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Oxidative Heck desymmetrisation of 2,2-disubstituted cyclopentene-1,3-diones†

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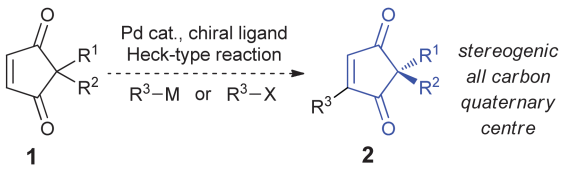
Oxidative Heck couplings have been successfully developed for 2,2-disubstituted cyclopentene-1,3-diones. The direct coupling onto the 2,2-disubstituted cyclopentene-1,3-dione core provides a novel expedient way of enantioselectively desymmetrising all-carbon quaternary centres.

The 2,2-disubstituted cyclopentene-1,3-dione core is found in several biologically active natural products, including madindolines A and B,[1] similin A[2] and ochroleucin A_1,[3] and metabolites such as preussidone[4] and involutone[5] (*e.g.* Fig. 1). As such, a direct, catalytic method for accessing such motifs would be of synthetic value, but no examples of such methods were available at the commencement of this project.[6,7] We therefore aimed to develop a Heck-type[8] desymmetrisation on easily accessible substrates **1**[9] using chiral enantiopure ligands[10] (Scheme 1),[11] as this is in principle one of the most direct ways of obtaining the stereogenic all-carbon quaternary centre found in **2**.[12]

During the preparation of this manuscript, an elegant base-mediated organocatalytic alkylation method was reported by Mukherjee and co-workers using nitroalkyls as the alkylating agent.[13] However, this alternative approach is necessarily limited to alkylations (R^3 = alkyl in **2**), which precludes it as a method towards non-alkyl substituted target products such as involutone, ochroleucin A_1 and preussidone (Fig. 1). Therefore, the development of a Heck-type desymmetrisation, capable of *arylating* enediones **1**, is still highly relevant for the access of other 2,2-disubstituted cyclopentene-1,3-dione targets.



Scheme 1 Heck-type desymmetrisation of 2,2-disubstituted cyclopentene-1,3-diones.

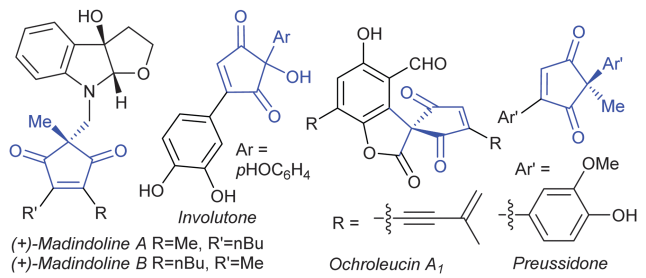


Fig. 1 Examples of natural products containing 2,2-disubstituted cyclopentene-1,3-dione cores.

Despite their obvious potential, Heck-type reactions have not previously been reported on cyclopentene-1,3-dione substrates such as **1**. This lack of literature precedence is most likely due to the fact that cyclic enones are notoriously reluctant to undergo Pd(0)-catalysed Mizoroki–Heck couplings and will often produce the conjugate addition products instead, as well as being stereochemically precluded from undergoing the final step in the traditional Pd(0) Heck cycle: the *syn* β-H elimination.[14] As substrates **1** are expected to be challenging substrates for the Heck-type reaction, our initial aim was to develop a racemic Heck-type protocol for **1**, followed by enantioselective desymmetrisations. Our successful efforts toward this goal are presented herein.

We decided to utilise Pd(II)-catalysed oxidative Heck[10d,15,16] methods as they have recently been shown to be more compatible with cyclic enones than Pd(0)-catalysed Heck couplings.[17] Nevertheless, examples of successful oxidative Heck couplings on cyclic enone derivatives are still fairly scarce[18] and do not include any examples of enediones. Therefore, a brief screen of conditions was carried out to evaluate the feasibility of such a reaction (Table 1). Firstly, our recently developed ligand- and base-free conditions for cyclohexenone derivatives[18a,j,k] failed

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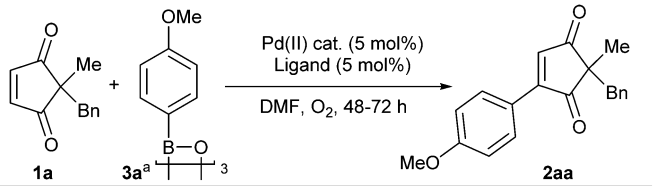
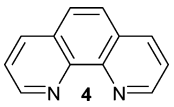
† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra and full characterisation of new compounds. See DOI: 10.1039/c5cc00407a

Table 1 Selected conditions



Entry	Ligand	Pd(II) cat.	Temp. (°C)	Result
1[b,c]	—	$Pd(OTf)_2$	70	No reaction
2[c]		$Pd(OAc)_2$	RT	Trace **2**, conjugate addition main product
3[e]	**4**	$Pd(OAc)_2$	70	77% yield[d]
4[e]	—	$Pd(OAc)_2$	70	<10% conv.

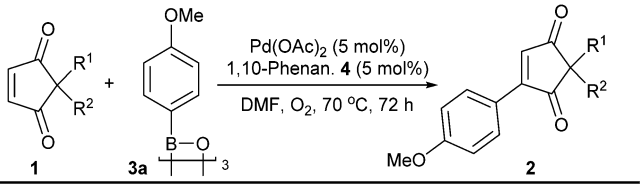
[a] Arylboronic acid (2 equiv.) is heated under vacuum to generate the arylboroxine prior to use. [b] DMSO used as solvent, $Pd(OTf)_2$ formed *in situ* using 5 mol% $Pd(OAc)_2$ and 9.9 mol% TfOH. [c] 48 h. [d] Isolated yields. [e] 72 h.

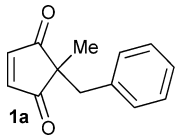
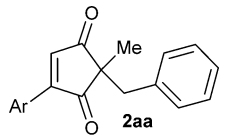
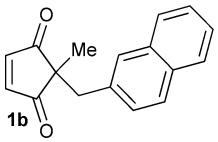
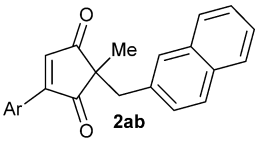
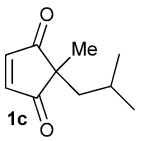
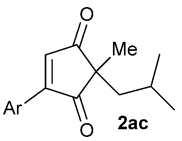
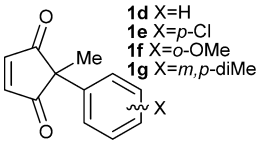
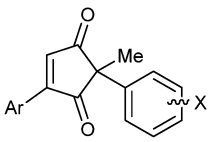
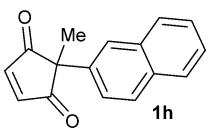
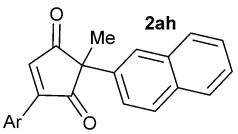
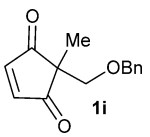
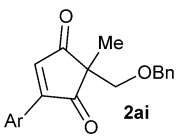
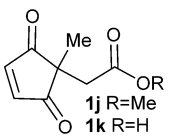
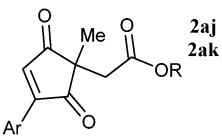
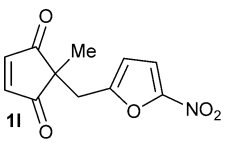
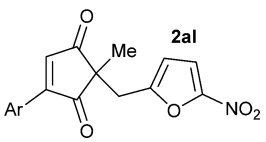
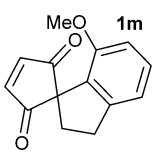
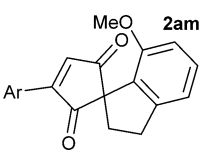
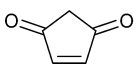
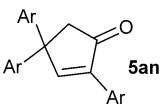
to promote oxidative Heck coupling of cyclopentene-1,3-dione **1a** and arylboroxine **3a** (entry 1, Table 1). We thus turned to conditions using N-ligands. While oxidative Heck reactions on simple cyclohexenones using molecular oxygen[19] as the oxidant have been reported to proceed at room temperature using 1,10-phenanthroline ligand **4**,[17] cyclopentene-1,3-dione **1a** produces only trace amounts of desired oxidative Heck product **2aa** at RT (entry 2) and requires higher temperatures (70 °C) for good conversion to **2aa** (entry 3). A control reaction without ligand also gives poor conversion (<10%, entry 4).

With the optimal conditions (entry 3, Table 1) in hand, a screen of cyclopentene-1,3-diones **1** was carried out (Table 2). Firstly, changing the benzyl group in **1a** to a bulkier naphthyl equivalent (**1b**) is not detrimental to the yield (77% *vs.* 76% respectively, entries 1 and 2). Replacing the benzyl in **1a** with an alkyl chain (**1c**), or with various aryls (**1d–1h**) are also tolerated (56–95%, entries 3–5). Next, substrates with more functionality were probed. The oxidative Heck reaction with **1i** and **1j** demonstrate that benzyl protected alcohols as well as esters are well tolerated (63% and 94%, entries 6 and 7). Pleasingly, even an unprotected carboxylic acid functionality is very well tolerated (83% **2ak**, entry 7) as is a heterocycle (70% **2al**, entry 8). These examples demonstrate that protecting groups are not always necessary for the oxidative Heck reaction. Spirocyclic **1m** also reacts well (82%, entry 9). The reaction does not, however, quite tolerate enolisable protons at the 2-position of the cyclopentene-1,3-dione (**1n**). Instead of the desired **2an**, the unexpected product **5an** is observed instead, with two additional aryls installed (entry 10).[20–22]

Next, the arylboroxine scope was investigated. It should be noted that heating the commercial arylboronic acids[23] under vacuum to dehydrate them to the corresponding arylboroxine prior to use provides much improved yields (*e.g.* 89% **2ga** Table 3 *vs.* 30% using arylboronic acid).[24] The reaction conditions used so far also had to be modified in order to obtain good yields across a wider spectrum of aryl coupling partners. Portion-wise

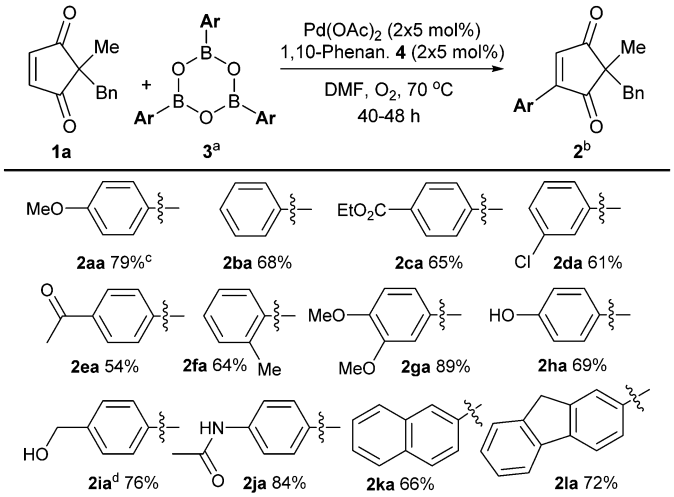
Table 2 Substrate scope: cyclopentene-1,3-diones



Entry[a]	Reactant (**1**)	Product (**2**)	Yield[b] (%)
1	 **1a**	 **2aa**	77
2	 **1b**	 **2ab**	76
3	 **1c**	 **2ac**	56
4	 **1d** X=H **1e** X=*p*-Cl **1f** X=*o*-OMe **1g** X=*m*,*p*-diMe	 **2ad** 79 **2ae** 95 **2af** 89 **2ag** 91	
5	 **1h**	 **2ah**	91
6	 **1i**	 **2ai**	63
7	 **1j** R=Me **1k** R=H	 **2aj** 94 **2ak** 83	
8	 **1l**	 **2al**	70
9	 **1m**	 **2am**	82
10[c]	 **1n**	 **5an**	19

[a] Arylboronic acid (2 equiv.) is heated under vacuum to generate the arylboroxine prior to use. Ar = *p*-MeO–C_6H_4–. [b] Isolated yields. [c] Desired product not observed.

Table 3 Substrate scope: arylboroxines



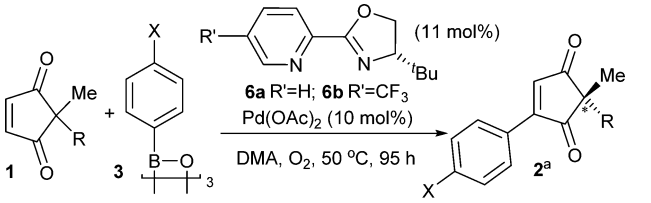
[a] Commercial arylboronic acid (2 equiv.) is heated under vacuum to generate the arylboroxine prior to use. [b] Isolated yields. [c] Conditions as in Table 2. [d] $Pd(OAc)_2$ (4 × 5 mol%), phenanthroline (4 × 6 mol%).

addition of the catalyst and ligand was found to be ideal for better conversions (see ESI†). Using these conditions, the arylboroxine substrate scope study shows that a wide variety of arylboroxines are suitable coupling partners (Table 3). Electron-withdrawing (**2ca–2ea**) as well as electron-donating substituents (**2aa**, **2fa–2ja**) are all tolerated well under the general reactions conditions as are *ortho* (**2fa**), *meta* (**2da**, **2ga**) and *para* substituents (**2aa**, **2ca**, **2ea**, **2ga–2ja**). Once again, tolerance to unprotected functional groups such as ketone (**2ea**), phenol (**2ha**), alcohol (**2ia**) and amide (**2ja**) is demonstrated. Furthermore, the ester, chloro and unprotected hydroxyl groups in **2ca**, **2da** and **2ha–2ia** respectively also provide a handle for further functionalisation. Polycyclic aromatic groups (**2ka**, **2la**), including 2-fluorene with a readily oxidisable position (**2la**) are also pleasingly tolerated.

Finally, initial attempts at enantioselective desymmetrisation using commercially available chiral PyOX ligands **6a**[25] or **6b**[26] produced very promising results (Table 4). In order to avoid issues with competitive ligation from DMF solvent,[10d] DMA was used as the solvent instead[27] and a lower temperature of 50 °C was also employed. To our delight, aryl substituted **1d–g** and naphthyl substituted **1h** substrates are desymmetrised in 74 : 26 to 94 : 6 er and excellent yields (85–100%) under these initial conditions, using both electron-donating (**3a**, **3h**) and -withdrawing (**3m**) substituted aryl boroxines, thereby showing the promise and validity of our proposed idea in Scheme 1. A current limitation is that the er is modest when R is not an aryl substituent (*e.g.* Bn in **1a**, giving 65 : 35 er **2aa**).

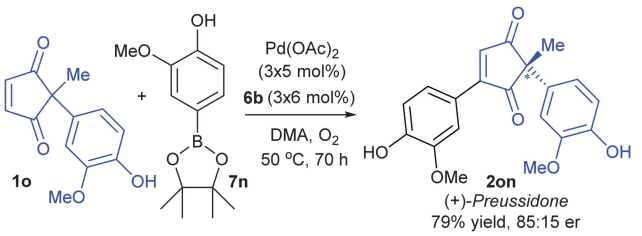
In order to ascertain the absolute stereochemistry of **2** by comparison with a known structure, a one-step synthesis of preussidone[4] was attempted from **1o**. To our delight, (+)-preussidone was successfully obtained in 79% yield and 85 : 15 er, without the need for OH protection (Scheme 2).[28] By comparison with literature values,[4] the *S* stereochemistry can be assigned for **2on** and thereby by analogy, also for the products in Table 4.

Table 4 Enantioselective oxidative Heck desymmetrisations of **1**



1h	R=2-Naphthyl	**3a** X=OMe	(*S*)-**2ah** 100%, 90:10 er[c]
1h	R=2-Naphthyl	**3h** X=OH	(*S*)-**2hh** 100%, 83:17 er[c]
1h	R=2-Naphthyl	**3b** X=Ph	(*S*)-**2bh** 97%, 74:26 er[b]
1h	R=2-Naphthyl	**3m** X=Cl	(*S*)-**2mh** 85%, 94:6 er[c]
1d	R=Ph	**3a** X=OMe	(*S*)-**2ad** 93%, 83:17 er[b]
1e	R=*p*-Cl-C_6H_4	**3a** X=OMe	(*S*)-**2ae** 90%, 80:20 er[c]
1f	R=*o*-OMe-C_6H_4	**3a** X=OMe	(*S*)-**2af** 85%, 78:22 er[b]
1g	R=*m*,*p*-(Me)$_2$-C_6H_3	**3a** X=OMe	(*S*)-**2ag** 100%, 80:20 er[b]
1a	R=Bn	**3a** X=OMe	(*S*)-**2aa** 81%, 65:35 er[b]

[a] Isolated yields. Er determined by chiral HPLC (Daicel IA or IB). [b] Using **6a**. [c] Using **6b**.



Scheme 2 Synthesis of (+)-preussidone.

In conclusion, oxidative Heck couplings have been developed for 2,2-disubstituted cyclopentene-1,3-diones **1** for the first time. These substrates were found to be more challenging oxidative Heck coupling partners compared to simple alkenes or cyclohexenones, as evidenced by the higher reaction temperatures (50–70 °C *vs.* RT) and stricter requirements for the dehydrated arylboroxine (*vs.* arylboronic acid). Nevertheless, the reaction is very functional group tolerant and reacts well even in the presence of unprotected alcohols, phenols, acids, amides and ketones. Our initial enantioselective results show that direct oxidative Heck reactions on 2,2-disubstituted cyclopentene-1,3-diones is potentially a powerful method to desymmetrise all-carbon quaternary centres on the cyclopentenedione core (up to 94 : 6 er and quant. yields), as exemplified by the synthesis of (+)-preussidone. Further investigations into this enantioselective method are currently underway and will be reported in due course.

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7 For review on desymmetrising cyclopentanes, see: M. S. Manna and S. Mukherjee, *Org. Biomol. Chem.*, 2015, **13**, 18.
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