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Synergistic Pd/Cu catalysis enabled cross-coupling of glycosyl stannanes with sulfonium salts to access *C*-aryl/alkenyl glycals

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ABSTRACT

A highly efficient coupling of glycosyl stannanes and sulfonium salts enabled by synergistic Pd/Cu catalysis is disclosed, facilitating the construction of *C*-aryl/alkenyl glycals under mild conditions in high yields. The protocol tolerates a wide scope of functional groups including ketone, cyano, ester, amide, nitro, halide. The one-pot formal C–H glycosylation starting from arene is demonstrated with a reaction sequence of dibenzothiophenylation/Stille coupling. Besides, a gram-scale reaction is performed successfully, showing the high applicability of this protocol.

C-glycosides are a class of carbohydrates in which a carbon moiety is connected to the anomeric carbon of the sugar ring *via* C–C bond linkage. Compared to *O*/*N*-glycosides, their analogs *C*-glycosides are less susceptible to both chemical and enzymatic deglycosylation *in vivo*, presenting an inherent advantage as potential drugs which allow for favourable pharmacological and superior biological properties [1,2]. Therefore, much effort in the development of novel strategies had been paid to construct this interesting subclass of sugar derivatives [3–18]. Among them, aryl/alkenyl *C*-glycals had gained increasing attention and been considered useful and versatile synthons. Aryl/alkenyl *C*-glycals are not only widely present in the synthesis of biologically active natural products, *e.g.*, bergenin [19] and forskolin (Scheme 1a) [20], but also allow the generation of novel structural features *via* diversity-oriented synthesis because of the rich reactivity of unsaturated enol-ether structure [21,22].

With the rapid advance in C–C bond formation employing the transition metal catalysis, various glycosyl donors were found to couple with aryl/alkenyl aglycones. Unsubstituted glycal, 1-iodo glycal, 1-sulfonyl glycal had been proved to be efficient glycosyl electrophiles to couple with aryl boronic acids (Scheme 1b) [23–28]. Besides, the ubiquitous hydrocarbon molecules were also confirmed to react with 1-iodoglycal to afford *C*-glycals (Scheme 1c) [29–33]. In addition, the carbohydrate-derived nucleophiles including glycosyl boronic acids and glycosyl stannanes were competent donors to react with aryl halides for the production of *C*-glycals (Scheme 1d) [19,34–38]. Despite great achievements have been made for *C*-aryl glycals synthesis, there are still some limitations, including unsatisfactory yields, the harsh reaction conditions and relatively narrow scope. Moreover, the method for efficient synthesis of dieno-glycosides [39–41] is less available and remains a daunting challenge. Therefore, the development of straightforward methods to access the synthetically useful *C*-aryl/alkenyl glycals is of great significance.

Sulfonium chemistry has recently emerged as an attractive topic because of its remarkably *para*-selective C–H functionalization of monosubstituted arenes, alkenes and distinguished reactivity [42–53]. It had been confirmed that oxidative addition to Pd(0) of sulfonium salt occurred at the specific C-S bond in the presence of C-Br, C-I bond. Furthermore, the intrinsic ionic characterization allowed for the formation of Pd(II) species without strongly coordinating anion that facilitated the following transmetallation and reductive elimination steps in the catalytic cycle. In light of its superiority, we envisioned that the employment of a sulfonium salt as

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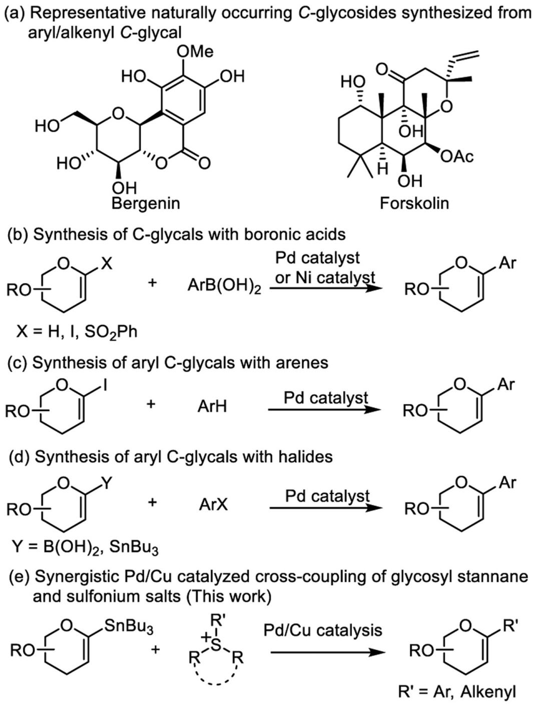
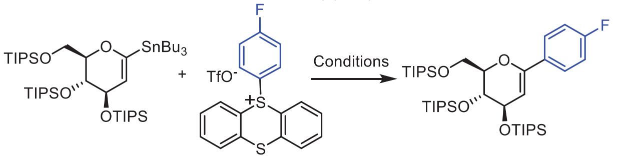


Scheme 1. Essential of aryl/alkenyl *C*-glycals and their synthetic strategies.

Table 1
Evaluation of reaction conditions for *C*-glycosylation.[a]



1a 2a 3a

Entry	Pd cat.	Cu Cat.	Base	Solvent	Temp (°C)	Time (h)	Yield of **3a** (%)
1	$Pd(PPh_3)_4$	CuI	NaF	DMF	80	10	30
2	$Pd(PPh_3)_4$	CuI	KF	DMF	80	10	73
3	$Pd(PPh_3)_4$	CuI	CsF	DMF	80	10	9
4	$Pd(PPh_3)_4$	CuI	KF	Toluene	80	10	0
5	$Pd(PPh_3)_4$	CuI	KF	Dioxane	80	10	29
6	$Pd(PPh_3)_4$	CuCl	KF	DMF	80	10	68
7	$Pd(PPh_3)_4$	CuI	KF	DMF	r.t.	1.5	98
8	Pd_2dba_3/dppf	CuI	KF	DMF	r.t.	1.5	76
9[b]	$Pd(PPh_3)_4$	CuI	KF	DMF	r.t.	1.5	99
10[c]	$Pd(PPh_3)_4$	CuI	KF	DMF	r.t.	1.5	84
11[d]	None	CuI	KF	DMF	r.t.	1.5	0
12[e]	$Pd(PPh_3)_4$	None	KF	DMF	r.t.	1.5	0
13[f]	None	none	KF	DMF	r.t.	1.5	0

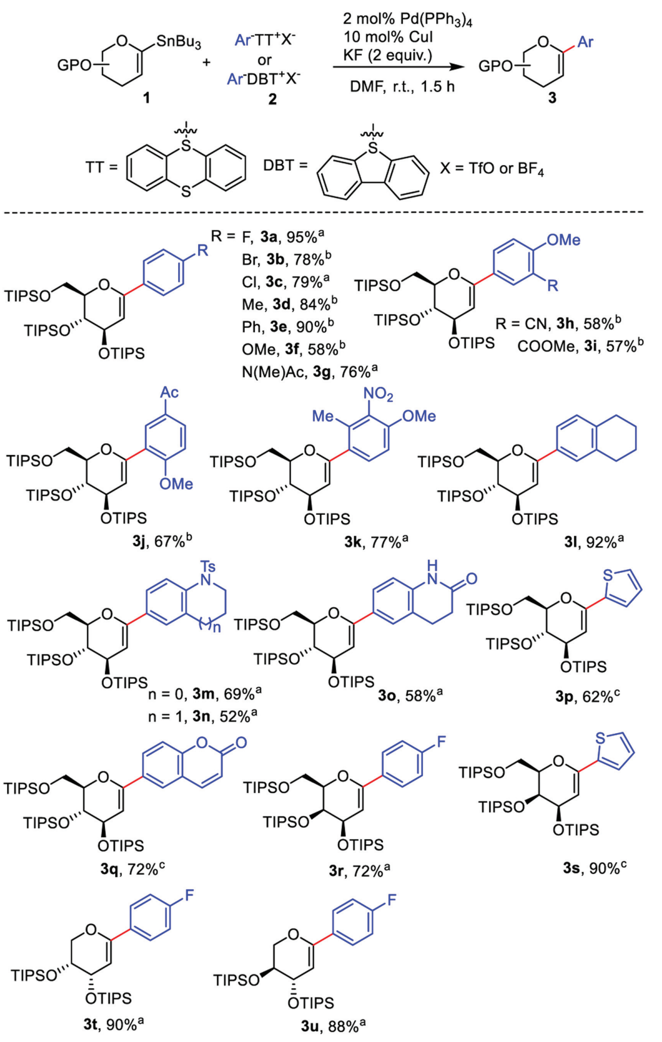
[a] Reaction conditions: **1a** (0.05 mmol, 1.0 equiv.), **2a** (0.06 mmol, 1.2 equiv.), solvent (1 mL), 10 mol% Pd cat., 10 mol% Cu cat., base (0.1 mmol, 2.0 equiv.), under N_2 atmosphere; the yield was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.
[b] 2 mol% $Pd(PPh_3)_4$.
[c] 1 mol% $Pd(PPh_3)_4$.
[d] No Pd cat.
[e] No Cu cat.
[f] No Pd and Cu cat.

an alternative of arene/alkene would address the limitation of narrow applicability, leading to rapid collection of structurally-defined aryl/alkenyl *C*-glycals (Scheme 1e).

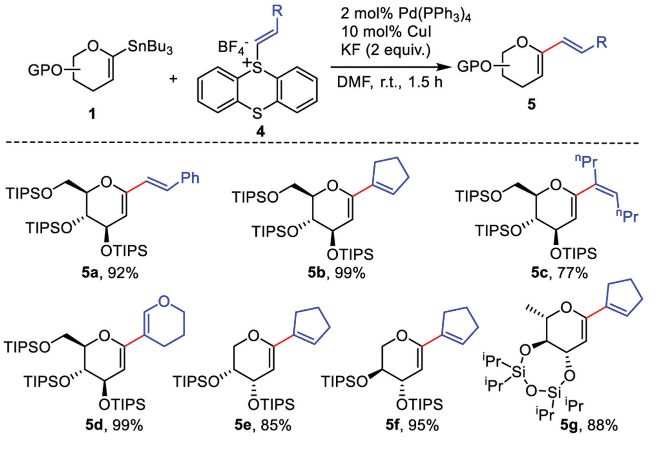
We began our study by using glycosyl stannane **1a** bearing non-transferable butyl ligand and 4-fluorophenyl sulfonium salt **2a** as model substrates. The choice of the TIPS-protected glycosyl stannane can be rationalized from the compromise of its stability and reactivity. Moreover, novel approaches were designed to avoid contamination by organotin residues, making the reaction more competitive [54]. In order to accomplish the *C*-glycosylation process, the combination of a palladium complex and a copper salt was chosen as the catalysts. Initial screening with a series of fluorides proposed that the tin moiety was substituted and formed polymeric tin precipitation, showing that KF represented the best reactivity in DMF at elevated temperature (Table 1, entries 1–3). Switching the solvent from DMF to less polar solvent such as toluene or dioxane resulted in a considerable decrease in the yields (Table 1, entries 4 and 5). The identification of copper salts revealed that CuI was optimal (Table 1, entry 6). Surprisingly, the yield was improved dramatically when the reaction was conducted at room temperature even shortening the reaction time (Table 1, entry 7). It might be attributed to the suppression of side reactions under mild conditions [55]. The examination of other palladium source gave an inferior result (Table 1, entry 8). We then turned out to use $Pd(PPh_3)_4$ as the catalyst. Reducing the loading of palladium catalyst from 10 mol% to 2 mol% did not affect the yield significantly (Table 1, entry 9). However, the reaction afforded a slightly lower yield with 1 mol% palladium catalyst (Table 1, entry 10). Finally, we reached the optimal conditions for efficient *C*-glycosylation in the presence of 2 mol% $Pd(PPh_3)_4$ and 10 mol% CuI with KF as the base at ambient temperature (Table 1, entry 9). Control experiments revealed that both Pd and Cu played a crucial role in the coupling (Table 1, entries 11–13). Reactions conducted without palladium catalyst completely did not give the desired product, the starting material **2a** remaining intact, whereas the reaction performed without copper catalyst led to the decomposition of sulfonium salt **2a**. Additionally, it was noteworthy that the desilylation of glycosyl donor **1a** was not observed during the optimization.

With the established conditions for *C*-glycosylation in hand, the scope of reaction with sulfonium salts derived from a variety of substituted arenes was investigated. As shown in Scheme 2, sulfonium salts derived from substituted arenes bearing halogen and electron-donating groups in the *para* position underwent glycosylation well (**3a**-**3g**). The formation of **3b** and **3c** in good yields indicated that the C-S bond was cleaved preferentially, leaving the C-Br/Cl bond untouched and enabling further transformation. Electron-withdrawing group including cyano (**3h**), ester (**3i**), ketone (**3j**), nitro (**3k**) was also tolerated in this protocol, albeit giving slightly decreased yields. The reaction with tetrahydronaphthalene-based substrate led to the formation of **3l** in high yield and selectivity. Interestingly, the heterocyclic moieties involving indoline (**3m**), tetrahydroquinoline (**3n**), lactam (**3o**), thiophene (**3p**) and coumarin (**3q**) could be linked to sugar scaffold smoothly, showing good compatibility for arylsulfonium salts. Meanwhile, versatile stannylated glycals were confirmed to be reactive under the optimal conditions. The stereogenic centers of sugar had neglectable effects on the reactivity. Notably, D-galactal, D-arabinal and D-xylal were converted to provide the corresponding *C*-aryl glycals (**3r**-**3u**) in excellent yields. Of note, the TIPS group is essentially required to promote the transformation.

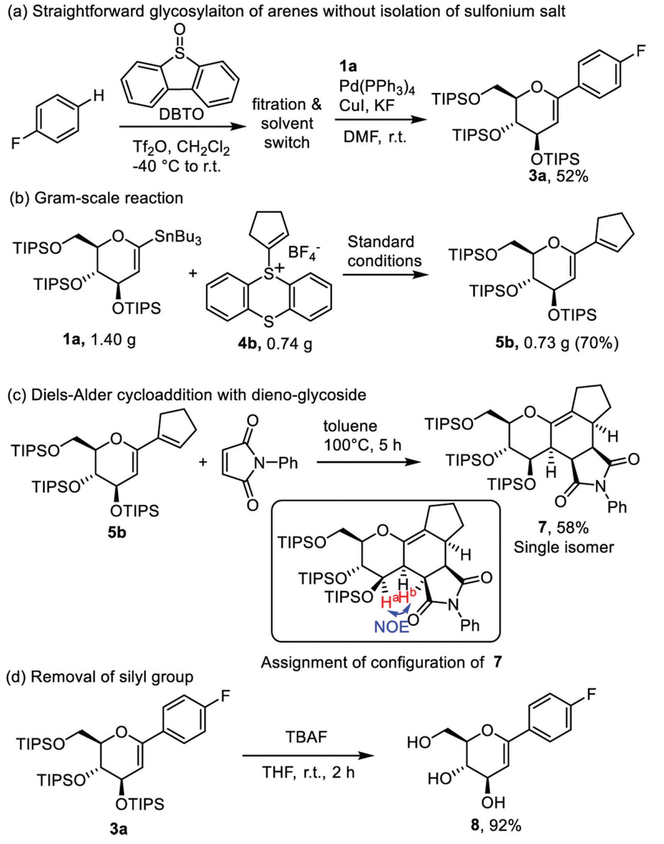
It is worth noting that the dieno structure of the expected *C*-alkenyl glycals can afford diverse reactivities [39–41]. Encouraged by the exciting results of *C*-aryl glycal, we moved to investigate the reactions of alkenylated sulfonium salts to further explore the utility of this protocol. Intriguingly, alkene-derived reactants represented higher reactivity than arene congeners. As illustrated in Scheme 3, both terminal and internal alkenyl substrates were able to be incorporated and gave the products exclusively without *E*/*Z* isomerization. For instance, treatment of sulfonium salts which were derived from styrene (**5a**), cyclopentene (**5b**), *E*-4-octene (**5c**) with **1a** proceeded in good to quantitative yields. Moreover, the enol-type dihydropyran derivative (**5d**) underwent glycosylation



Scheme 2. Scope for aryl *C*-glycals. Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2** (0.12 mmol), DMF (1 mL), 2 mol% Pd(PPh$_3$)$_4$, 10 mol% CuI, KF (0.2 mmol), under N$_2$ atmosphere, isolated yield. [a] TT, TfO$^-$; [b] TT, BF$_4$$^-$; [c] DBT, TfO$^-$.



Scheme 3. Scope for alkenyl *C*-glycals. Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **4** (0.12 mmol), DMF (1 mL), 2 mol% Pd(PPh$_3$)$_4$, 10 mol% CuI, KF (0.2 mmol), under N$_2$ atmosphere, isolated yield.

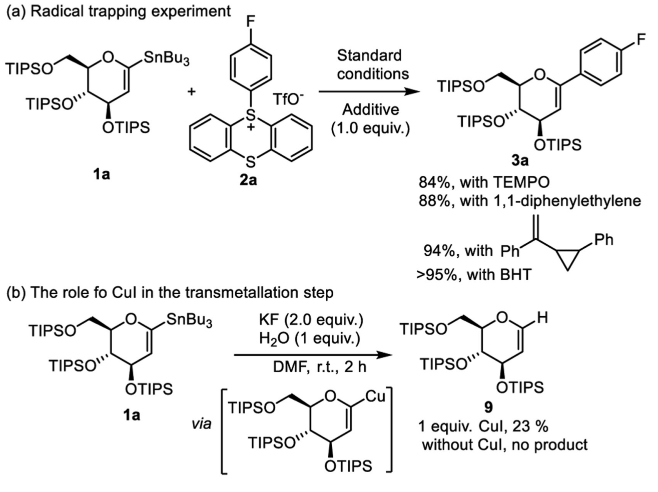


Scheme 4. Straightforward glycosylation of arenes, scalable reaction and derivatization of the aryl/alkenyl *C*-glycoside.

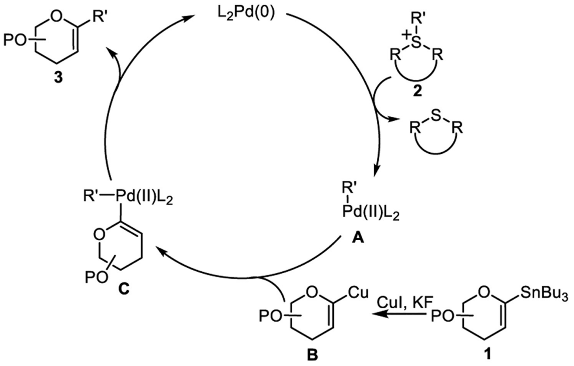
efficiently. Interestingly, the reactions with different sugar substrates such as D-arabinal, D-xylal and D-rhamnal worked well, providing the corresponding dieno-glycosides (**5e**-**5g**) in excellent yields.

For operational simplicity of the methodology, the possibility of sequential reactions starting from the arene directly was investigated, which would avoid the isolation of the sulfonium salt (Scheme 4a). To our delight, the product **3a** was formed in a decent yield for this one-pot two-step synthesis by employing dibenzothiophene-*S*-oxide (DBTO)/Tf$_2$O as the activator for arene. Furthermore, to demonstrate the utility of the protocol, a gram-scale reaction of 1.40 g of **1a** and 0.74 g of **4b** was carried out under the standard conditions. Impressively, the reaction completed within 1.5 h and 0.73 g of product **5b** was obtained in 70% isolated yield, indicating this protocol was scalable (Scheme 4b). Diels-Alder cycloaddition of dieno-glycoside constituted a useful approach to optically pure complex natural products [20]. Therefore, we conducted a reaction by treating the electron-rich dieno-glycoside **5b** with an electron-poor *N*-phenylmaleimide in toluene at 100 °C. Pleasingly, a tetracyclic terpene-like glycoside **7** could be generated stereoselectively, affording an *endo* isomer exclusively in good yield (Scheme 4c) [56]. The assignment of configuration of cycloadduct **7** was based on the observed NOE of proton H^a and proton H^b (see Supporting information for details). Moreover, desilylation took place in the presence of TBAF at ambient temperature, giving the desired product in excellent yield (Scheme 4d).

Moving forward, a series of experiments were performed to gain insights into its reaction mechanism. Initially, various scavengers were subjected to the model reaction under otherwise identical conditions (Scheme 5a). Addition of TEMPO or 1,1-diphenyl



Scheme 5. Mechanistic studies.



Scheme 6. Proposed catalytic cycle for the transformation.

ethylene afforded slightly decreased yields. The employment of cyclopropylvinyl derivative or BHT completely did not interfere the catalytic system. These results indicated that the radical scavenger has a negligible effect on the transformation. Therefore, a radical pathway might possibly be ruled out. Next, the role of CuI was investigated through a protonation process with water as the terminating reagent. In the presence of 1.0 equiv. of CuI, 23% of protonation product **9** was observed, whereas the reaction did not occur without CuI (Scheme 5b). These results suggested that the copper salt played a key role in the transfer of glycosyl moiety [57–61].

Based on the above findings and previous reports [54,62,63], a mechanistic pathway for this synergistic Pd/Cu catalysis is proposed in Scheme 6. First, Pd(0) undergoes oxidative addition with the sulfonium salt to generate an aryl/alkenyl ligated Pd(II) complex **A**. A glycosyl copper species **B** is formed from stannylated glycal **1** under the activation of CuI and KF [57–61]. Next, the intermediate **B** is engaged in the subsequent transmetallation with **A** to give the intermediate **C**. Finally, a reductive elimination process occurs to afford the *C*-glycoside and regenerate the active Pd(0) species.

In conclusion, a highly efficient coupling of glycosyl stannanes and sulfonium salts enabled by synergistic Pd/Cu catalysis is disclosed for the preparation of *C*-aryl/alkenyl glycals. The protocol features broad substrate tolerance and could be operated under remarkably mild conditions. The further utilization of this method for the construction of natural products is ongoing in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] P.G. Hultin, Curr. Top. Med. Chem. 5 (2005) 1299–1331.
[2] P. Compain, O.R. Martin, Bioorg. Med. Chem. 9 (2001) 3077–3092.
[3] Y. Yang, B. Yu, Chem. Rev. 117 (2017) 12281–12356.
[4] M.J. McKay, H.M. Nguyen, ACS Catal. 2 (2012) 1563–1595.
[5] H. Liao, J. Ma, H. Yao, X. Liu, Org. Biomol. Chem. 16 (2018) 1791–1806.
[6] D.Y.W. Lee, M. He, Curr. Top. Med. Chem. 5 (2005) 1333–1350.
[7] N. Hussain, A. Hussain, RSC Adv. 11 (2021) 34369–34391.
[8] K. Kitamura, Y. Ando, T. Matsumoto, K. Suzuki, Chem. Rev. 118 (2018) 1495–1598.
[9] I.S. Aidhen, N. Thoti, Chem. Rec. 21 (2021) 3131–3177.
[10] É. Bokor, S. Kun, D. Goyard, et al., Chem. Rev. 117 (2017) 1687–1764.
[11] J. Li, G. Qu, N. Shang, et al., Green. Synth. Catal. 2 (2021) 45–53.
[12] Y. Wei, B. Ben-zvi, T. Diao, Angew. Chem. Int. Ed. 60 (2021) 9433–9438.
[13] L. Xia, W. Fan, X. Yuan, S. Yu, ACS Catal. 11 (2021) 9397–9406.
[14] Y. Ma, S. Liu, Y. Xi, et al., Chem. Commun. 55 (2019) 14657–14660.
[15] S.O. Badir, A. Dumoulin, J.K. Matsui, G.A. Molander, Angew. Chem. Int. Ed. 57 (2018) 6610–6613.
[16] Y. Jiang, Q. Wang, X. Zhang, M.J. Koh, Chem 7 (2021) 3377–3392.
[17] Y. Li, Z. Wang, L. Li, et al., Angew. Chem. Int. Ed. 61 (2022) e202110391.
[18] G. Liu, C. Li, X. Zhang, et al., Chin. Chem. Lett. 29 (2018) 1–10.
[19] K. Parkan, R. Pohl, M. Kotora, Chem. Eur. J. 20 (2014) 4414–4419.
[20] A. Mukhopadhyay, S.M. Ali, M. Husain, S.N. Suryawanshi, D.S. Bhakuni, Tetrahedron Lett. 30 (1989) 1853–1856.
[21] Z. Guo, J. Bai, M. Liu, D. Xiong, X. Ye, Chin. J. Org. Chem. 40 (2020) 3094–3111.
[22] H.H. Kinfe, Org. Biomol. Chem. 17 (2019) 4153–4182.
[23] D. Xiong, L. Zhang, X. Ye, Org. Lett. 11 (2009) 1709–1712.
[24] L. Gong, H. Sun, L. Deng, et al., J. Am. Chem. Soc. 141 (2019) 7680–7686.
[25] M. Robichon, A. Bordessa, M. Malinowski, et al., Chem. Commun. 55 (2019) 11806–11808.
[26] A.K. Singh, V.K. Kanaujiya, V. Tiwari, S. Sabiah, J. Kandasamy, Org. Lett. 22 (2020) 7650–7655.
[27] M.R. Leidy, J.M. Hoffman, R. Pongdee, Tetrahedron Lett. 54 (2013) 6889–6891.
[28] U. Lehmann, S. Awasthi, T. Minehan, Org. Lett. 5 (2003) 2405–2408.
[29] M. Liu, Y. Niu, Y. Wu, X. Ye, Org. Lett. 18 (2016) 1836–1839.
[30] S. Zhang, Y. Niu, X. Ye, Org. Lett. 19 (2017) 3608–3611.
[31] R. Benhaddou, S. Czernecki, G. Ville, J. Org. Chem. 57 (1992) 4612–4616.
[32] Y. Liu, Y. Wang, W. Dai, et al., Angew. Chem. Int. Ed. 59 (2020) 3491–3494.
[33] J. Wu, N. Kaplaneris, S. Ni, F. Kaltenhäuser, L. Ackermann, Chem. Sci. 11 (2020) 6521–6526.
[34] E. Dubois, J. Beau, J. Chem. Soc., Chem. Commun. (1990) 1191–1192.
[35] H. Zhang, M. Brakta, G.D. Daves, Tetrahedron Lett. 24 (1993) 1571–1574.
[36] D.C. Koester, E. Kriemen, D.B. Werz, Angew. Chem. Int. Ed. 52 (2013) 2985–2989.
[37] R.W. Friesen, C.F. Sturino, J. Org. Chem. 55 (1990) 2572–2574.
[38] J. Choutka, R. Pohl, K. Parkan, ACS Omega 3 (2018) 7875–7887.
[39] R.W. Frissen, R.W. Loo, J. Org. Chem. 56 (1991) 4821–4823.
[40] R.M. Giuliano, J.H. Buzby, N. Marcopulos, J.P. Springer, J. Org. Chem. 55 (1990) 3555–3562.
[41] A. Abas, R.L. Beddoes, J.C. Conway, P. Quayle, C.J. Urch, Synlett (1995) 1264–1266.
[42] L. Zhang, T. Ritter, J. Am. Chem. Soc. 144 (2022) 2399–2414.
[43] F. Berger, M.B. Plutschack, J. Riegger, et al., Nature 567 (2019) 223–228.
[44] J. Srogl, G.D. Allred, L.S. Liebeskind, J. Am. Chem. Soc. 119 (1997) 12376–12377.
[45] M.H. Aukland, F.J.T. Talbot, J.A. Fernández-Salas, et al., Angew. Chem. Int. Ed. 57 (2018) 9785–9789.
[46] Z. Tian, Y. Hu, H. Teng, C. Zhang, Tetrahedron Lett. 59 (2018) 299–309.
[47] X. Chen, Y. Huang, J. Zhou, P. Wang, Chin. J. Chem. 38 (2020) 1269–1272.
[48] S.I. Kozhushkov, M. Alcarazo, Eur. J. Inorg. Chem. (2020) 2486–2500.
[49] A. Selmani, A.G. Gevondian, F. Schoenebeck, Org. Lett. 22 (2020) 4802–4805.
[50] K. Yamada, T. Yanagi, H. Yorimitsu, Org. Lett. 22 (2020) 9712–9718.
[51] C. Chen, M. Wang, H. Lu, B. Zhao, Z. Shi, Angew. Chem. Int. Ed. 60 (2021) 21756–21760.
[52] D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, Chem. Rev. 119 (2019) 8701–8780.
[53] J. Fang, T. Li, X. Ma, et al., Chin. Chem. Lett. 33 (2022) 288–292.
[54] E.L. Grognec, J. Chrétien, F. Zammattio, J. Quintard, Chem. Rev. 115 (2015) 10207–10260.
[55] P. Espinet, A.M. Echavarren, Angew. Chem. Int. Ed. 43 (2004) 4704–4734.

[56] U. Pindur, G. Lutz, C. Otto, Chem. Rev. 93 (1993) 741–761.
[57] Y. Wang, D.J. Burton, Org. Lett. 8 (2006) 1109–1111.
[58] L.S. Liebeskind, R.W. Fengl, J. Org. Chem. 55 (1990) 5359–5364.
[59] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L.S. Liebeskind, J. Org. Chem. 59 (1994) 5905–5911.
[60] J.B. Behling, K.A. Babiak, A.L. Campbell, et al., J. Am. Chem. Soc. 110 (1988) 2641–2643.
[61] A. Casitas, X. Ribas, Chem. Sci. 4 (2013) 2301–2318.
[62] V. Lee, Org. Biomol. Chem. 17 (2019) 9095–9123.
[63] C. Cordovilla, C. Bartolomé, J.M. Martínez-Ilarduya, P. Espinet, ACS Catal. 5 (2015) 3040–3053.