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Aqueous hemin catalyzed sulfonium ylide formation and subsequent [2,3]-sigmatropic rearrangements†

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A mild hemin catalytic system for sulfonium ylide generation *via* a metal carbenoid and a subsequent [2,3]-sigmatropic rearrangement reaction in aqueous solvent is well-established, with the assistance of cyclodextrin (CD) and Triton X-100. The protocol displays high catalytic activity with a broad substrate scope of aryl/alkyl allyl sulfides and diazo reagents, affording homoallyl sulfide products in up to 99% yield. Notably, this catalytic system is successful for water-insoluble allyl sulfides but ineffective for allyl amines or allyl ethers. Moreover, an unprecedented cascade reaction of sulfonium ylide formation, [2,3]-sigmatropic rearrangement and C–H insertion was reported.

Diazo compounds have attracted great attention for decades, because of their broad applications in organic synthesis *via* thermal, photochemical, or catalytic processes with extrusion of dinitrogen. Among all these reactions, metal carbenoids generated through the reaction between transition metal-catalysts and diazo compounds have been deeply explored to achieve diverse transformations, such as C–H insertion, X–H insertion (X = N, S, O, Si, B, *etc.*), cyclopropanation, and ylide formation.[1]

The [2,3]-sigmatropic rearrangement of sulfonium ylide generated from a transition metal carbenoid and allyl sulfide, namely the Doyle–Kirmse reaction,[2] has emerged as a powerful synthetic strategy for C–C bond construction.[3] Since its discovery in the 1960s, numerous studies have reported that copper[4]- and rhodium[5]-based catalysts are effective for this type of ylide transformation. Subsequently, a variety of other transition-metal complexes based on ruthenium,[6] palladium,[7] cobalt,[8] iron,[9] gold[10] and silver[11] have also been proven as capable catalysts. However, most of the reported catalytic systems are conducted in organic solvent under an inert atmosphere. As water is a desirable solvent for chemical reactions in consideration of cost, safety and environmental sustainability, it is of great significance to perform this reaction in water-based green solvents. To the best of our knowledge, the first example of the Doyle–Kirmse reaction carried out in aqueous solution was reported by Wang and his co-workers in 2007 using Rh[II] as the catalyst.[5b]

Iron porphyrins (especially hemin) are abundantly distributed in nature, acting as a catalytic oxidation cofactor in different enzymes. In the last few years, Arnold[12] and Fasan[13] have made big progress in hemoprotein-catalyzed carbenoid-related reactions. In 2015, Fasan and co-workers reported mutmyoglobin-catalyzed sigmatropic rearrangement of allyl sulfide,[13d] which was subsequently further investigated systematically.[13e] Very recently, Arnold and co-workers demonstrated that a sulfimidation/[2,3]-sigmatropic rearrangement sequence can be conducted in whole cell containing cytochrome variants.[12b] However, the utility of iron porphyrin in organic synthesis is very limited, due to its low solubility in both organic and aqueous solvents. Gross has previously reported the catalytic activity of iron corroles and porphyrins for the reactions of diazoacetates with nucleophilic substrates.[9b] Recently, we developed hemin-catalyzed intermolecular N–H insertion of diazo carbonyl compounds under aqueous conditions with the assistance of cyclodextrin.[14] With our continuing interest in expanding the catalytic ability of hemin in carbenoid chemistry, herein, we established a highly efficient aqueous system for [2,3]-sigmatropic rearrangement of sulfonium ylide derived from iron-carbenoid and allyl sulfide, using hemin as a catalyst, and cyclodextrin and Triton X-100 as promoters.

Firstly, phenyl allyl sulfide (**1a**) and ethyl diazo acetate (EDA, **2a**) were chosen as the model substrates to optimize the reaction conditions (Table 1). When the hemoenzyme HRP was employed as the catalyst in this reaction, no desired product was detected (entry 1). However, when the reaction was treated with 5 mol% of its cofactor, hemin, in water at 40 °C for 48 hours, the desired product 2-(phenylthio)-4-pentenoic acid ethyl ester (**3a**) was obtained in 46% yield according to ^{1}H NMR analysis (entry 2). Encouraged by the results in our previous work, we tried cyclodextrins as additives. As expected,

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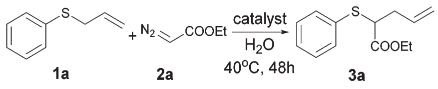
Table 1 Optimization of the reaction conditions[a]



Entry	2a/1a	Catalysts (mol %)	β-CD (mol %)	Surfactant (mol %)	Yield[b] (%)
1	1	HRP (0.01)	—	—	0
2	1	Hemin (5)	—	—	46
3	1	Hemin (5)	20	—	60
4	1.5	—	20	—	0
5	1.5	Hemin (1)	20	—	65
6	1.5	Hemin (2.5)	20	—	77
7	1.5	Hemin (5)	20	—	71
8	1.5	Hemin (2.5)	—	—	65
9	1.5	Hemin (2.5)	5	—	65
10	1.5	Hemin (2.5)	10	—	68
11	1.5	Hemin (2.5)	20	—	77
12	2	Hemin (2.5)	20	—	83
13	2	Hemin (2.5)	20	TBAB (2.5)	57
14	2	Hemin (2.5)	20	PEG2000 (2.5)	52
15	2	Hemin (2.5)	20	NaDDBS (2.5)	70
16	2	Hemin (2.5)	20	Triton X-100 (2.5)	93
17	2	Hemin (2.5)	—	Triton X-100 (10)	58
18	2	$FeCl_3\cdot 6H_2O$	20	Triton X-100 (2.5)	0
19	2	Cu(II) protoporphyrin IX	20	Triton X-100 (2.5)	0

[a] Reaction was carried out with 3 mL of H_2O at 40 °C for 48 h in a thermo shaker. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture.

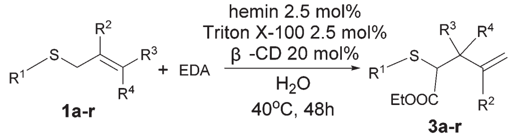
the yield of **3a** improved to 60% when 20 mol% β-CD was added to this reaction system (entry 3, the screening results of different CDs are presented in Table S1, ESI†). Meanwhile, a control reaction performed in the absence of hemin led to no detectable product (entry 4), indicating that cyclodextrin itself does not exhibit any catalytic ability. Further screening showed that a 2.5 mol% and 20 mol% loading amount of hemin and β-CD respectively gave a 77% yield of the product (entries 5–11). Subsequently, two equivalents of **2a** promoted the reaction to 83% yield (entry 12, see the ESI† for details).

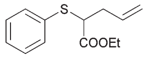
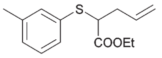
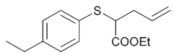
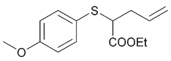
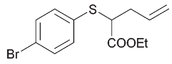
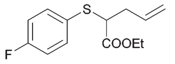
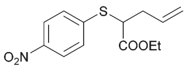
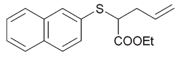
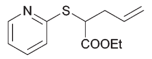
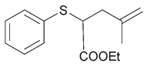
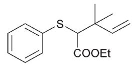
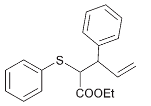
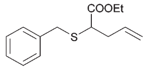
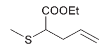
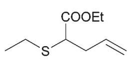
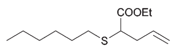
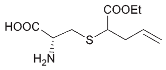
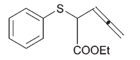
Considering the aggregation of hemin in water, frequently used surfactants, such as tetrabutylammonium bromide (TBAB), PEG 2000, sodium dodecylbenzene sulfonate (NaDDBS) and Triton X-100, were introduced in the reaction system (entries 13–16). To our delight, when 2.5 mol% of the non-ionic surfactant Triton X-100, which has been previously employed as a dispersing agent for hemin,[15] was added, the yield of **3a** further improved to 93% (entry 16), while other surfactants had no obvious effect on the transformation. A control experiment in the absence of β-CD only gave rise to 58% product formation (entry 14), indicating that both cyclodextrin and Triton X-100 contribute synergistically to the catalytic system. Notably, the simple iron salt $FeCl_3\cdot 6H_2O$ (entry 18) and Cu(II) protoporphyrin IX (entry 19) had no catalytic effect in this reaction under the same reaction conditions, revealing that hemin plays an irreplaceable role in this catalytic system. Compared with the reported Doyle–Kirmse reactions, our approach possesses a relatively lower *E*-factor of about 1.7 (for details see the ESI†).

In most previously reported cases, aryl allyl sulfides mainly result in the cyclopropanation products of a double bond or the homo-coupling products of the diazo compound.[6b] Additionally, iron porphyrin complexes have been proven to be active catalysts for the cyclopropanation of alkenes with EDA.[16] However, no cyclopropanation or [1,2]-rearrangement product was detected in our catalytic system. Only a small amount of the byproduct EDA-dimer was observed.

Having identified the optimal conditions, we next examined the substrate scope of this catalytic reaction system. Firstly, various allyl sulfides were tested under these standard reaction conditions using EDA as the carbene precursor as shown in Table 2. All the allyl aryl sulfides underwent the Doyle–Kirmse reaction smoothly, and the electronic properties of the substituent on the phenyl ring of the sulfide did not show an obvious influence on the reactivity. Sulfides bearing electron-donating or electron-withdrawing substituents at either the *meta* or the *para* position on the phenyl ring were well tolerated, giving fairly good to excellent yields of the desired pro-

Table 2 Hemin-catalyzed Doyle–Kirmse reaction of various sulfides[a,b]

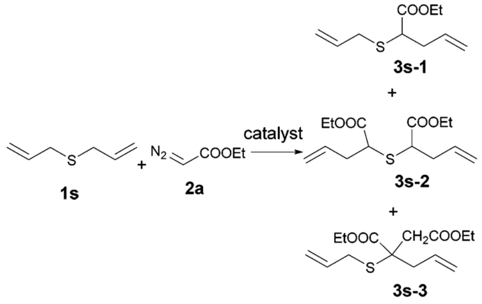


 **3a**, 93% (86%, 71%[c])	 **3b**, 80% (69%)	 **3c**, 53% (48%)
 **3d**, 93% (85%)	 **3e**, 64% (60%)	 **3f**, 84% (71%)
 **3g**, 51% (46%)	 **3h**, 79% (66%)	 **3i**, 83% (70%)
 **3j**, 86% (72%)	 **3k**, 89% (85%)	 **3l**, 65% (52%) d.r. 56 : 44[d]
 **3m**, 89% (84%)	 **3n**, 95% (88%)	 **3o**, 99% (97%)
 **3p**, 92% (88%)	 **3q**, 0%	 **3r**, 65% (60%)

[a] Reaction conditions: EDA (0.6 mmol) was added to a water solution of the sulfide (0.3 mmol), hemin (2.5 mol%), Triton X-100 (2.5 mol%) and β-CD (20 mol%). The reaction was carried out at 40 °C for 48 h in a thermo shaker. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture. Values in parentheses are isolated yields. [c] Yield of the gram-scale reaction. [d] d.r. = diastereomeric ratio, determined by ^1H NMR.

ducts (**3a–b** and **3d–f**), except for the *para* ethyl-substituted and *para* nitro-substituted materials, giving moderate results (**3c** and **3g**). When the R^1 group was 2-pyridyl or 2-naphthyl, the corresponding rearranged products were obtained in high yields (**3h** and **3i**). Notably, alkyl allyl sulfides also exhibited excellent reactivity toward the ylide-involved [2,3]-sigmatropic rearrangement reaction (**3n–p**). Moreover, the effect of the substitutions on the allyl unit was also studied. Introduction of methyl groups into the allyl unit had only marginal effect on the reaction, resulting in 86% and 89% yields respectively for **3j** and **3k**, which is distinct from the silver-catalyzed protocol.[11] Due to the steric effect, cinnamylic phenyl sulfide afforded a 65% diastereomeric mixture of **3l** in a 56 : 44 ratio. In addition, a gram-scale synthesis of **3a** was performed under the optimized reaction conditions giving a 71% isolated yield (1.678 g). Unfortunately, when we examined water-soluble *S*-allyl-L-cysteine, neither the desired rearranged product (**3q**) nor the N–H/O–H insertion product was detected. We rationalized that the aqueous hemin catalytic system might have some "on water" effect,[17] or the soluble substrate can't enter the hydrophobic cavity of β-CD. Further investigation showed that the [2,3]-sigmatropic rearrangement reaction also worked well for phenyl propargyl sulfide affording the corresponding allene product **3r** in 65% yield.

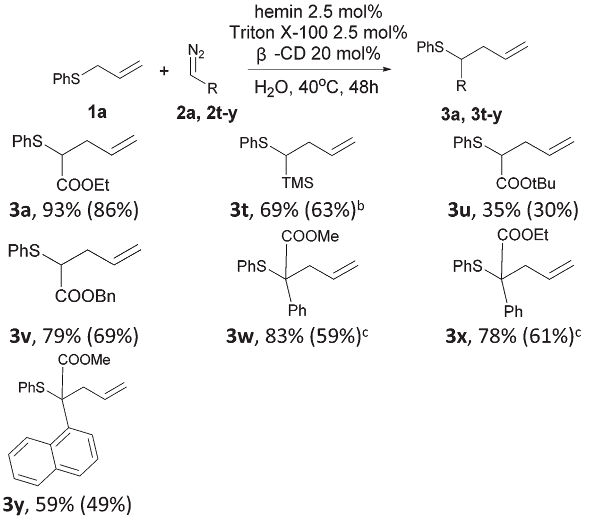
When the diallyl sulfide was employed as a substrate, the outcome of the reaction mainly relies on the amount of EDA used (Scheme 1). The standard reaction conditions preferred the single rearranged product (**3s-1**). In contrast, the major product was shifted to the double-rearranged product (**3s-2**) when 4 equivalents or 8 equivalents of EDA were added. Notably, another unexpected minor product (**3s-3**) was also isolated, which was formed through subsequent C–H insertion by EDA at the tertiary carbon of a single rearranged product. However, our attempts to further improve the efficiency of the cascade process failed.



1s : 2a	Yield[a] (%)		
	3s-1	3s-2	3s-3
1 : 1	84	14	1
1 : 2	77	20	2
1 : 4	13	79	8
1 : 8	9	83	8

Scheme 1 Results from the reaction of EDA with diallyl sulfide. Reaction conditions: EDA was added to a water solution of the sulfide (0.3 mmol), hemin (2.5 mol%), Triton X-100 (2.5 mol%) and β-CD (20 mol%). The reaction was carried out at 40 °C for 48 h in a thermo shaker. [a] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture.

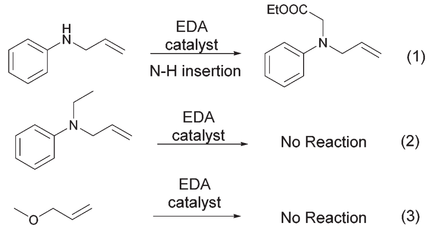
Table 3 Hemin-catalyzed Doyle–Kirmse reaction of different diazo compounds[a]



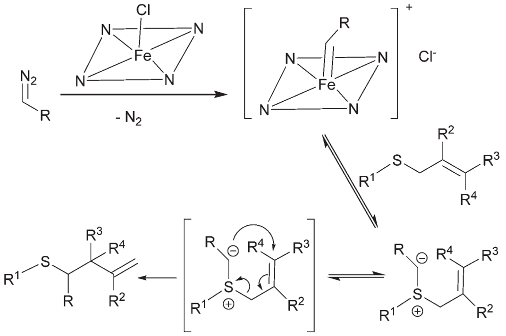
[a] Reaction conditions: the diazo compound (0.6 mmol) was added to a water solution of **1a** (0.3 mmol), hemin (2.5 mol%), Triton X-100 (2.5 mol%) and β-CD (20 mol%). The reaction was carried out at 40 °C for 48 h in a thermo shaker. Yield was determined by ^{1}H NMR analysis of the crude reaction mixture. Values in parentheses are isolated yields. [b] The molar ratio **1a**/**2t** was 1/5. [c] The reaction was stirred at 80 °C for 20 h.

As an extension of this catalytic system, the diazo reagent scope of the Doyle–Kirmse reactions was investigated under the optimized conditions (Table 3). When (trimethylsilyl)diazomethane (TMSD) was subjected to the rearrangement system, **3t** was obtained in 69% yield in the presence of 5 equivalents of TMSD. Consistent with Plietker's work,[9a] TMSD showed lower reactivity than EDA, albeit with the opposite conclusion to that proposed by Van Vranken's work on the $dppeFeCl_2$ system.[9c,18] *tert*-Butyl diazoacetate also turned out to be less reactive than EDA, furnishing the product in a relatively modest yield (**3u**, 35%), presumably due to the steric issue. However, fairly good yield (**3v**, 79%) was observed when benzyl diazoacetate was used. Moreover, various aryl diazoacetates were also investigated, which turned out to be much more sluggish than alkyl diazoacetates. Methyl phenyldiazoacetate (MPDA) and ethyl phenyldiazoacetate (EPDA), as acceptor–donor diazo species, led to the corresponding desired product in good yield (83%, 78% for **3w** and **3x** respectively) at a higher reaction temperature, 80 °C, in which the reaction time was also elongated to 20 hours. In addition, the rearrangement product of methyl naphthyldiazoacetate was generated in moderate yield (**3y**, 59%) under standard reaction conditions.

To further explore the potential of this catalytic system, allyl phenyl amines and allyl ether were tested under the optimal reaction conditions (Scheme 2). However, none of the products



Scheme 2 Results from the reactions of EDA with allyl amines and allyl ether.



Scheme 3 Proposed mechanism.

expected from ammonium or oxonium ylide rearrangement were observed. The N–H insertion product was mainly isolated when the allylic secondary amine was employed (eqn (1)), in line with previous research.[6b] Essentially no reaction occurred when an allylic tertiary amine or an allyl methyl ether was subjected to the standard conditions (eqn (2) and (3)).

It is well-established that the reaction of iron porphyrin with diazo compounds would furnish iron-carbenoid species, some of which have been characterized by X-ray crystallography.[19] More importantly, the process of the Doyle–Kirmse reaction is strongly supposed to involve free sulfonium ylide intermediates rather than the metal-associated ylide.[4b,5a,8,20] Consequently, a proposed mechanism pathway is drawn in Scheme 3 on the basis of previous reports. Firstly, the diazo compound was transferred by hemin to form a carbenoid intermediate. Then the carbenoid species reacts *in situ* with allylic sulfides followed by dissociation of the catalytically active hemin to generate a free sulfonium ylide, which could then spontaneously undergo a five-membered, six-electron transition state with an envelope conformation to deliver the desired [2,3]-sigmatropic rearrangement product.

In summary, mild and efficient Doyle–Kirmse reactions between allyl sulfides and diazo compounds in water were developed with the synergistic introduction of hemin, Triton X-100 and β-CD. This catalytic system displays a broad functional-group tolerance and possesses a relatively lower *E*-factor. The mild reaction conditions and the use of eco-friendly water as the solvent will greatly facilitate future sustainable chemical catalysis and biocatalysis.

Acknowledgements

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Notes and references

1 For selected reviews, see: (*a*) M. P. Doyle, *Acc. Chem. Res.*, 1986, **19**, 348; (*b*) M. P. Doyle, *Chem. Rev.*, 1986, **86**, 919; (*c*) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981; (*d*) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911; (*e*) S.-F. Zhu and Q.-L. Zhou, *Natl. Sci. Rev.*, 2014, **1**, 580; (*f*) Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577; (*g*) G. Maas, *Organic Synthesis, Reactions and Mechanisms*, Springer, 1987.

2 (*a*) W. Kirmse and M. Kapps, *Chem. Ber.*, 1968, **101**, 994; (*b*) M. P. Doyle, J. H. Griffin, M. S. Chinn and D. Van Leusen, *J. Org. Chem.*, 1984, **49**, 1917.

3 For selected reviews, see: (*a*) Y. Zhang and J. Wang, *Coord. Chem. Rev.*, 2010, **254**, 941–953; (*b*) T. H. West, S. S. M. Spoehrle, K. Kasten, J. E. Taylor and A. D. Smith, *ACS Catal.*, 2015, **5**, 7446–7479; (*c*) Z. Sheng, Z. Zhang, C. Chu, Y. Zhang and J. Wang, *Tetrahedron*, 2016, DOI: 10.1016/j.tet.2016.11.045.

4 (*a*) X. Zhang, Z. Qu, Z. Ma, W. Shi, X. Jin and J. Wang, *J. Org. Chem.*, 2002, **67**, 5621; (*b*) M. Ma, L. Peng, C. Li, X. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2005, **127**, 15016.

5 (*a*) S. Kitagaki, Y. Yanamoto, H. Okubo, M. Nakajima and S. Hashimoto, *Heterocycles*, 2001, **54**, 623; (*b*) M. Liao and J. Wang, *Green Chem.*, 2007, **9**, 184; (*c*) Z. Li, B. T. Parr and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 10942; (*d*) Z. Li and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 396.

6 (*a*) C. Poriel, Y. Ferrand, P. le Maux, C. Paul, J. Rault-Berthelot and G. Simonneaux, *Chem. Commun.*, 2003, **18**, 2308; (*b*) G. Simonneaux, E. Galardon, C. Paul-Roth, M. Gulea and S. Masson, *J. Organomet. Chem.*, 2001, **617**, 360.

7 K. L. Greenman, D. S. Carter and D. L. Vranken, *Tetrahedron*, 2001, **57**, 5219.

8 T. Fukuda, R. Irie and T. Katsuki, *Tetrahedron*, 1999, **55**, 649.

9 (*a*) M. S. Holzwarth, I. Alt and B. Plietker, *Angew. Chem., Int. Ed.*, 2012, **51**, 5351; (*b*) I. Aviv and Z. Gross, *Chem. – Eur. J.*, 2008, **14**, 3995; (*c*) D. S. Carter and D. L. Van Vranken, *Org. Lett.*, 2000, **2**, 1303; (*d*) J. B. Perales, N. F. Makino and D. L. Van Vranken, *J. Org. Chem.*, 2002, **67**, 6711.

10 P. W. Davies and S. J. C. Albrecht, *Chem. Commun.*, 2008, 238.

11 P. W. Davies, S. J. C. Albrecht and G. Assanelli, *Org. Biomol. Chem.*, 2009, **7**, 1276.

12 (*a*) P. S. Coelho, E. M. Brustad, A. Kannan and F. H. Arnold, *Science*, 2013, **339**, 307; (*b*) C. K. Prier, T. K. Hyster,

C. C. Farwell, A. Huang and F. H. Arnold, *Angew. Chem., Int. Ed.*, 2016, **128**, 4789; (*c*) H. Renata, R. D. Lewis, M. J. Sweredoski, A. Moradian, S. Hess, Z. J. Wang and F. H. Arnold, *J. Am. Chem. Soc.*, 2016, **138**, 12527; (*d*) Z. J. Wang, N. E. Peck, H. Renata and F. H. Arnold, *Chem. Sci.*, 2014, **5**, 598.

13 (*a*) M. Bordeaux, V. Tyagi and R. Fasan, *Angew. Chem., Int. Ed.*, 2015, **127**, 1764; (*b*) G. Sreenilayam and R. Fasan, *Chem. Commun.*, 2015, **51**, 1532; (*c*) V. Tyagi and R. Fasan, *Angew. Chem., Int. Ed.*, 2016, **128**, 2558; (*d*) V. Tyagi, R. B. Bonn and R. Fasan, *Chem. Sci.*, 2015, **6**, 2488; (*e*) V. Tyagi, G. Screenilayam, P. Bajaj, A. Tinoco and R. Fasan, *Angew. Chem., Int. Ed.*, 2016, **55**, 13562.

14 X. Xu, C. Li, Z. Tao and Y. Pan, *Adv. Synth. Catal.*, 2015, **357**, 3341.

15 W. Liu and R. Guo, *Photochem. Photobiol.*, 2010, **86**, 835.

16 J. R. Wolf, C. G. Hamaker, J.-P. Djukic, T. Kodadek and L. K. Woo, *J. Am. Chem. Soc.*, 1995, **117**, 9194.

17 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.

18 R. Prabharasuth and D. L. Van Vranken, *J. Org. Chem.*, 2001, **66**, 5256.

19 Y. Li, J.-S. Huang, Z.-Y. Zhou, C.-M. Che and X.-Z. You, *J. Am. Chem. Soc.*, 2002, **124**, 13185.

20 M. Reggelin, *Sulfur-Mediated Rearrangements II*, Springer, 2007.