

## COMMUNICATION

Pd-Catalyzed Allylic C-H Activation to Seven-Membered *N,O*-HeterocyclesReceived 00th January 20xx,  
Accepted 00th January 20xx

Álvaro Velasco-Rubio, Jesús A. Varela and Carlos Saá\*

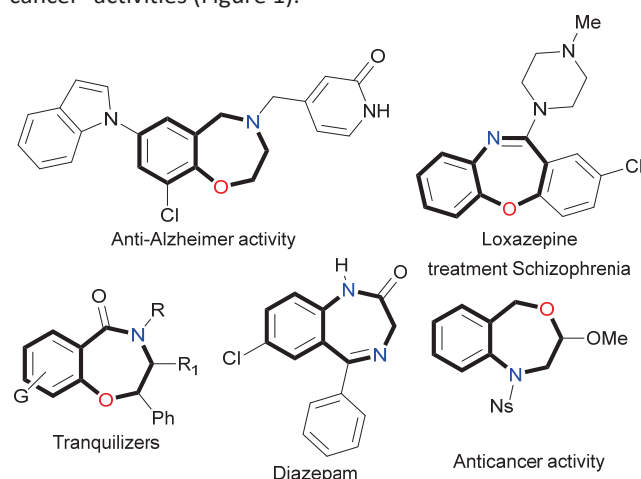
DOI: 10.1039/x0xx00000x



This article may be used for non-commercial purposes in accordance with Royal Society of Chemistry Terms and Conditions for self-archiving.

**Pd-catalyzed allylic C-H activation of simple olefins allows an easy entry to seven-membered *N,O*-heterocycles such as 1,4-benzoxazepines (1,4-BZOs), 1,4-benzodiazepinones (1,4-BZDs) and 1,4-oxazepanes in good to excellent yields. Straightforward derivatizations of the olefinated 1,4-BZO shows the synthetic utility of this methodology.**

Seven-membered heterocycles bearing two heteroatoms (*N, O*) compose a well-known family of bioactive drugs and pharmaceuticals.<sup>1</sup> In particular, the benzofused members 1,4-benzoxazepines (1,4-BZOs) and 1,4-benzodiazepines (1,4-BZDs) are well recognized useful drugs that possess anti-Alzheimer,<sup>2</sup> psychotropic,<sup>3</sup> anti-inflammatory,<sup>4</sup> schizophrenia<sup>5</sup> or anti-cancer<sup>6</sup> activities (Figure 1).



**Figure 1.** Bioactive 1,4-benzodiazepines (1,4-BZDs) and 1,4-benzoxazepines (1,4-BZOs).

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain. E-mail: [carlos.saa@usc.es](mailto:carlos.saa@usc.es)

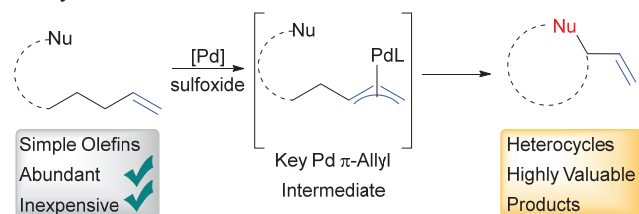
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Their great relevance as widely used drugs have inspired the development of many synthetic strategies throughout the last decades.<sup>1b, d</sup> Classical Friedel-Crafts cyclization,<sup>7</sup> click chemistry,<sup>8</sup> or lactonization<sup>9</sup> have been employed as key steps in the synthesis of these seven-membered benzofused heterocyclic rings. However, although all of them are considered very useful, they lack in sustainability owing to the generation of stoichiometric amounts of hazardous waste. In this regard, trapping of electrophilic metal- $\pi$ -allylic intermediates from functionalized allylic substrates (Tsuji-Trost type reaction)<sup>10</sup> has been employed as an efficient tool to progress to a more sustainable approaches. In fact, this methodology has been successfully applied to the synthesis of benzofused seven-membered heterocycles. In 2012, Kitamura described the formation of azepane-type *N*-heterocycles in a Ru-catalyzed asymmetric dehydrative functionalization of terminal allylic alcohols.<sup>11</sup> In 2018, Shi/Mei's group reported a new access to 1,4-BZOs through an Iridium catalyzed (4+3) cyclization of vinyl aziridines with *p*-quinone methide derivatives and its asymmetric reaction using a Pd/Trost ligand system.<sup>12</sup> More recently, our group described the Rh-catalyzed asymmetric hydrofunctionalization of internal alkynes and allenes to 1,4-BZDs and 1,4-BZOs.<sup>13</sup> On the other hand, Carreira also applied the powerful Ir-catalyzed asymmetric functionalization of internal allylic alcohols to the syntheses of non-benzofused oxazepane and diazepanes cores.<sup>14</sup>

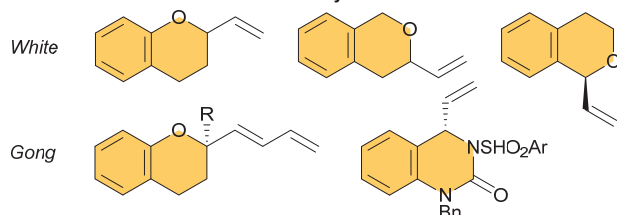
The main drawback of all these synthetic strategies is probably the necessity of using prefunctionalized  $\pi$  bonds (external and internal allylic alcohols, allenes, alkynes) to create the key electrophilic intermediates to be trapped with the corresponding heteronucleophile. In an attempt to move forward to a more sustainable approach, we were inspired by White's pioneer work on Pd(sulfoxide)-catalyzed acetoxylation of simple alkenes through electrophilic Pd- $\pi$ -allyl intermediates (Scheme 1, eq 1).<sup>15</sup> An extensive study to create new C–C, C–O and C–N bonds through intermolecular reactions to afford branched<sup>16</sup>/linear<sup>17</sup> products was then developed. Furthermore, benzofused six-membered *N*- and *O*-heterocycles has been successfully synthesized by White<sup>18</sup> and Gong<sup>19</sup>

(Scheme 1, eq 2).<sup>20</sup> Herein, we now expand the boundary of this methodology with the report of a novel Pd-catalyzed allylic C-H activation of simple alkenes to seven-membered *N,O*-heterocycles (Scheme 1, eq 3).

### 1. Allylic C-H Functionalization



### 2. Benzofused Six-Membered Heterocycles



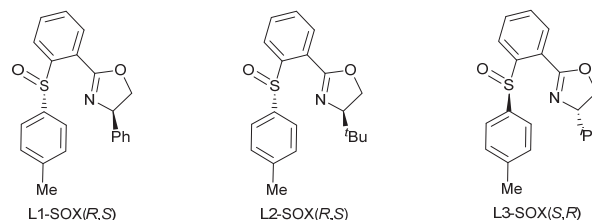
**Scheme 1.** Pd-catalyzed Allylic C-H Functionalization to *N,O*-heterocycles

We initiated our investigation by examining the conditions for the cyclization of benzylic alcohol **1a** (Table 1). Firstly, the combination of White's catalyst and Cr salts as co-catalyst<sup>18a</sup> gave a low 20% yield of the desired product **2a** (entry 1) or a moderate 40% yield when using *rac*-BNP as Brønsted acid (entry 2). Application of slightly modified White's conditions,<sup>18b</sup> 10 mol% of Pd(OAc)<sub>2</sub>, 11 mol% of *rac*-BNP acid, 11 mol% of *rac*-L1-SOX, 1.5 equiv 2,5-DtBBQ in toluene 0.15 M at 60 °C, gave a 45% yield of **2a** after 24 h of reaction (entry 3),<sup>18b</sup> that could be increased to 90% when the reaction was carried out for 2 days (entry 4). The reaction resulted very sensitive to the Brønsted acid used since typical PPTS and chloroacetic acid failed in the cyclization (entries 5 and 6). Changes in solvent polarity by using ethereal solvents gave lower yields (entries 7 and 8), and even the reaction under non-polar chlorinated DCE failed to give the desired product (entry 9). Finally, some control experiments were performed that showed temperature as an important factor since the reaction did not start after 10 days at rt (entry 10). In the absence of palladium catalyst or *rac*-L1-SOX ligand the reaction met with failure (entries 11 and 12) whereas with chiral (*S*)-BNP acid afforded **2a** in a 92% yield as a racemic mixture (entry 13). Interestingly, when chiral L-SOX ligands were employed promising results were obtained. Thus, L1-SOX(*R,S*) gave a 90% yield of **2a** in a 70:30 er (entry 14). Unfortunately, modification of the size of the substituent in L2-SOX(*R,S*) or L3-SOX(*S,R*) did not improve the enantiomeric ratio (entries 15 and 16).

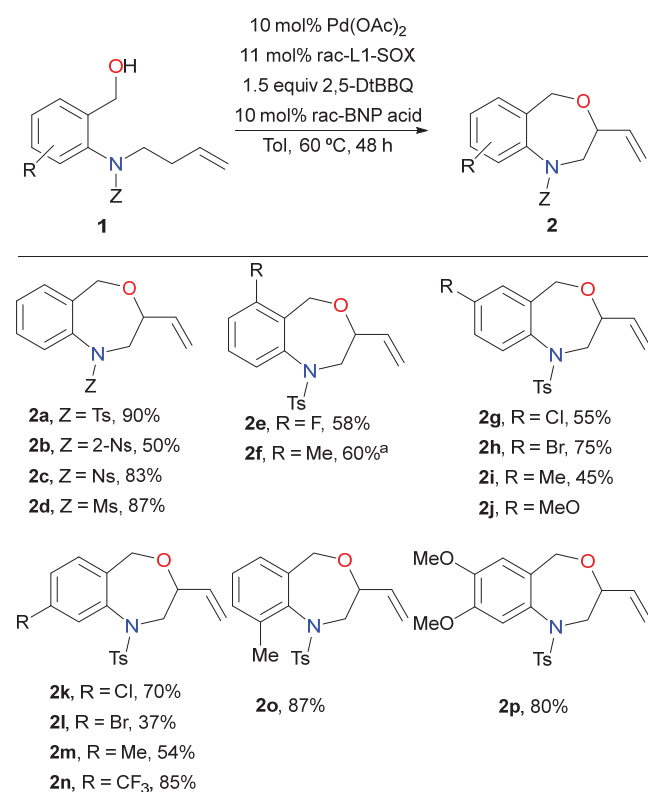
**Table 1.** Optimization of Reaction Conditions<sup>a</sup>

Entry	Catalyst	Additive	Solvent	<b>2a</b> (%) <sup>b</sup>
1 <sup>c,d</sup>	White's cat	Cr(Salen)Cl	DCE	20
2 <sup>c</sup>	White's cat	<i>rac</i> -BNP acid	Tol	40
3 <sup>e</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	45
4	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	90
5	Pd(OAc) <sub>2</sub>	PPTS	Tol	traces
6	Pd(OAc) <sub>2</sub>	Chloroacetic acid	Tol	traces
7	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	1,4-dioxane	60
8	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	THF	45
9	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	DCE	traces
10 <sup>f</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	traces
11	-	<i>rac</i> -BNP acid	Tol	-
12 <sup>c</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	-
13	Pd(OAc) <sub>2</sub>	( <i>S</i> )-BNP acid	Tol	92
14 <sup>g</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	90 (70:30 er)
15 <sup>h</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	80 (56:44 er)
16 <sup>i</sup>	Pd(OAc) <sub>2</sub>	<i>rac</i> -BNP acid	Tol	97 (34:66 er)

a) **1a** (0.1 mmol), 0.15 M. b) Isolated yields c) Without *rac*-L1-SOX. d) BQ instead of 2,5-DtBBQ. e) 1 day. f) rt, 10 days. g) L1-SOX(*R,S*). h) L2-SOX(*R,S*). i) L3-SOX(*S,R*). Tol= toluene, 2,5-DtBBQ= 2,5-di-*tert*-butyl-1,4-benzoquinone, White's cat = 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate, *rac*-BNP acid = binaphthyl hydrogen phosphate.



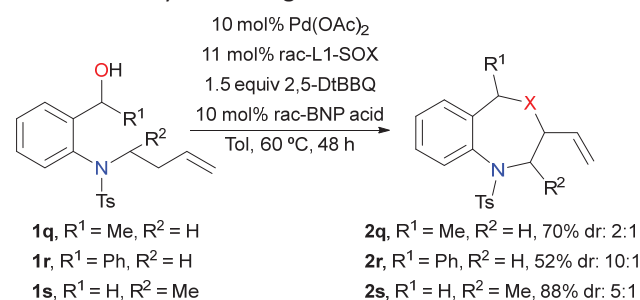
Having established the optimized conditions, we next turned to explore the scope of the cyclization of *N*-(buten-3-1-yl)-*N*-(2-hydroxymethyl)phenyl sulfonamides **1** (Scheme 2). The reaction tolerates different sulfonamides **1a-1d** (Ts, 2-Ns, 4-Ns and Ms) as *N*-protecting groups giving the corresponding 1,4-BZOs **2a-2d** in good to excellent yields. In addition, aryl substituted with EWG (CF<sub>3</sub>) and EDG (OMe), halides (Cl, Br, F) and alkyl (Me) groups are well tolerated in any position giving the corresponding substituted 1,4-BZOs **2e-2p** in moderate to excellent yields.<sup>21</sup>



<sup>a</sup> 15 mol% Pd(OAc)<sub>2</sub>, 16 mol% *rac*-BNP acid, 16 mol% *rac*-L1-SOX.

**Scheme 2.** Pd-catalyzed Allylic C-H Activation of *N*-protected Alkenols **1a-o** to 1,4-Benzoxazepines **2a-o**

Diastereoselectivity of the reaction was next explored (Scheme 3). Firstly, the secondary benzylic alcohol **1q** bearing a small Me substituent gave rise to the 1,4-BZO **2q** in a 70% yield with a low 2:1 dr. Pleasingly, on changing the nature of the substituent to a Ph group (**1r**) the diastereoselectivity of the reaction increased to a 10:1 dr but with a moderate 52% yield of 1,4-BZO **2r**. When the Me substituent is located in the alkyl chain  $\alpha$  to the N atom (**1s**) the reaction smoothly proceeded to give **2s** with an excellent 88% yield and a good 5:1 dr.



**Scheme 3.** Diastereoselectivity of the Cyclization

We then pursued the evaluation of the Thorpe-Ingold effect in the course of the cyclization (Table 2).<sup>22</sup> The reaction resulted unaffected on changing the nature of the carbon tether (C<sub>sp3</sub> vs C<sub>sp2</sub>) between functionalities. Thus, the cyclization of the neopentyl alcohol derivative **1t** under standard conditions gave the expected dimethyl substituted oxazepane **2t** in 65% yield. Moreover, the parent unsubstituted primary alcohol **1u**, with no added beneficial Thorpe-Ingold effect, could be cyclized to the

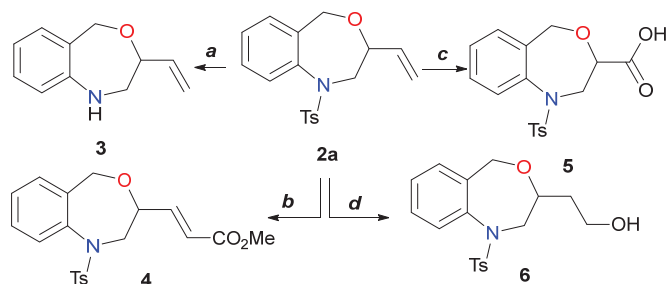
oxazepane **2u** in a very good 72% yield, although a bit more loading of Pd catalyst was needed (entry 1). Regarding the nature of the nucleophile, phenol **1v** can also be cyclized under standard conditions to give the 1,4-BZO **2v** in a reasonable 60% yield (entry 2). Satisfactorily, even the less nucleophilic benzoic acid **1w** can also be transformed into the expected 1,4-benzoxazepanone **2w** in a very good 75% yield (entry 3). On changing the nature of the heteronucleophile (**1x**), the cyclization also smoothly occurred to give the desired 1,4-benzodiazepinone **2x** in 55% yield (entry 4).

**Table 2.** Non-benzofused Oxazepanes and Nucleophile Range

Entry	Olefin <b>1</b>	Product <b>2</b>
1	 <b>1t</b> , R = Me <b>1u</b> , R = H	 <b>2t</b> , R = Me, 65% <b>2u</b> , R = H, 72% <sup>a</sup>
2		 <b>2v</b> , 60%
3		 <b>2w</b> , 75%
4		 <b>2x</b> , 55%

<sup>a</sup> 15 mol% Pd(OAc)<sub>2</sub>, 16 mol% *rac*-BNP acid, 16 mol% *rac*-L1-SOX.

Derivatizations of 1,4-BZO **2a** were then analyzed (Scheme 4). The protecting tosyl group can be removed under mild conditions (Na, naphthalene) to afford the aniline **3** in 70% yield. The alkene of **2a** participate in a Hoveyda-Grubbs 2<sup>nd</sup>G-catalyzed cross-metathesis with methyl acrylate to provide the ester **4** in an excellent 90% yield. Interestingly, a Ru-catalyzed oxidative cleavage of the alkene provides the  $\alpha$ -alkoxy carboxylic acid **5** in an excellent 87% yield. Finally, hydroboration of the alkene followed by oxidation provides the primary alcohol **6** in 72% yield.



Conditions: (a) Na (6 equiv), naphthalene (10 mol%), THF, rt, 16 h, 70% yield. (b) Methyl acrylate (10 equiv), Hoveyda-Grubbs 2<sup>nd</sup> G. catalyst (10 mol%), toluene, 55 °C, 90% yield. (c) RuCl<sub>3</sub> (2 mol%), NaIO<sub>4</sub> (6 equiv), MeCN/H<sub>2</sub>O/AcOEt, rt, 2 h, 85% yield. (d) (i) 9-BBN (2 equiv), THF, overnight, 60 °C. (ii) NaBO<sub>3</sub>·4H<sub>2</sub>O (7 equiv), THF/H<sub>2</sub>O, overnight, rt, 72% yield.

**Scheme 4.** Derivatizations of 1,4-BZO 2a

In summary, we have developed a new Pd-catalyzed allylic C-H activation of simple alkenes to bioactive benzofused seven-membered *N,O*-heterocycles, such as 1,4-benzoxazepines 1,4-BZO, non-benzofused 1,4-oxazepanes and other 1,4-BZO and 1,4-benzodiazepinones derivatives. The alkene functionality of 1,4-BZO 2a shows a rich synthetic versatility that highlights the potential utility of our approach.

We acknowledge financial support from MINECO (project CTQ2017-87939R and ORFEO-CINQA network RED2018-102387-T), the Xunta de Galicia (project ED431C 2018/04 and Centro singular de investigación de Galicia accreditation 2019-2022, ED431G 2019/03) and the European Union (European Regional Development Fund – ERDF). A.V.-R. thanks Xunta de Galicia for a predoctoral fellowship (ED481A-2018/34, 2018-2021).

## Conflicts of interest

There are no conflicts to declare

## Notes and references

- (a) A. Levai, *Heterocycles*, 2008, **75**, 2155-2185; (b) H. Kwicien, M. Smist and A. Wrzesniewska, *Curr. Org. Synth.*, 2012, **9**, 828-850; (c) Á. Velasco-Rubio, J. A. Varela and C. Saá, *Adv. Synth. Catal.*, 2020, **362**, 4861-4875; (d) A. M. M. M. Faisca Phillips and A. J. L. Pombeiro, in *Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, ed. A. M. M. M. Faisca Phillips, John Wiley & Sons Ltd., 2021, ch. 15, pp. 437-500.
- B. M. Fox, H. P. Beck, P. M. Roveto, F. Kayser, Q. Cheng, H. Dou, T. Williamson, J. Treanor, H. Liu, L. Jin, G. Xu, J. Ma, S. Wang and S. H. Olson, *J. Med. Chem.*, 2015, **58**, 5256-5273.
- S. J. A. Grove, M. Zhang and M. Shahid, WO2002100865A1, 2002.
- L. R. Swett, R. G. Stein and E. T. Kimura, *J. Med. Chem.*, 1972, **15**, 42-45.
- O. Axelsson, D. Peters, J. Scheel-Kruger and N. E. Ostergaard, WO9807710A1, 1998.
- M. Diaz-Gavilan, F. Rodriguez-Serrano, J. A. Gomez-Vidal, J. A. Marchal, A. Arana, M. A. Gallo, A. Espinosa and J. M. Campos, *Tetrahedron*, 2004, **60**, 11547-11557.
- (a) C. Fattorusso, S. Gemma, S. Butini, P. Huleatt, B. Catalanotti, M. Persico, M. De Angelis, I. Fiorini, V. Nacci, A. Ramunno, M. Rodriguez, G. Greco, E. Novellino, A. Bergamini, S. Marini, M. Coletta, G. Maga, S. Spadari and G. Campiani, *J. Med. Chem.*, 2005, **48**, 7153-7165; (b) M. Brindisi, S. Gemma, G. Alfano, G. Kshirsagar, E. Novellino, G. Campiani and S. Butini, *Tetrahedron Lett.*, 2013, **54**, 5387-5390.
- T. M. A. Barlow, D. Tourwe and S. Ballet, *Eur. J. Org. Chem.*, 2017, **2017**, 4678-4694.
- (a) L. Liu, S. Xu and H. Zhou, *Tetrahedron*, 2013, **69**, 8386-8391; (b) Y.-F. Ao, D.-H. Leng, D.-X. Wang, L. Zhao and M.-X. Wang, *Tetrahedron*, 2014, **70**, 4309-4316; (c) E. Ruysbergh, K. Van Hecke, C. V. Stevens, N. De Kimpe and S. Mangelinckx, *J. Org. Chem.*, 2017, **82**, 6210-6222.
- (a) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395-422; (b) B. M. Trost, T. Zhang and J. D. Sieber, *Chem. Sci.*, 2010, **1**, 427-440.
- T. Seki, S. Tanaka and M. Kitamura, *Org. Lett.*, 2012, **14**, 608-611.
- F. Jiang, S.-R. Yuan, L.-W. Jin, G.-J. Mei and F. Shi, *ACS Catal.*, 2018, **8**, 10234-10240.
- Á. Velasco-Rubio, R. Bernárdez, J. A. Varela and C. Saá, *J. Org. Chem.*, 2021, **86**, 10889-10902.
- M. A. Schafroth, S. M. Rummelt, D. Sarlah and E. M. Carreira, *Org. Lett.*, 2017, **19**, 3235-3238.
- M. S. Chen and M. C. White, *J. Am. Chem. Soc.*, 2004, **126**, 1346-1347.
- (a) M. S. Chen, N. Prabakaran, N. A. Labenz and M. C. White, *J. Am. Chem. Soc.*, 2005, **127**, 6970-6971; (b) D. J. Covell and M. C. White, *Angew. Chem. Int. Ed.*, 2008, **47**, 6448-6451.
- (a) S. A. Reed and M. C. White, *J. Am. Chem. Soc.*, 2008, **130**, 3316-3318; (b) A. J. Young and M. C. White, *J. Am. Chem. Soc.*, 2008, **130**, 14090-14091; (c) J. M. Howell, W. Liu, A. J. Young and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 5750-5754; (d) C. C. Pattillo, I. I. Strambeanu, P. Calleja, N. A. Vermeulen, T. Mizuno and M. C. White, *J. Am. Chem. Soc.*, 2016, **138**, 1265-1272; (e) W. Liu, S. Z. Ali, S. E. Ammann and M. C. White, *J. Am. Chem. Soc.*, 2018, **140**, 10658-10662; (f) R. Ma and M. C. White, *J. Am. Chem. Soc.*, 2018, **140**, 3202-3205.
- (a) S. E. Ammann, G. T. Rice and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 10834-10837; (b) S. E. Ammann, W. Liu and M. C. White, *Angew. Chem. Int. Ed.*, 2016, **55**, 9571-9575.
- (a) P.-S. Wang, P. Liu, Y.-J. Zhai, H.-C. Lin, Z.-Y. Han and L.-Z. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 12732-12735; (b) P.-S. Wang, M.-L. Shen, T.-C. Wang, H.-C. Lin and L.-Z. Gong, *Angew. Chem. Int. Ed.*, 2017, **56**, 16032-16036; (c) For a selected review of Gong chemistry, see: P.-S. Wang and L.-Z. Gong, *Acc. Chem. Res.*, 2020, **53**, 2841-2854.
- (a) For other cyclizations and conditions, see: K. J. Fraunhofer and M. C. White, *J. Am. Chem. Soc.*, 2007, **129**, 7274-7276; (b) H. Du, B. Zhao and Y. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 8590-8591; (c) L. Wu, S. Qiu and G. Liu, *Org. Lett.*, 2009, **11**, 2707-2710; (d) P. E. Gormisky and M. C. White, *J. Am. Chem. Soc.*, 2011, **133**, 12584-12589; (e) I. I. Strambeanu and M. C. White, *J. Am. Chem. Soc.*, 2013, **135**, 12032-12037; (f) T. J. Osberger and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 11176-11181; (g) R. Ma, J. Young, R. Promontorio, F. M. Dannheim, C. C. Pattillo and M. C. White, *J. Am. Chem. Soc.*, 2019, **141**, 9468-9473; (h) Y. Bunno, Y. Tsukimawashi, M. Kojima, T. Yoshino and S. Matsunaga, *ACS Catal.*, 2021, **11**, 2663-2668.
- CCDC 2108910 and 2108911 contain the supplementary crystallographic data for the compounds 2l and 2p, respectively. See ESI for details.
- M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735-1766.