ChemComm

Heteroannulation of bicyclobutane derivatives via Au-catalyzed hydration to enol ethers and intramolecular cyclization giving spirocyclobutanes

Journal:	*ChemComm*
Manuscript ID	CC-COM-04-2023-001955.R1
Article Type:	Communication

COMMUNICATION

Heteroannulation of bicyclobutane derivatives via Au-catalyzed hydration to enol ethers and intramolecular cyclization giving spirocyclobutanes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Masaharu Takatsuki,[a] Hiroshi Aoyama,[a] Kenichi Murai,[a] Mitsuhiro Arisawa*[a] and Makoto Sako*[a]

We report the heteroannulations of bicyclobutane derivatives bearing enol ether groups in the presence of H_2O under mild conditions. The reaction affords spirocyclobutanes with cyclic acetal groups via the Au-catalyzed hydration of the enol ether group and subsequent intramolecular cyclization.

In current drug discovery research, drug modality has been diversified due to the development of conceptually novel drug innovations.[1] Small-molecule drugs, which have been extensively studied by medicinal chemists, are a mainstay in the field of drug discovery. However, in recent drug development research, the discovery of novel small-molecule drug targets using existing generic structures has become increasingly challenging. To innovate small-molecule pharmaceuticals, novel approaches, such as the advanced use of existing skeletons by adding novel moieties, structurally novel skeletons, and elemental replacement strategies, are required. A promising substructure is the cyclobutane skeleton, which often occurs in biologically active compounds and can both provide access to otherwise inaccessible vectors and increase the metabolic stability due to its stronger C-H bonds with higher s-character than conventional C-H bonds (Figure 1).[2] Therefore, the development of efficient reactions to synthesize functionalized cyclobutane derivatives is highly desirable for advanced drug modalities.

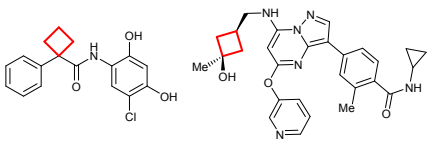
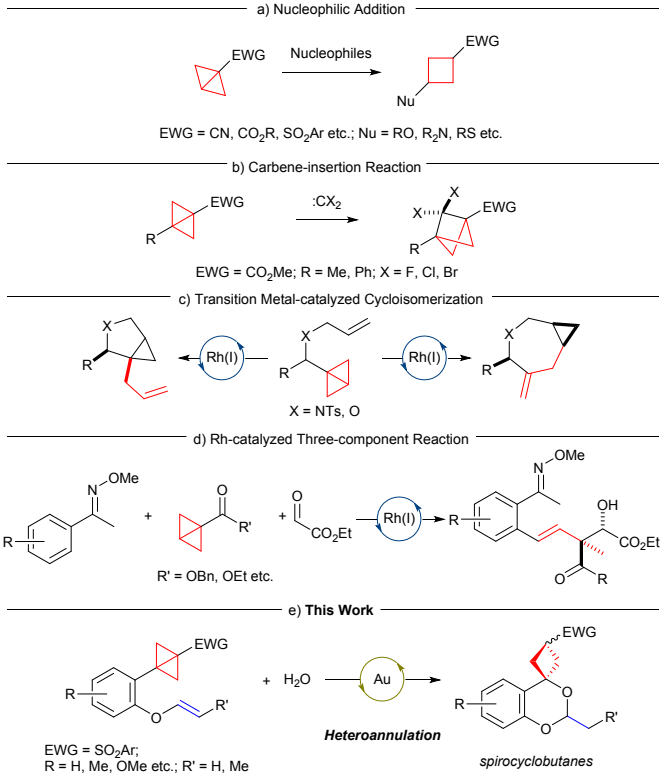


Figure 1 Pharmaceuticals containing cyclobutane skeletons.



Scheme 1 Representative reactions of BCBs.

Ring-strained compounds attract attention in research because of their high reactivities due to ring strain.[3] Among them, bicyclo[1.1.0]butane (BCB)[4] has been used as a C4 building block[5] and covalent drug[6], exploiting its high reactivity. As representative transformations, BCBs may be converted to cyclobutane derivatives via ring-opening reactions (Scheme 1a).[2a,7] Additionally, utilizing the high, unique reactivities of BCBs, converting them to other cyclic molecules, such as bicyclopentanes, via carbene insertion (Scheme 1b) is possible.[8] Transition-metal-catalyzed transformations may expand the

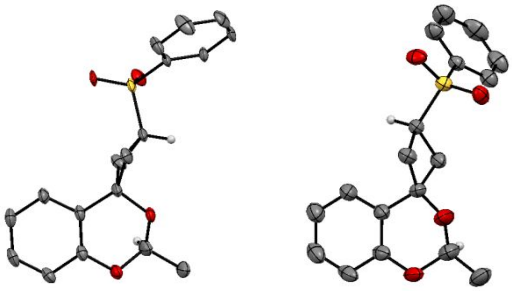
[a] *Graduate School of Pharmaceutical Sciences, Osaka University, Yamadaoka, Suita-shi, Osaka 565-0871, Japan. E-mail: arisaw@phs.osaka-u.ac.jp; sako-m@phs.osaka-u.ac.jp*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

synthetic utilities of BCBs, as indicated by the Rh(I)-catalyzed cycloisomerizations of BCB derivatives bearing allyl amine units reported by the Wipf group (Scheme 1c).[9] Additionally, in the Rh-catalyzed three-component reaction reported by the Glorius group, the BCB is fully opened to yield a quaternary carbon center (Scheme 1d).[10]

Thus, the application of BCBs in a series of transformations should contribute to the syntheses of structurally significant molecules. In this context, BCB derivatives bearing enol ether groups as electrophilic substituents were designed. As enol ethers are activated by Au catalysts to react with nucleophiles[11], we propose the heteroannulations of BCB derivatives to form spirocyclobutane compounds via the nucleophilic addition of water and intramolecular cyclization (Scheme 1e).

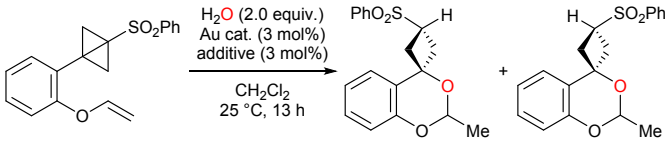
We explored this heteroannulation using the model starting material **1a** with bicyclobutane and enol ether units as electrophilic moieties. Various reaction conditions were screened and sedulous optimization was performed (see details in the EIS). The reaction of **1a** with 2.0 equivalents of H_2O in the presence of 3 mol% of PPh_3AuCl and AgOTf in CH_2Cl_2 at 25 °C yields the spiro heterocyclic product **2a** with an acetal-cyclobutane skeleton as a diastereomixture (**2a**:**2a'** = 1.1:1) in a NMR yield of 86% (Table 1, entry 1). The diastereomers were separated via silica gel column chromatography, and their structures were confirmed using X-ray crystallography (Figure 2, CCDC 2247662 for **2a** and 2247661 for **2a'**). Other Ag additives, such as $AgNTf_2$, $AgBF_4$, $AgSbF_6$ and AgOAc, are less effective in this reaction (entries 2–5). The use of the XPhosAuCl or JohnPhosAuCl precatalyst results in a lower product yield (entries 6 and 7). When Au catalysts bearing *N*-heterocyclic carbene ligands are used, the products are generated in lower yields (entries 8 and 9). The product was obtained in only 57% yield without Au catalysts (entry 10). The reaction with 1.0 equivalent of H_2O proceeds smoothly (NMR yield: 78%, entry 11), but a larger amount of H_2O results in lower chemical yields of the products (entries 12 and 13).



2a CCDC 2247662 **2a'** CCDC 2247661

Figure 2 X-ray crystal structures of **2a** and **2a'**.

Table 1 Optimization of the reaction conditions[a]



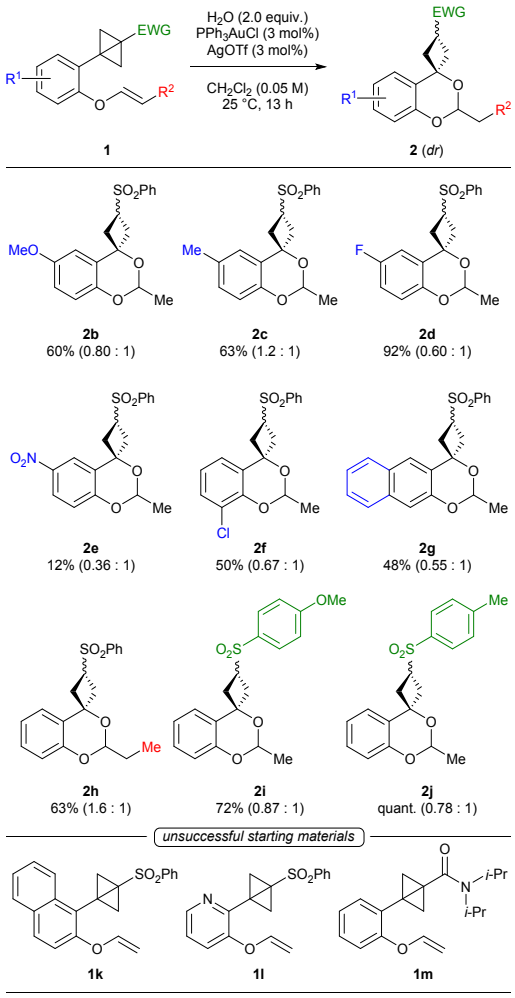
1a **2a** **2a'**

Entry	Au cat.	Additive	Yield (%, **2a**:**2a'**)[b]
1	PPh_3AuCl	AgOTf	86 (1.1:1), 85[c]
2	PPh_3AuCl	$AgNTf_2$	55 (0.8:1)
3	PPh_3AuCl	$AgBF_4$	34 (1.8:1)
4	PPh_3AuCl	$AgSbF_6$	54 (0.8:1)
5	PPh_3AuCl	AgOAc	no reaction
6	XPhosAuCl	AgOTf	83 (1.1:1)
7	JohnPhosAuCl	AgOTf	55
8	$IPrAuNTf_2$	—	67 (1.5:1)
9	$IPrAu(MeCN)BF_4$	—	not detected
10[d]	—	AgOTf	57 (0.67:1)
11[e]	PPh_3AuCl	AgOTf	78 (1.1:1)
12[f]	PPh_3AuCl	AgOTf	45 (1.7:1)
13[g]	PPh_3AuCl	AgOTf	10 (1.1:1)

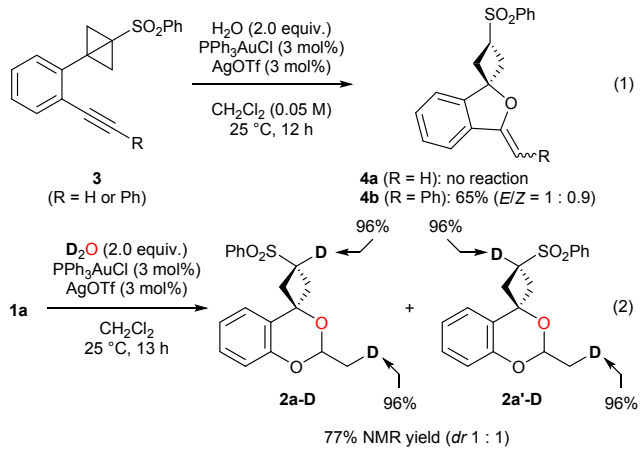
[a]Reaction Conditions: **1a** (0.15 mmol), H_2O (2.0 equiv.), Au cat. (3 mol.%), additive (3 mol.%), CH_2Cl_2 (3.0 mL), 25 °C, 13 h. [b]Yields and diastereomeric ratios were determined via ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield (%). [d]6 mol% of AgOTf. [e]1.0 equiv. of H_2O. [f]5.0 equiv. of H_2O. [g]10 equiv. of H_2O.

After optimizing the reaction conditions, the substitution effect at R^1 on the benzene ring was investigated (Scheme 2). Methoxy- and methyl-substituted products **2b** and **2c**, respectively, are obtained in moderate yields. Bicyclobutane derivative **1d** bearing a fluoro substituent is converted to the product in a 92% yield, whereas **2e** with a nitro group is obtained in a yield of only 12%. The use of **1f**, with a chloro substituent at the ortho position relative to oxygen, or **1g**, with a naphthalene structure, affords the corresponding product **2f** (50%) or **2g** (48%). In addition to the terminal alkene, **1h** with an internal alkene is converted in this reaction, furnishing **2h** in a 63% yield. When (4-methoxyphenyl)sulfonyl- or *p*-tosyl-substituted **1i** and **1j** are respectively used as starting materials, the reactions proceed smoothly to furnish the products in good yields. In both cases, the products are isolated as diastereomeric mixtures. Reactions employing **1k–1m** do not afford the corresponding products.

As an Au catalyst may activate alkynes due to its high π-Lewis acidity[12], we developed a heteroannulation using a bicyclobutane derivative with an alkyne unit instead of an enol ether unit. Thus, reactions with the designed starting materials **3** were conducted under the same reaction conditions, and the expected heterocycles, spiro(isobenzofuran)s, are obtained in good yields when the R substituent on the alkyne is a phenyl group (eq. 1).

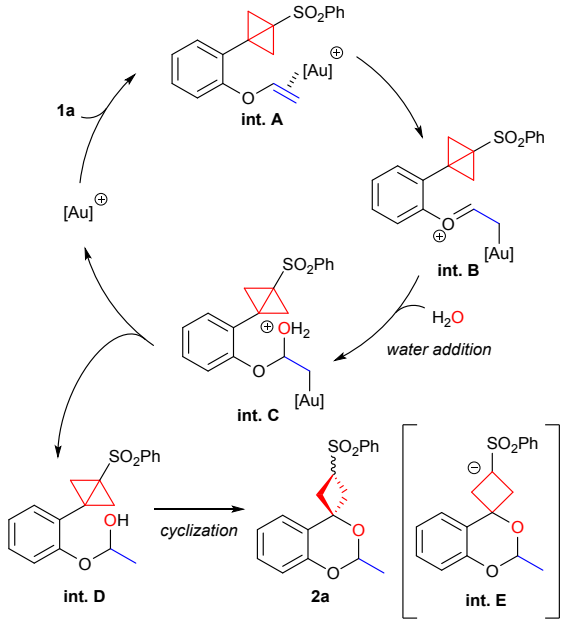


Scheme 2 Substrate scope.



As a control experiment, D_2O was used instead of H_2O, and the deuterated products **2a-D** and **2a'-D** are obtained with >90% D incorporation (eq. 2). Therefore, an H_2O molecule reacts with **1a** to induce heteroannulation. To elucidate whether electrophilic bicyclobutane or enol ether reacts with H_2O first, a time-course ^1H NMR study was performed using a homogeneous catalytic system with $IPrAuNTf_2$ in $CDCl_3$. The enol ether unit is hydrated before the bicyclobutane unit because the peaks representing the enol ether are no longer observed and the characteristic singlet peaks representing the bicyclobutane unit are shifted (Figure 3 and ESI). The singlet peaks of the bicyclobutane unit gradually disappear. These studies also suggest that the reaction does not proceed via the isomerization of bicyclobutane to cyclobutene and D is not incorporated at the methylene carbons of cyclobutane, and no peaks representing cyclobutene are observed in the NMR spectra.

Based on these results, a plausible reaction mechanism of the intramolecular cyclization is proposed (Scheme 3). The generation of cationic Au species ($[Au]^+$) from PPh_3AuCl and AgOTf initiates the catalytic cycle by activating **1a**. The generated **int. A** is in equilibrium with **int. B**, which may easily react with H_2O to produce **int. C**. After the regeneration of the active Au species, **int. D** finally undergoes cyclization via the ring opening of BCB to form **2a**. To generate the observed diastereomeric ratio, the cyclization proceeds stepwise via the formation of **int. E**.



Scheme 3 Plausible reaction mechanism.

In summary, we developed the heteroannulations of BCB derivatives via Au-catalyzed H_2O addition to enol ethers, followed by intramolecular cyclization. The established reaction could be conducted under mild conditions, affording spirocyclobutane compounds with cyclic acetal skeletons. This method was also utilized to synthesize spiro(isobenzofuran)s using BCBs bearing alkyne units. The reaction pathway was deduced using a control experiment with D_2O and time-course NMR studies.

M.T. designed and performed the experiments and characterized the compounds. H.A. conducted X-ray crystallographic analysis. K.M helped supervise the project. M.A. and M.S. conceived and supervised the project, wrote the manuscript, and secured financial support.

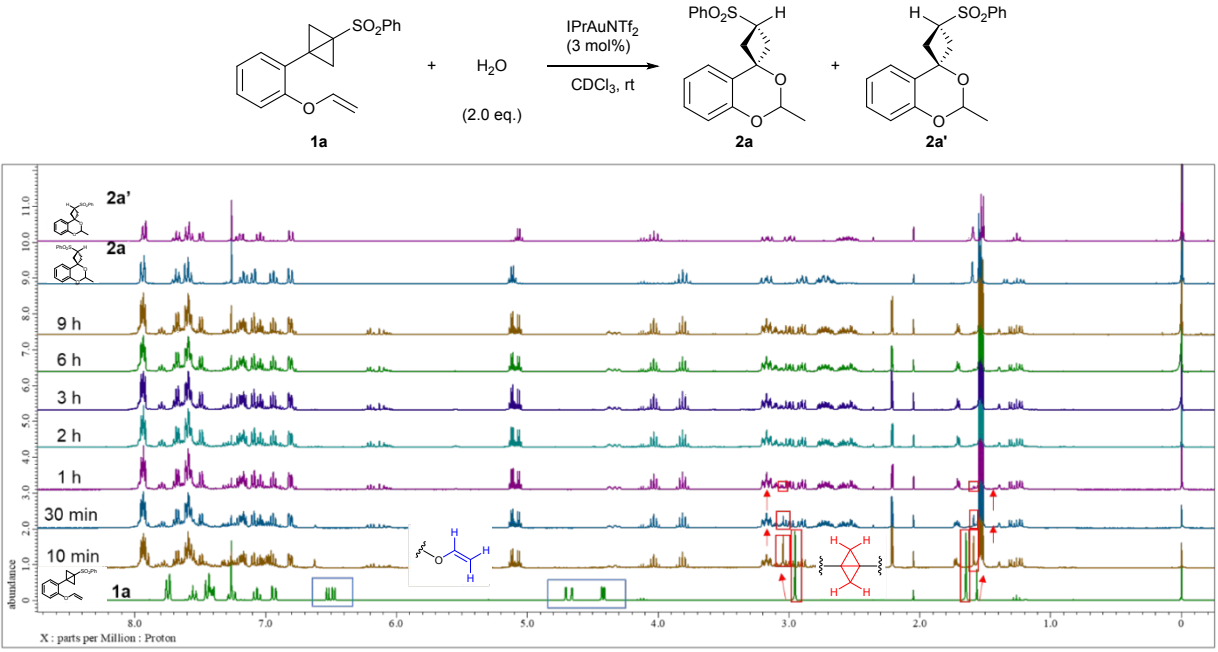


Figure 3 Time-course NMR studies (conversion from **1a** to **2a/2a'**).

This work was supported by JSPS KAKENHI Grant Numbers JP22K05114 (M.S.), JP22H05366 (M.S.), JP22KK0073 (M.S.)), Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from the AMED under Grant Number JP22ama121054, Grant-in-Aid from Iketani Science and Technology Foundation, TOKUYAMA SCIENCE FOUNDATION, and The Foundation for The Promotion of Ion Engineering.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 E. Valeur, S. M. Guéret, H. Adihou, R. Gopalakrishnan, M. Lemurell, H. Waldmann, T. N. Grossmann and A. T. Plowright, *Angew. Chem. Int. Ed. Engl.*, 2017, **56**, 10294.

2 (a) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1; (b) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559; (c) Y. Y. Fan, X. H. Gao and J. M. Yue, *Sci. China Chem.*, 2016, **59**, 1126; (d) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020; (e) L. A. Marchetti, L. K. Kumawat, N. Mao, J. C. Stephens and R. B. P. Elmes, *Chem*, 2019, **5**, 1398; (f) M. R. Bauer, P. D. Fruscia, S. C. C. Lucas, L. N. Michaelides, J. E. Nelson, R. L. Storer and B. C. Whitehurst, *RSC Med. Chem.*, 2021, **12**, 448.

3 (a) E. Vogel, *Angew. Chem. Int. Ed.*, 1963, **2**, 1; (b) K. Mukai, K. Jskizu and B. Gert Kobrichl, *Angew. Chem. Int. Ed.*, 1973, **12**, 464; (c) P. R. Khoury, J. D. Goddard and W. Tam, *Tetrahedron*, 2004, **60**, 8103.

4 (a) E. P. Blanchard, Jr. and A. Cairncross, *J. Am. Chem. Soc.*, 1966, **88**, 487; (b) D. M. Lemal, F. Menger and G. W. Clark, *J. Am. Chem. Soc.*, 1963, **85**, 2529; (c) H. Mizoguchi and A. Sakakura, *Chem. Lett.*, 2021, **50**, 792; (d) C. B. Kelly, J. A. Milligan, L. J. Tilley and T. M. Sodano, *Chem. Sci.*, 2022, **13**, 11721.

5 (a) M. Golfmann and J. C. L. Walker, *Commun. Chem.*, 2023, **6**, 9; (b) M. Ueda, M. A. A. Walczak and P. Wipf, *Tetrahedron Lett.*, 2008, **49**, 5986.

6 (a) K. Tokunaga, M. Sato, K. Kuwata, C. Miura, H. Fuchida, N. Matsunaga, S. Koyanagi, S. Ohdo, N. Shindo and A. Ojida, *J. Am. Chem. Soc.*, 2020, **142**, 18522; (b) P. Zhang, R. Zhuang, X. Wang, H. Liu, J. Li, X. Su, X. Chen and X. Zhang, *Bioconjug. Chem.*, 2018, **29**, 467.

7 (a) S. Hoz and D. Aurbach, *Tetrahedron*, 1979, **35**, 881; (b) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *Science*, 2016, **351**, 241; (c) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 3209; (d) M. Jung and V. N. G. Lindsay, *J. Am. Chem. Soc.*, 2022, **144**, 4764; (e) M. Jung, J. E. Muir and V. N. G. Lindsay, *Tetrahedron*, 2023, **134**, 133296.

8 J. M. Anderson, N. D. Measom, J. A. Murphy and D. L. Poole, *Angew. Chem. Int. Ed.*, 2021, **60**, 24754.

9 (a) M. A. A. Walczak, T. Krainz and P. Wipf, *Acc. Chem. Res.*, 2015, **48**, 1149; (b) M. A. A. Walczak and P. Wipf, *J. Am. Chem. Soc.*, 2008, **130**, 6924; (c) P.-P. Chen, P. Wipf and K. N. Houk, *Nat. Commun.*, 2022, **13**, 7292.

10 T. Pinkert, M. Das, M. L. Schrader and F. Glorius, *J. Am. Chem. Soc.*, 2021, **143**, 7648.

11 (a) S. A. Z. Ahmad, T. K. Jena and F. A. Khan, *Chem. - An Asian J.*, 2021, **16**, 1685; (b) A. Hamasaki, E. Yamamoto, H. Itoh and M. Tokunaga, *J. Organomet. Chem.*, 2011, **696**, 202; (c) T. Ma, C. Sun, X. Yuan, X. Li and Z. Zhao, *RSC Adv.*, 2017, **7**, 1062.

12 (a) L. Lempenauer, G. Lemière and E. Duñach, *Adv. Synth. Catal.*, 2019, **361**, 5284; (b) S. M. Abu Sohel and R.-S. Liu, *Chem. Soc. Rev.*, 2009, **38**, 2269; (c) J. Xiao and X. Li, *Angew. Chem. Int. Ed. Engl.*, 2011, **50**, 7226; (d) S. B. Alyabyev and I. P. Beletskaya, *Russ. Chem. Rev.*, 2018, **87**, 984.