zou, J. Chen, T. Shi, Y. Hou, F. Cao, Y. Wang, X. Wang, Z. Jia, Q. Zhao and Z. Wang, *ACS Catal.*, 2019, **9**, 11426–11430; (g) Y.-F. Li, Y.-F. Wei, J. Tian, J. Zhang, H.-H. Chang and W.-C. Gao, *Org. Lett.*, 2022, **24**, 5736–5740.
- 23 M. De Greef, Novel applications of xanthate radical chemistry: masked radical formylation, synthesis of structurally divers spiroketals and synthesis of phosphorus-containing compounds, 2006, 20140701.
- 24 Deposition number 2250745 (for **3c**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- 25 The base plays an important role in the transmetalation process of cross coupling, please see: A. A. C. Braga, N. H. Morgon, G. Ujaque and F. Maseras, *J. Am. Chem. Soc.*, 2005, **127**, 9298–9307.
- 26 (a) A. Scozzafava, A. Mastrolorenzo and C. T. Supuran, *J. Enzyme Inhib.*, 2001, **16**, 55–63; (b) A. Krasovskiy, A. Gavryushin and P. Knochel, *Synlett*, 2005, 2691–2693; (c) D. Enders, A. Rembiak and J. X. Liebich, *Synthesis*, 2011, 281–286; (d) Z.-B. Dong, X. Liu and C. Bolm, *Org. Lett.*, 2017, **19**, 5916–5919; (e) M.-T. Zeng, W. Xu, X. Liu, C.-Z. Chang, H. Zhu and Z.-B. Dong, *Eur. J. Org. Chem.*, 2017, 6060–6066; (f) Z. Wu, M. Lai, S. Zhang, X. Zhong, H. Song and M. Zhao, *Eur. J. Org. Chem.*, 2018, 7033–7036; (g) W. Xu, F. Gao and Z.-B. Dong, *Eur. J. Org. Chem.*, 2018, 821–828; (h) J. B. Williamson, C. G. Na, R. R. Johnson III, W. F. M. Daniel, E. J. Alexanian and F. A. Leibfarth, *J. Am. Chem. Soc.*, 2019, **141**, 12815–12823; (i) Y. Cheng, H.-Y. Peng and Z.-B. Dong, *Tetrahedron Lett.*, 2019, **60**, 617–620; (j) C. Cheng, M. Zhao, M. Lai, K. Zhai, B. Shi, S. Wang, R. Luo, L. Zhang and Z. Wu, *Eur. J. Org. Chem.*, 2019, 2941–2949; (k) Z.-B. Huang, X.-J. Xia, Z.-H. Huang, L. Xu, X.-Y. Zhang and R.-Y. Tang, *Org. Biomol. Chem.*, 2020, **18**, 1369–1376.
- 27 J. Swietoslawski, A. Silowiecki, E. Skotnicki, Z. Zerkowski and B. Kurowska, PL Pat. 133539 B1, 1986.
- 28 X. Xu, L. Yan, S. Wang, P. Wang, A.-X. Yang, X. Li, H. Lu and Z.-Y. Cao, *Org. Biomol. Chem.*, 2021, **19**, 8691–8695.

