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# Dehydroxylation of alcohols for nucleophilic substitution†

Jia Chen, Jin-Hong Lin and Ji-Chang Xiao*

**The $Ph_3P/ICH_2CH_2I$ system-promoted dehydroxylative substitution of alcohols was achieved to construct C–O, C–N, C–S and C–X (X = Cl, Br, and I) bonds. Compared with the previous approaches such as the Appel reaction and Mitsunobu reaction, this protocol offers some practical advantages such as safe operation and a convenient amination process.**

Nucleophilic substitution at tetravalent carbon ($sp^3$) centers is a fundamental class of reactions that have found widespread applications in organic synthesis.[1] A good leaving group attached to the tetravalent carbon is usually required because the leaving group has a dramatic influence on the rate of nucleophilic substitution. The nucleophilic substitution of readily available chemicals would be an attractive strategy to obtain target molecules. Owing to the wide availability of alcohols, the nucleophilic substitution of alcohols has been demonstrated to have broad synthetic utility.[2] As the hydroxyl group in alcohols is a poor leaving group, the conversion of this moiety into a better leaving group such as a tosylate or a triflate may be required in traditional substitution methods (Fig. 1, eqn (1)).[3] Compared with traditional methods which lack efficiency, the nucleophilic substitution of alcohols through direct dehydroxylation under mild conditions would be preferred.

In recent years, there have been significant advances in the chemistry of phosphonium salts. Phosphonium salts can act as catalysts including phase-transfer catalysts[4] and Lewis acid catalysts,[5] and intermediates for deoxy-functionalization owing to the high affinity of phosphorus towards oxygen. Some deoxy-functionalization reactions include the Wittig reaction,[6] Arbuzov reaction,[7] Appel reaction,[8] and Mitsunobu reaction.[9] The dehydroxylation of alcohols and subsequent nucleophilic substitution is involved in the Appel reaction and Mitsunobu reaction. The Appel reaction has proved to be an efficient approach for halogenation, and the catalytic Appel reaction has been recently developed (Fig. 1, eqn (2)).[10] However, this reaction can only be applied to the construction of C–X (X = Cl, Br, and I) bonds.

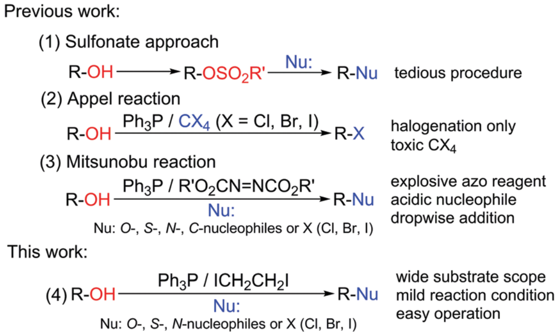

Fig. 1 Dehydroxylation of alcohols for nucleophilic substitution.

The Mitsunobu reaction, the substitution of alcohols with nucleophiles promoted by azodicarboxylate or azodicarbonamide reagents (usually azodicarboxylate) and a triaryl- or trialkylphosphine, has received particular attention as this reaction allows the formation of C–O, C–S, C–N, or C–C bonds (Fig. 1, eqn (3)).[9b] Since its discovery in 1967,[9c] the Mitsunobu reaction has enjoyed widespread prominence and recognition in organic synthesis and medicinal chemistry owing to its stereospecificity, wide substrate scope, and mild reaction conditions. However, this reaction still has some limitations:[9b] first, the nucleophile has to be a relatively acidic component with $pK_a \leq 15$, preferably below 11. Second, azodicarboxylate reagents are susceptible to explosion upon strong heating or impact. Third, a dropwise addition procedure is usually required. Therefore, the development of safe and operationally convenient protocols for deoxy-functionalization of alcohols is highly desirable.

Generally, triphenylphosphine ($Ph_3P$) would readily undergo alkylation with alkyl iodides to produce alkyl phosphonium salts. Unexpectedly, it was found that 1,2-diiodoethane ($ICH_2CH_2I$) did not lead to the alkylation of triphenylphosphine.

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*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: jchxiao@sioc.ac.cn*

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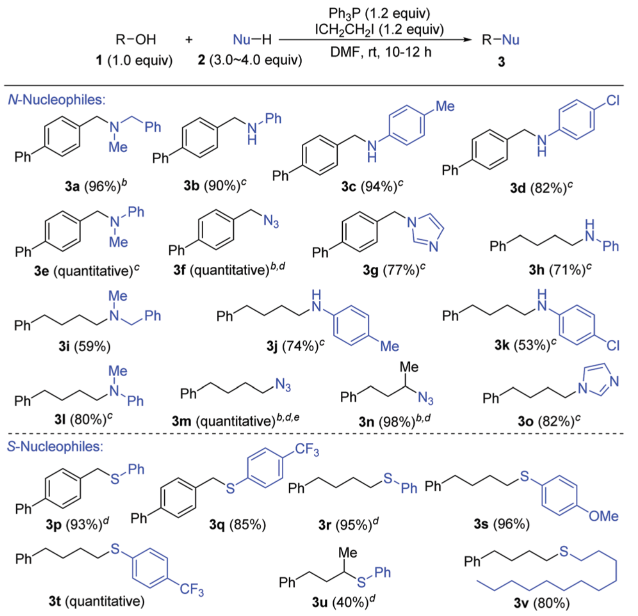
Table 1 Dehydroxylation of alcohols to form C–N and C–S bonds[a]



[a] The yields in parentheses are isolated yields. Reaction conditions: **1** (0.5 mmol), *N*-nucleophile (4 equiv.) or *S*-nucleophile (3 equiv.), $Ph_3P$ (1.2 equiv.), $ICH_2CH_2I$ (1.2 equiv.) in DMF (5 mL) at room temperature for 10–12 h. [b] 3 equiv. of *N*-nucleophile were used. [c] The reaction temperature was 50 °C. [d] $Nu^-Na^+$ was used instead of Nu–H. [e] Irrespective of whether a base (2 equiv. of 2,6-lutidine) was used or not, a quantitative yield was obtained.

Instead, deiodination of $ICH_2CH_2I$ by $Ph_3P$ occurred to generate ethylene and iodophosphonium species ($Ph_3P^+I\ I^-$). Our research interest in the chemistry of phosphonium salts[11] prompted us to investigate the applicability of this species. It was found that the phosphonium salt ($Ph_3P^+I\ I^-$) could enable the convenient nucleophilic substitution of alcohols in DMF through its dehydroxylation to form C–O, C–N, C–S and C–X (X = Cl, Br, and I) bonds (Fig. 1, eqn (4)).

Free amines (primary and secondary) cannot act as nucleophiles in the Mitsunobu reaction as the proton in the N–H moiety is not acidic enough. Although dehydroxy-amination of alcohols with amines could be readily achieved *via* a hydrogen autotransfer strategy,[12] expensive transition metals and high reaction temperatures (usually above 100 °C) are required. It was found that the amination of alcohols promoted by the $Ph_3P/ICH_2CH_2I$ system in DMF was successful to give the desired product. A brief survey of the reaction conditions revealed that a high yield could be obtained by using a slight excess of $Ph_3P$ and $ICH_2CH_2I$ at room temperature [see the ESI†]. With the optimized reaction conditions in hand, the applicability of the dehydroxylation of alcohols to form C–N and C–S bonds was investigated.

As shown in Table 1, benzyl alcohols (**3a–3g**) were highly reactive towards the formation of C–N bonds. Various amines including an alkyl amine (**3a**) and aryl amines (**3b–3e**) could act as excellent nucleophiles. Both primary (**3b–3d**) and secondary amines (**3a** and **3e**) were suitable for this transformation. Owing to the lower nucleophilicity of aryl amines, heating conditions were required for the substitution with aryl amines (**3b–3d**). Notably, the secondary amines (**3b–3d**) obtained from primary amines did not convert further into tertiary amines. A quantitative yield was obtained for the substitution with an azide anion (**3f**). The use of an unprotected imidazole as a nucleophile gave the functionalized imidazole in good yield (**3g**). Although alkyl alcohols showed a slightly lower reactivity compared with benzyl alcohol, various amines (alkyl- and aryl-amines, primary and secondary amines), the azide anion, and unprotected imidazole could all undergo substitution of the hydroxyl group (**3h–3o**). The substitution of the secondary alcohol with an azide anion also occurred to give the product **3n** in high yield.

The dehydroxylation would result in the generation of a proton from the hydroxyl group. As the proton could be neutralized by the excessive nucleophiles and the reaction solvent DMF, very acidic conditions would not be formed from the reaction systems. But in the case of the $N_3^-$ nucleophile, the hazardous $HN_3$ may still be produced without the presence of a base. Fortunately, it was found that the use of 2,6-lutidine as a base to inhibit the formation of $HN_3$ could also give a high yield of the desired product (**3m**).

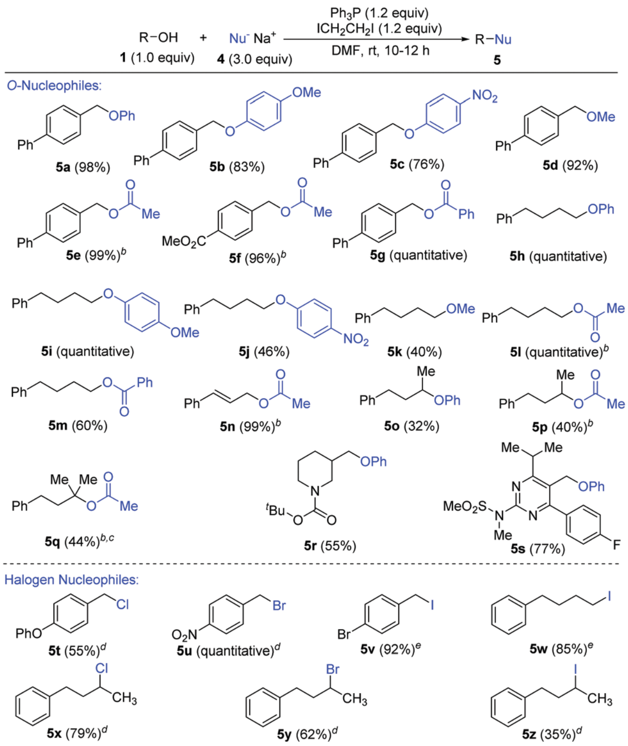
In the Mitsunobu reaction, sulfur nucleophiles usually have to be neutral S–H compounds.[9b] In this protocol, both thiolate anions (**3p**, **3r** and **3u**) and neutral S–H compounds (**3q**, **3s**, **3t** and **3v**) could substitute the hydroxyl group in benzyl and alkyl alcohols. A lower yield was obtained for the transformation of secondary alcohols (**3u**). Besides arylthiols (**3p–3u**), alkylthiol could also be used as a nucleophile to realize dehydroxythiolation (**3v**).

In contrast to phenylthiols, phenols cannot directly act as nucleophiles, probably because the nucleophilicity of phenols is lower owing to its stronger electronegativity and intermolecular hydrogen bonding. It was found that the use of phenolate anions as nucleophiles could give the etherification products in high yields (Table 2, **5a–5c**). Dehydroxy-etherification with an alkoxy anion also proceeded smoothly (**5d**). Carboxylate anions were found to be excellent nucleophiles for the dehydroxyesterification of alcohol (**5e–5g**). Besides benzyl alcohols, alkyl alcohols (**5h–5m**) and allylic alcohol (**5n**) were also quite reactive towards etherification and esterification. Secondary alcohols showed a lower reactivity (**5o–5p**). An elevated reaction temperature (60 °C) allowed for the dehydroxy-esterification of tertiary alcohol albeit in a low yield (**5q**). A high level of functional group tolerance was observed for the C–O bond formation (**5r–5s**).

As organohalogenated compounds are of increasing importance in various areas such as functional materials and organic synthesis,[2c,e,13] halogenation of alcohols was also investigated. It was found that chlorination, bromination, and iodination all occurred well by using halide anions as nucleophiles (**5t–5z**). Interestingly, the external addition of an iodide anion was not necessary for iodination (**5v–5w** and **5z**) because the $Ph_3P/ICH_2CH_2I$ system can generate an iodide anion.

Although the $Ph_3P/ICH_2CH_2I$ system could lead to the direct iodination of alcohols, the iodination byproducts were hardly observed in the other dehydroxy-functionalization reactions

Table 2 Dehydroxylation of alcohols to form C–O and C–X (X = Cl, Br, and I) bonds[a]

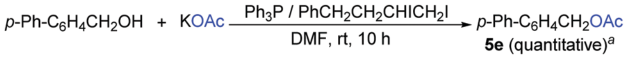


[a] The yields in parentheses are isolated yields. Reaction conditions: **1** (0.5 mmol), $Nu^-Na^+$ (3 equiv.), $Ph_3P$ (1.2 equiv.), $ICH_2CH_2I$ (1.2 equiv.) in DMF (5 mL) at room temperature for 10–12 h. [b] $MeCO_2^-$ $K^+$ was used as the nucleophile. [c] 60 °C of reaction temperature and 5 h of reaction time were used. [d] For chlorination and bromination, $^nBu_4N^+$ $X^-$ was used as the nucleophile. [e] NaI was not required as the iodide anion was generated from $ICH_2CH_2I$; 60 °C of reaction temperature and 2 h of reaction time in $CH_3CN$ were used.

discussed above, probably because the other C–Y (Y = O, S, N, Cl, and Br) bonds are stronger than the C–I bond.

Besides 1,2-diiodoethane, other alkyl vicinal diiodides such as 1,2-diiodo-4-phenylbutane could also be used for dehydroxy-functionalization (Fig. 2), further demonstrating the synthetic utility of this dehydroxylation strategy.

The $^{18}O$-labeling technique has found widespread application in a variety of research areas, such as quantitative proteomics and mechanistic investigations in organic synthesis.[14] Although $^{18}O$-labeled alcohols can be obtained *via* various approaches, multi-step procedures or prohibitively expensive $^{18}O_2$ has to be used in these approaches.[15] Recently, Rozen described a general route for the efficient synthesis of $^{18}O$-labeled alcohols using the $H^{18}OF{\cdot}CH_3CN$ complex, but the preparation of this complex required the use of a hazardous agent, fluorine gas.[16] It was found that the use of $Na^{18}OH$ [made from $H_2{}^{18}O$ ($^{18}O$ content: 95%)] as a nucleophile could readily give the expected $^{18}O$-labeled alcohol (Fig. 3). But a low yield was obtained for the synthesis of labeled alkyl alcohols such as $^{18}O$-4-phenylbutan-1-ol (27% yield and a low labeling ratio). This protocol is straightforward and attractive for labeling benzyl alcohols owing to its mild reaction conditions and convenient procedure.



$$p\text{-Ph-}C_6H_4CH_2OH + KOAc \xrightarrow[\text{DMF, rt, 10 h}]{Ph_3P\,/\,PhCH_2CH_2CHICH_2I} p\text{-Ph-}C_6H_4CH_2OAc \quad \mathbf{5e}\ \text{(quantitative)}^a$$

Fig. 2 Dehydroxy-esterification promoted by a $Ph_3P/RCHICH_2I$ system. [a] The yield was determined *via* $^1H$ NMR spectroscopy.

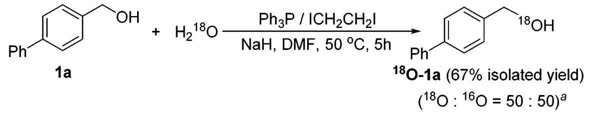


Fig. 3 The synthesis of $^{18}O$-labeled alcohol. [a] Determined using MS-EI.

On the basis of the above results and the experimental evidence shown in the ESI† due to length limits, we propose the plausible reaction mechanism, as shown in Fig. 4. The reaction of $Ph_3P$ with $ICH_2CH_2I$ proceeds very rapidly *via* a halogen bonding process as shown in Fig. S2 (ESI†) to generate the active intermediates, diiodophosphorus **F** ($Ph_3PI_2$) and iodophosphonium salt **G** ($Ph_3P^+I\ I^-$), an equilibrium between which is established. Intermediate **G** is a strong Lewis acid and its coordination with DMF provides intermediate **B**. The nucleophilic attack of the iodide anion at intermediate **B** would release $Ph_3P{=}O$ with the simultaneous formation of the Vilsmeier–Haack type intermediate **C**. Both intermediates **B** and **C** are electrophilic and would be easy to be attacked by an alcohol to afford intermediate **H**. Its subsequent nucleophilic substitution with a nucleophile gives the final product. $Ph_3P{=}O$ can be isolated in 79% yield from the dehydroxylation of alcohol (see the ESI†), which further supports this proposed mechanism.

The final substitution of intermediate **H** should proceed *via* an $S_N2$ process. Indeed, inversion of configuration with partial racemization was observed for the transformation of enantiopure ***S*-1w** under the optimal reaction conditions, as shown in Fig. 5.

Although partial racemization for the substitution of enantiopure alcohols and lower efficiency for the substitution of secondary or tertiary alcohols with bulky nucleophiles (**3u**, **5o–5q**) are major shortcomings of this protocol compared with the Mitsunobu reaction, this protocol is still quite attractive due to safe operation and a convenient amination process. In addition, good yields still

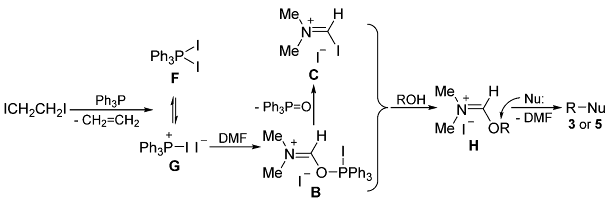


Fig. 4 The proposed mechanism for dehydroxylation of alcohols.

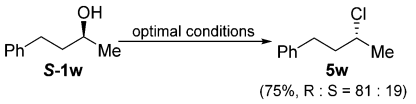


Fig. 5 Inversion of configuration during dehydroxy-chlorination.

could be obtained for the substitution of secondary alcohols with small nucleophiles (**3n**, **5x–5y**).

Intermediate **G** could also be formed from the $Ph_3P/I_2$ system, and the $Ph_3P/I_2$ system has been applied to esterification[17] and iodination.[18] However, its use in nucleophilic substitution of alcohols *via* dehydroxylation has never been systematically investigated, and has been limited to iodination.[18] Furthermore, $I_2$ is toxic and would thus lead to operational inconvenience. In sharp contrast, the $Ph_3P/ICH_2CH_2I$ system could be applied to convenient and efficient substitution of alcohols with various nucleophiles under mild conditions.

In summary, the combination of $Ph_3P$ and $ICH_2CH_2I$ has been demonstrated to be a very efficient reagent system for the dehydroxylation of alcohols and subsequent nucleophilic substitution to form C–N, C–S, C–O, C–Cl, C–Br, and C–I bonds. The dehydroxylation strategy can be applied to the synthesis of $^{18}O$-labeled alcohols. In contrast to the Mitsunobu reaction, in which the azodicarboxylate reagents are susceptible to explosion and the nucleophiles have to be relatively acidic components, this protocol offers some practical advantages including safe operation and convenient amination to afford unprotected amines. Major shortcomings of this protocol include partial racemization for the substitution of enantiopure alcohols and low efficiency for the substitution of secondary or tertiary alcohols with bulky nucleophiles. The $Ph_3P/ICH_2CH_2I$ system may also find synthetic utility in other substitution reactions.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

1 (*a*) F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, Springer Science + Business Media, LLC, New York, 5th edn, 2007; (*b*) W. L. Hase, *Science*, 1994, **266**, 998–1002; (*c*) S. L. Craig and J. I. Brauman, *Science*, 1997, **276**, 1536–1538; (*d*) L. Sun, K. Song and W. L. Hase, *Science*, 2002, **296**, 875–878; (*e*) J. Mikosch, S. Trippel, C. Eichhorn, R. Otto, U. Lourderaj, J. X. Zhang, W. L. Hase, M. Weidemueller and R. Wester, *Science*, 2008, **319**, 183–186; (*f*) M. Stei, E. Carrascosa, M. A. Kainz, A. H. Kelkar, J. Meyer, I. Szabo, G. Czako and R. Wester, *Nat. Chem.*, 2016, **8**, 151–156.

2 (*a*) D. B. Adinarayana Doddi, Thomas Bannenberg, Peter G. Jones and Matthias Tamm, *Angew. Chem., Int. Ed.*, 2014, 1–6; (*b*) E. D. Hughes, C. K. Ingold, R. J. L. Martin and D. F. Meigh, *Nature*, 1950, **166**, 679; (*c*) C. M. Vanos and T. H. Lambert, *Angew. Chem., Int. Ed.*, 2011, **50**, 12222–12226; (*d*) S. V. Pronin, C. A. Reiher and R. A. Shenvi, *Nature*, 2013, **501**, 195–199; (*e*) P. H. Huy, S. Motsch and S. M. Kappler, *Angew. Chem., Int. Ed.*, 2016, **55**, 10145–10149.

3 (*a*) S. F. Zhu, Y. Cai, H. X. Mao, J. H. Xie and Q. L. Zhou, *Nat. Chem.*, 2010, **2**, 546–551; (*b*) N. S. Keddie, A. M. Slawin, T. Lebl, D. Philp and D. O'Hagan, *Nat. Chem.*, 2015, **7**, 483–488; (*c*) C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. Kou, J. Qin, R. Lilien and R. Sarpong, *Nature*, 2015, **528**, 493–498.

4 S. Shirakawa, T. Tokuda, A. Kasai and K. Maruoka, *Org. Lett.*, 2013, **15**, 3350–3353.

5 J. M. Bayne and D. W. Stephan, *Chem. Soc. Rev.*, 2016, **45**, 765–774.

6 (*a*) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863–927; (*b*) S. P. Marsden, *Nat. Chem.*, 2009, **1**, 685–687; (*c*) P. A. Byrne and D. G. Gilheany, *Chem. Soc. Rev.*, 2013, **42**, 6670–6696; (*d*) V. G. Wittig and G. Geissler, *Justus Liebigs Ann. Chem.*, 1953, **580**, 44–57; (*e*) E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, 1990, **112**, 3905–3909.

7 (*a*) B. A. Arbuzov, *Pure Appl. Chem.*, 1964, **9**, 307–335; (*b*) A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, 1981, **81**, 415–430; (*c*) H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, *J. Am. Chem. Soc.*, 1957, **79**, 2608–2612; (*d*) P. Y. Renard, P. Vayron, E. Leclerc, A. Valleix and C. Mioskowski, *Angew. Chem., Int. Ed.*, 2003, **42**, 2389–2392.

8 (*a*) R. Appel, *Angew. Chem., Int. Ed.*, 1975, **14**, 801–811; (*b*) R. Rahinowitz and R. Marcus, *J. Am. Chem. Soc.*, 1962, **84**, 1312–1313; (*c*) E. Bergin, C. T. O'Connor, S. B. Robinson, E. M. McGarrigle, C. P. O'Mahony and D. G. Gilheany, *J. Am. Chem. Soc.*, 2007, **129**, 9566–9567.

9 (*a*) O. Mitsunobu, *Synthesis*, 1981, 1–28; (*b*) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman and K. V. P. P. Kumar, *Chem. Rev.*, 2009, **109**, 2551–2651; (*c*) O. Mitsunobu and Y. Yamada, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2380–2382; (*d*) E. Grochowski, B. D. Hilton, R. J. Kupper and C. J. Michejda, *J. Am. Chem. Soc.*, 1982, **104**, 6876–6877; (*e*) D. L. Hughes, R. A. Reamer, J. J. Bergan and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1988, **110**, 6487–6491; (*f*) T. Y. S. But and P. H. Toy, *J. Am. Chem. Soc.*, 2006, **128**, 9636–9637; (*g*) D. Hirose, T. Taniguchi and H. Ishibashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 4613–4617; (*h*) J. A. Buonomo and C. C. Aldrich, *Angew. Chem., Int. Ed.*, 2015, **54**, 13041–13044; (*i*) D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, *Chem. Sci.*, 2016, **7**, 5148–5159.

10 (*a*) R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025–3027; (*b*) R. M. Denton, X. Tang and A. Przeslak, *Org. Lett.*, 2010, **12**, 4678–4681; (*c*) R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis and A. M. Poulton, *J. Org. Chem.*, 2011, **76**, 6749–6767.

11 (*a*) J. Zheng, L. Wang, J.-H. Lin, J.-C. Xiao and S. H. Liang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13236–13240; (*b*) Z. Deng, J.-H. Lin and J.-C. Xiao, *Nat. Commun.*, 2016, **7**, 10337; (*c*) J. Zheng, R. Cheng, J.-H. Lin, D.-H. Yu, L. Ma, L. Jia, L. Zhang, L. Wang, J.-C. Xiao and S. H. Liang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3196–3200; (*d*) J. Yu, J.-H. Lin and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 16669–16673.

12 G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611–1641.

13 (*a*) G. W. Gribble, *Acc. Chem. Res.*, 1998, **31**, 141–152; (*b*) C. Dai, J. M. Narayanam and C. R. Stephenson, *Nat. Chem.*, 2011, **3**, 140–145; (*c*) T. V. Nguyen and A. Bekensir, *Org. Lett.*, 2014, **16**, 1720–1723; (*d*) P. H. Huy, T. Hauch and I. Filbrich, *Synlett*, 2016, 2631–2636.

14 (*a*) A. D. Allen, M. Fujio, O. S. Tee, T. T. Tidwell, Y. Tsuji, Y. Tsuno and K.-I. Yatsugi, *J. Am. Chem. Soc.*, 1995, **117**, 8974–8981; (*b*) A. B. Sorokin, E. V. Kudrik and D. Bouchu, *Chem. Commun.*, 2008, 2562–2564; (*c*) E. V. Kudrik and A. B. Sorokin, *Chem. – Eur. J.*, 2008, **14**, 7123–7126.

15 (*a*) L. Kupczyk-Subotkowska and H. J. Shine, *J. Labelled Compd. Radiopharm.*, 1992, **31**, 381–385; (*b*) G. A. Sowa, A. C. Hengge and W. W. Cleland, *J. Am. Chem. Soc.*, 1997, **119**, 2319–2320.

16 J. Gatenyo, I. Vints and S. Rozen, *Chem. Commun.*, 2013, **49**, 7379–7381.

17 (*a*) G. Pathak and L. Rokhum, *ACS Comb. Sci.*, 2015, **17**, 483–487; (*b*) S. P. Morcillo, L. Alvarez de Cienfuegos, A. J. Mota, J. Justicia and R. Robles, *J. Org. Chem.*, 2011, **76**, 2277–2281.

18 (*a*) P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, 1979, 978–980; (*b*) G. Bringmann and S. Schneider, *Synthesis*, 1983, 139–141.