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Intramolecular Hetero-Michael Addition of β-Hydroxyenones for the Preparation of Highly Substituted Tetrahydropyranones

Maud Reiter, Hazel Turner, and Véronique Gouverneur*[a]

Abstract: Structurally diverse β-hydroxyenones are shown to undergo nonoxidative 6-*endo*-trig ring closure to form highly substituted tetrahydropyranones. Amberlyst-15, $Al(ClO_4)_3{\cdot}9H_2O$ and $[Pd(MeCN)_4](BF_4)_2$ were found to be suitable catalysts for these intramolecular conjugate additions, preventing side reactions, such as dehydration or retroaldolisation. The use of $[Pd(MeCN)_4](BF_4)_2$ is particularly effective, as this palladium-mediated reaction is under kinetic control and generates tri- and tetrasubstituted tetrahydropyranones with high levels of diastereocontrol. In the presence of the Lewis acid $Al(ClO_4)_3{\cdot}9H_2O$, the reaction proceeded with a similar level of diastereocontrol; however, in contrast to $[Pd(MeCN)_4](BF_4)_2$, this catalyst can promote enolisation. The palladium-mediated reaction was also found to be compatible with an enantioenriched β-hydroxyenone substrate, giving no loss of enantiopurity upon ring closure. The most distinctive synthetic development to emerge from this new chemistry is the possibility to access tri- and tetrasubstituted 2,6-*anti*-tetrahydropyranones from *anti*-aldol precursors. These compounds are particularly difficult to access by using alternative methodologies. Two modes of activation were envisaged for the ring closure, involving metal coordination to either the C=C or C=O functional groups. Experimental results suggest that C=O coordination was the preferred mode of activation for reactions performed in the presence of $Al(ClO_4)_3{\cdot}9H_2O$ or $[Pd(MeCN)_4](BF_4)_2$.

Keywords: hydroxyenones · Michael addition · palladium(II) catalysts · synthetic methods · tetrahydropyranones

Introduction

Tetrahydropyranones (THPs) are valuable intermediates for the synthesis of a large variety of biologically active compounds and there has been a long-standing interest in their stereoselective construction.[1] Some of the most widely used methods for their preparation are based on manipulations of carbohydrates,[2] hetero-Diels–Alder (HDA) reactions,[3] oxy-Cope/Prins cascades[4] and simple Prins cyclisations,[5] variants of the Maitland–Japp reaction (Knoevenagel/Michael-addition cascades)[6] and Bu_2BOTf-mediated aldol-type cyclisations.[7] These methodologies rely on complementary retrosynthetic approaches. In the HDA reaction, the C–C and C–O bonds are constructed simultaneously, whereas for the Prins cyclisation, ring closure occurs with C–C bond formation only. The Maitland–Japp reaction relies on an intramolecular conjugate Michael addition, for which a C–O bond is formed upon cyclisation (Scheme 1).

Perhaps the most impressive of these approaches is the HDA reaction. This transformation allows for the diastereo- and enantioselective formation of up to three stereocentres in a single step, provided that a single geometrical diastereomer of the starting diene is used. The groups of Jacobsen and Hashimoto et al.[3] developed elegant catalytic asymmetric cycloadditions, involving a range of carbonyl dienophiles and Danishefsky dienes possessing only one oxygenated substituent. This route provides a direct entry into all-*syn* trisubstituted THPs with excellent enantio- and diastereomeric excesses. The Diels–Alder route is, however, more commonly used for the preparation of dihydropyranones (DHPs) rather than THPs. This is due to the limited number of catalytic asymmetric routes available for the more demanding cycloadditions involving less activated dienes.[9] Mechanistically, only limited data are available for the HDA reaction leading to THPs, whereas it is well established that the formation of DHPs can proceed through both concerted and stepwise pathways.

[a] Dr. M. Reiter, H. Turner, Dr. V. Gouverneur
University of Oxford, Chemistry Research Laboratory
12, Mansfield Road, Oxford OX1 3TA (UK)
Fax: (+44) 1865-275-644
E-mail: veronique.gouverneur@chem.ox.ac.uk

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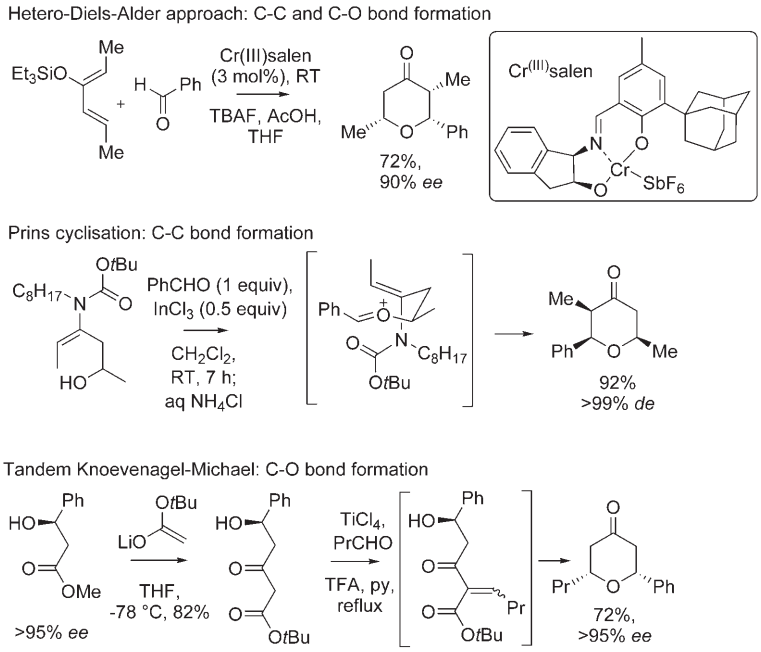
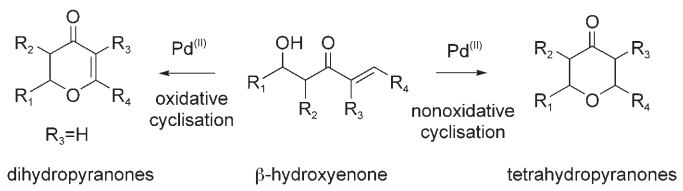


Scheme 1. Representative approaches towards tetrahydropyranones. TBAF = tetrabutylammonium fluoride; TFA = trifluoroacetic acid; *de* = diastereomeric excess.

Although a range of intermolecular additions of alcohols onto α,β-unsaturated ketones have been reported in the literature, to the best of our knowledge, examples of endocyclic oxy-Michael additions to proximal α,β-unsaturated systems leading to THPs are rare.[8,9] This approach can be regarded as a variant of the stepwise HDA reaction, involving the formation of a β-hydroxyenone, followed by a nonoxidative ring closure.[10] In previous studies, we have shown that $PdCl_2$ in the presence of the co-oxidants CuCl and oxygen catalyzed the intramolecular oxidative cyclisation of β-hydroxyenones to give DHPs.[11] In this paper, we report on how to reroute the ring closure pathway towards a nonoxidative cyclisation, with the result of preparing tetrahydropyranones instead of dihydropyranones from the same β-hydroxyenone precursors (Scheme 2).

Inspired by the established palladium(II)-mediated intermolecular hydroalkoxylation and amidation addition reactions to enones,[12] we selected several palladium(II)-based catalysts to mediate the intramolecular nonoxidative ring closure. We also tested Brønsted and Lewis acids, which were shown to promote other nonoxidative intermolecular Michael conjugate additions.[13] The efficiency of these catalysts was initially tested in racemic series with the preparation of a representative trisubstituted tetrahydropyranone from the corresponding β-hydroxyenone. For the most effective catalysts, we conducted a detailed study on the scope and generality of these intramolecular Michael additions with a variety of structurally diverse aldol products. We have also examined the stereochemical outcome of these nonoxidative cyclisations by varying the relative stereochemistry of diastereomerically enriched β-hydroxyenones and the substitution pattern of their C–C double bonds. The synthesis of THPs featuring from one up to four stereogenic centres is reported. The methodology was also challenged with the cyclisation of an enantioenriched β-hydroxyenone substrate. Finally, we discuss the mechanism of the most successful nonoxidative ring closures conducted in the light of control experiments and the observed stereoselectivities upon cyclisation.

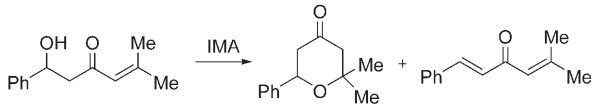


Scheme 2. Pd^{II}-mediated oxidative and nonoxidative ring closure of β-hydroxyenones.

Results and Discussion

Cyclisation versus competitive dehydration or retro-aldolisation: The groups of Kobayashi,[14] Spencer[13] and Banik et al.[15] have recently published work on the intermolecular aza- and oxy-Michael addition of weakly basic nitrogen-containing nucleophiles, such as carbamates, oxazolidinones or benzylic alcohols, to α,β-unsaturated ketones. They have shown that these intermolecular Michael additions can be catalyzed by a range of Brønsted and Lewis acids, as well as Pd^{II}-catalysts. These catalysts are believed to enhance the electrophilicity of the enone substrates, thereby allowing the reaction to proceed under mild conditions. Despite the fact that Spencer et al. had only limited success with the intermolecular Michael addition of oxygen nucleophiles, we set out to study an entropically more favourable intramolecular variant of this reaction by using β-hydroxyenones as the starting materials. Upon cyclisation, these substrates could lead to side reactions, such as competitive dehydration or retroaldolisation processes. The most suitable catalyst for the intermolecular Michael addition of alcohols to enones might, therefore, differ from the catalyst of choice for the 6-*endo*-trig cyclisation of β-hydroxyenones. We investigated in detail the ring closure of the representative aldol **1a** in the presence of numerous Brønsted and Lewis acids, as well as palladium(II) complexes (Table 1). Several organic acids

Table 1. Optimisation study for the intramolecular Michael addition (IMA) of **1a**.



1a **2a** **3a**

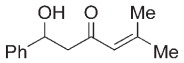
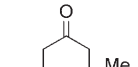
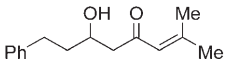
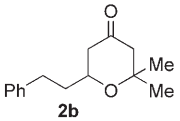
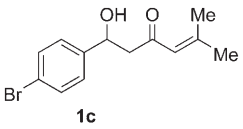
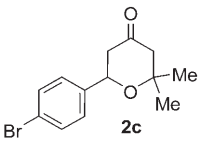
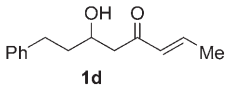
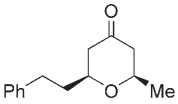
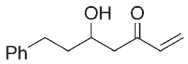
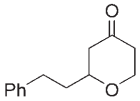
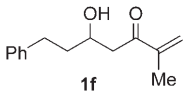
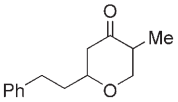
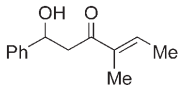
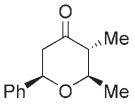
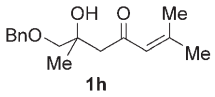
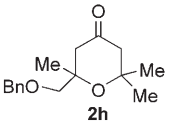
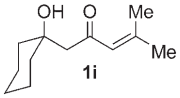
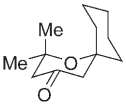
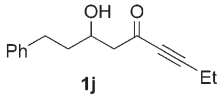
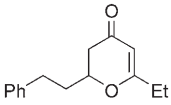
Entry	Catalyst (10 mol %)	Conditions	Ratio **2a**/**3a**	Yield **2a** [%]
1	AcOH	MeCN, 18 h	–	0
2	TFA[a]	MeCN, 18 h	100:0	20
3	$NHTf_2$	MeCN, 18 h	1:5	14
4	*p*TSA	MeCN, 18 h	1:1	–
5	HBF_4	MeCN, 18 h	4:1	–
6	Amberlyst-15 (**A**)[b]	CH_2Cl_2, 3 h	100:0	90
7	$Bi(OTf)_3$	MeCN, 18 h	3:7	–
8	$Cu(OTf)_2$	MeCN, 18 h	2:1	–
9	$ZrO(ClO_4)_2 \cdot 8H_2O$	MeCN, 18 h	2:1	–
10	$Fe(ClO_4)_2 \cdot H_2O$	MeCN, 18 h	100:0	60
11	$Al(OCl_4)_3 \cdot 9H_2O$ (**B**)	MeCN, 3 h	100:0	71
12	NEt_3	CH_2Cl_2, 70 h	–	0
13	KO*t*Bu	THF, 0.5 h	–	0
14	NaH	CH_2Cl_2, RT, 3 h	–	0
15	$PdCl_2$ or $Pd(OAc)_2$	CH_2Cl_2, 18 h	–	0
16	$PdCl_2$ or $Pd(OAc)_2$, LiBr (200 mol %)	CH_2Cl_2, 18 h	–	0
17	$[Pd(MeCN)_4](BF_4)_2$ (**C**)	CH_2Cl_2, 1 h	100:0	72
18	$[PdCl_2(MeCN)_2]$ (**D**)	CH_2Cl_2, 18 h	7:1	68

[a] No reaction for 10 mol %, results shown for 200 mol %. [b] Amount used = 2 equiv w/w.

were tested first (entries 1–6). Acetic and trifluoroacetic acid gave no or very low conversions, with mainly starting material being recovered (entries 1–2). Upon treatment with $NHTf_2$, HBF_4 or *p*TSA (*p*TSA = *para*-toluenesulfonic acid), a competitive dehydration process took place and the cyclised product **2a** was obtained in low yields (entry 3–5). We then tested Amberlyst-15, a catalyst employed by Kalesse et al.[8] for the formation of tetrahydropyrans and by Spencer et al.[13] for intermolecular Michael additions to enones. With this mild sulfonic acid resin, aldol **1a** was cleanly converted into the desired THP **2a** with an isolated yield of 90 % (entry 6). Various Lewis acids, including $Cu(OTf)_2$ and $ZrO(ClO_4)_2 \cdot 8H_2O$, were used next, but they predominantly gave mixtures of cyclic and dehydrated products (entries 7–9). The Lewis acid $Fe(ClO_4)_2 \cdot H_2O$ gave the desired THP **2a** in 60 % yield (entry 10). The use of $Al(ClO_4)_3 \cdot 9H_2O$ proved to be even more suitable, as this reaction gave **2a** within three hours in a 71 % isolated yield without any detectable dehydration (entry 11). This Lewis acid was therefore retained for further cyclisations. As anticipated, the use of basic conditions was unsuccessful. In the presence of NEt_3, only starting material was recovered, NaH and KO*t*Bu led to significant side reactions, such as retroaldolisations (entries 12–14). The efficiency of four palladium(II) catalysts was also examined, namely palladium(II)diacetate $Pd(OAc)_2$ and palladium(II)dichloride $PdCl_2$, bis(acetonitrile)palladium(II)dichloride $[Pd(MeCN)_2]Cl_2$ and tetrakis(acetonitrile)-palladium(II)tetrafluoroborate $[Pd(MeCN)_4](BF_4)_2$ (entries 15–18). When used in combination with CuCl and oxygen, palladium dichloride was a suitable catalyst for the oxidative cyclisation of β-hydroxyenones featuring at least one β-hydrogen on the double bond.[11] Under nonoxidising conditions, neither $PdCl_2$ nor $Pd(OAc)_2$ promoted the cyclisation event (entry 15). Although the addition of halide ions was shown in some cases to further promote the IMA reaction, under the present conditions their addition did not have a noticeable effect (entry 16).[16] However, when the reaction was conducted in the presence of the two palladium(II) catalyst featuring acetonitrile ligands ($[PdCl_2(MeCN)_2]$ and $[Pd(MeCN)_4](BF_4)_2$), **1a** was successfully cyclised into **2a** in 68 and 72 % yields, respectively (entries 17–18). The cationic palladium species was clearly the best catalyst for this reaction, as reflected by the shorter reaction time (entry 18). The results summarised in Table 1 revealed that the most suitable catalysts for the ring closure of β-hydroxyenones differed significantly from the intermolecular series, in which the Brønsted acid $NHTf_2$ was superior to the palladium(II) salts. The most efficient catalysts for the IMA of the β-hydroxyenone **1a** were Amberlyst-15 (**A**), $Al(ClO_4)_3 \cdot 9H_2O$ (**B**), $[Pd(MeCN)_4](BF_4)_2$ (**C**) and $[PdCl_2(MeCN)_2]$ (**D**).

Scope and generality: The substrate tolerance of these four catalysts was investigated next for the ring closure of a series of achiral and racemic β-hydroxyenones featuring one or no stereocentre (Table 2). For the palladium(II)-mediated cyclisations, we favoured the use of catalyst **C**, as this catalyst gave better yields of the desired product within shorter reaction times and with lower catalytic loading. β-Hydroxyenones **1a–g** ring closed cleanly to give the corresponding tetrahydropyranones **2a–g** in good yields (54–91 %, Table 2, entries 1–7). Interestingly, for the hydroxyenones **1d–g**, featuring a β-hydrogen on the double bond, the nonoxidative Michael conjugate addition was found to be the only reaction pathway taking place in the presence of two palladium(II) catalysts **C** and **D**. No traces of the unwanted oxidised dihydropyranone products were detected in the crude reaction mixture. For substrate **1d**, significant 1,5-stereoinduction was observed in the presence of Brønsted acid catalyst **A**, leading to the preferential formation of the *syn*-diequatorial THP **2d**. The two diastereomeric products were separated cleanly by silica-gel chromatography. In contrast, no significant level of stereoinduction was observed for the Pd^{II}-mediated reaction, which led to the formation of *syn*- and *anti*-**2d** in almost equal proportions (entry 4). When using the highly active cationic palladium catalyst **C**, the β-hydroxyenones featuring no double-bond substituent α to

Table 2. Preparation of racemic tetrahydropyranones **2a–i** and dihydropyranone **2j**.

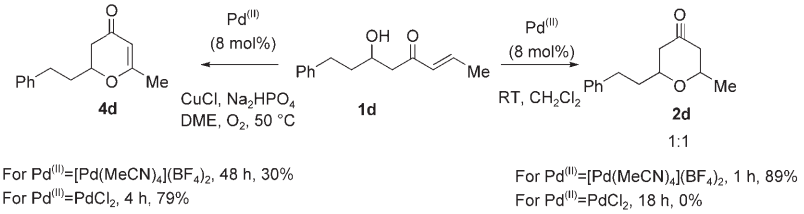
Entry	Starting material	Yield [%]	Product	Catalyst, *t* [h][a]	Yield [%]	*dr*[b]
1	 **1a**	96	 **2a**	**A**, 3 **B**, 3 **C**, 1 **D**, 18	90 71 72 68	– – – –
2	 **1b**	82	 **2b**	**A**, 3 **C**, 1 **D**, 18	91 79 78	– – –
3	 **1c**	73	 **2c**	**A**, 3 **C**, 1	67 65	– –
4	 **1d**	74	 **2d**	**A**, 3 **D**, 12	90 89	93:7 (99:1) 1:1 (99:1)[c]
5	 **1e**	84	 **2e**	**C**, 1	63	–
6	 **1f**	55	 **2f**	**C**, 12	58	1:1
7	 **1g**	96	 **2g**	**A**, 18 **C**, 18	54 65	4:1[d] 9:1[d]
8	 **1h**	98	 **2h**	**C**, 44	55	–
9	 **1i**	97	 **2i**	**C**, 44	54	–
10	 **1j**	74	 **2j**	**C**, 12	60	–

[a] **A** = Amberlyst-15, CH_2Cl_2, RT; **B** = $Al(ClO_4)_3 \cdot 9H_2O$, MeCN, RT; **C** = $[Pd(MeCN)_4](BF_4)$, CH_2Cl_2, RT. [b] Number in brackets indicates *dr* obtained after purification. [c] Yield for the *syn* isomer is 47%. [d] Minor diastereomer is all-*syn* **2g**.

the carbonyl, cyclised within one hour, but the α-methylated β-hydroxyenones **1f–g** required overnight stirring (entries 6–7). The THP **2f** was obtained as a mixture of diastereomers in the presence of **C**, indicating that no 1,4-stereoinduction had occurred (entry 6). Noteworthy, is that the β-hydroxyenone substrate **1f** did not cyclize under oxidative conditions ($PdCl_2$, CuCl, O_2).[11] For **1g**, featuring a trisubstituted *E* double bond, both catalysts **A** and **C** gave predominantly the trisubstituted THP *anti*,*anti*-**2g**. NOE and X-ray analysis confirmed that the major diastereomer featured all three substituents in equatorial positions. The minor diastereomer was identified as the all-*syn* **2g** product. For aldols **1h–i**, derived from ketone acceptors, much longer reaction times (up to 44 h) were required in comparison to aldols **1a–g** derived from aldehyde precursors. A similar trend was observed for intermolecular Michael additions.[12] A competitive dehydration process also took upon ring closure of **1h–i**, which resulted in lower chemical yields for the formation of **2h–i**

(54–55%, entries 8–9). Finally, we found that the palladium-mediated methodology was not limited to β-hydroxyenones; in the presence of catalyst **C**, the β-hydroxyynone **1j** cyclised into the corresponding dihydropyranone **2j** in 60% yield (entry 10).

Oxidative versus nonoxidative cyclisation: We verified whether we could obtain the oxidised or the nonoxidised cyclic product derived from a given β-hydroxyenone substrate by using the same catalyst, but fine-tuning the reaction conditions (Scheme 3). Aldol **1d** cyclised within one hour in the presence of cationic $[Pd(MeCN)_4](BF_4)_2$ in dichloromethane under an argon atmosphere to give **2d** in 89% yield as a mixture of two diastereomers. No reaction, however, occurred in the presence of $PdCl_2$. When we submitted **1d** to the same cationic catalyst **C** (8 mol%) under oxidising conditions (CuCl, Na_2HPO_4, O_2 in DME at 50°C),[11] the cyclisation reaction required 48 h to reach completion and the desired oxidised DHP product **4d** was formed in 30% yield, along with products of decomposition. Interestingly, no product resulting from an intramolecular conjugate addition was isolated. In contrast, in the presence of $PdCl_2$ under oxidising conditions, **4d** was formed in 79% yield within 4 h of stirring at 50°C.[11]

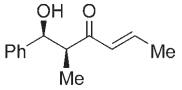
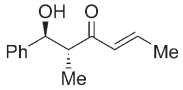
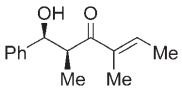
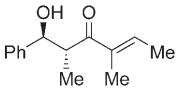
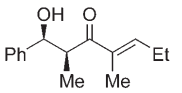
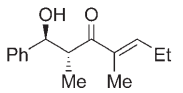


Scheme 3. Role of the catalyst in the ring closure. DME = dimethoxyethane.

Intramolecular Michael addition of *syn*- and *anti*-α-methyl-β-hydroxyenones: We then directed our attention to the cyclisation of aldol products possessing two stereogenic centres. The *syn*- and *anti*-β-hydroxyenones **1k–m** were obtained following previously published procedures,[11] which were adapted from the diastereoselective boron-mediated aldol reaction developed by Paterson et al.[17] The *syn*-aldols **1k–l** were formed with excellent diastereocontrol by coupling (*E*)-4-hexen-3-one, (*E*)-4-methylhex-4-en-3-one or (*E*)-4,6-dimethylhept-4-en-3-one with benzaldehyde in the presence of nBu$_2$BOTf and iPr$_2$EtN. The use of cHex$_2$BCl and EtMe$_2$N preferentially gave *anti*-aldols **1k–l** with moderate diastereoselectivities. The *anti* stereoisomers were obtained in pure form upon silica-gel chromatography; however, this was only possible for aldol products derived from benzaldehyde. With these more heavily substituted substrates in hand, we performed the subsequent intramolecular Michael additions. Three stereochemical issues were raised by these cyclisations: the stereochemical integrity of the existing stereocentres of the starting aldols under the reaction conditions, the level of diastereocontrol upon ring closure and the directionality of the final protonolysis step. Catalysts **A–C** were selected for this study to determine which catalyst might be the most useful synthetically. We also hoped to shed some light on their respective mode of action (Table 3).

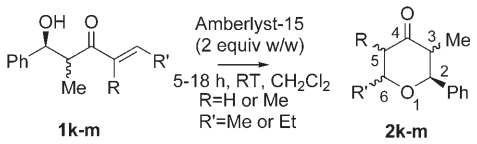
Brønsted acid mediated IMA: In the first set of experiments, we investigated the stereochemical outcome of the Amberlyst-15-mediated IMA reaction of *syn*- and *anti*-enones **1k–m**. Most cyclisations reached completion after 5 h at RT, but *anti*-**1k–m** substrates required an extended reaction time of 18 h (Table 4). The Brønsted acid mediated cyclisation of *syn*-**1k** led to the formation of all-*syn*-**2k** and *anti*,*anti*-**2k** in a total yield of 75% and in a ratio of 7:3 (Table 4, entry 1). The level of control for the ring closure was excellent, with both isolated diastereomers featuring an equatorial methyl group at the newly formed stereocentre at the 6-position. The minor diastereomer *anti*,*anti*-**2k** resulted from an epimerisation of the stereocentre at the 3-position. This was possibly caused by a lack of stereocontrol upon protonolysis, combined with an enolisation process occurring either before or after the cyclisation event. For the cyclisation of *syn*-**1l**, an excellent level of control was also observed, with all three diastereomers featuring an equatorial methyl group at the 6-position. For the major diastereomer, *syn*,*anti*,*anti*-**2l**, the relative *syn*-stereochemistry of the starting aldol was faithfully translated and the protonolysis step led to an equatorial methyl group

Table 3. Preparation of *syn*- and *anti*-β-hydroxyenones **1k–m**.

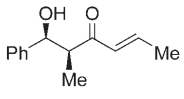
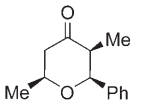
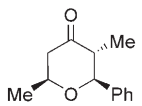
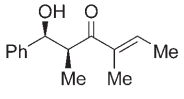
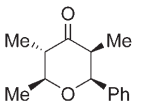
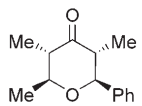
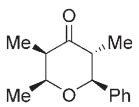
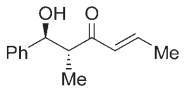
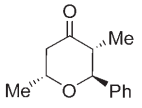
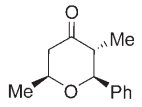
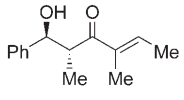
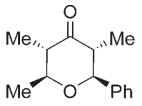
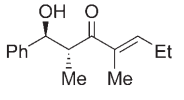
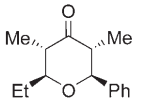
Entry	1	*syn*-β-Hydroxyenones	Yield [%], *dr*	Entry	*anti*-β-Hydroxyenones	Yield [%], *dr*
1	**1k**		62, 99:1	4		72, 4:1 (99:1)[a]
2	**1l**		50, 99:1	5		40, 9:1 (99:1)[a]
3	**1m**		67, 99:1	6		45, 3:1, (99:1)[a]

[a] Number in brackets indicates *dr* for major diastereomer after purification.

Table 4. Diastereomeric distribution for Amberlyst-15-mediated IMA.



1k-m **2k-m**

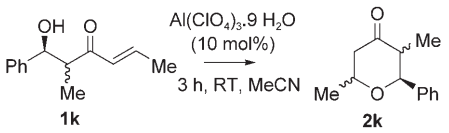
Entry	β-Hydroxyenone	THPs			*dr*	Yield [%]
1	 *syn*-**1k**	 *syn,syn*-**2k**	 *anti,anti*-**2k**	–	7:3	75
2	 *syn*-**1l**	 *syn,anti,anti*-**2l**	 *anti,syn,anti*-**2l**	 *anti,anti,syn*-**2l**	10:2:3	90
3	 *anti*-**1k**	 *anti,syn*-**2k**	 *anti,anti*-**2k**	–	93:7	84
4	 *anti*-**1l**	 *anti,syn,anti*-**2l**	–	–	12:1:1	75
5	 *anti*-**1m**	 *anti,syn,anti*-**2m**	–	–	12:1:1	70

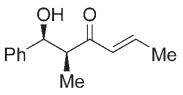
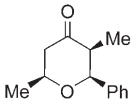
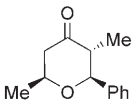
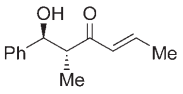
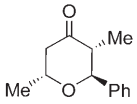
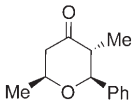
[a] *syn* or *anti* annotation assigned anticlockwise according to Cahn–Ingold–Prelog priorities.

at the 5-position. For the minor *anti*,*syn*,*anti*-diastereomer, an enolisation process had taken place at the 3-position, which meant that the *syn* relationship of the starting material was no longer present in the cyclic products. For the third *anti*,*anti*,*syn*-diastereomer, the protonolysis step had induced an axial methyl group at the 5-position. The acid-mediated ring closure of *anti*-**1k** led to two diastereomers in a 93:7 ratio. The major diastereomer, *anti*,*syn*-**2k**, featured an axial methyl group at the 6-position, whereas the minor product was the all-equatorial *anti*,*anti*-**2k** (entry 3). Both diastereomers were isolated in pure form after silica-gel chromatography. Upon cyclisation of aldol *anti*-**1l**, the resulting reaction mixture was composed of an inseparable mixture of diastereomers formed in a 12:1:1 ratio. Only the major diastereomer could be identified irrefutably as the all equatorial THP *anti*,*syn*,*anti*-**2l**. Similar results were obtained with aldol *anti*-**1m**. The stereochemistry of all THPs was unambiguously assigned on the basis of their NMR coupling constants and NOE experiments.[SI]

Lewis acid mediated IMA: The level of stereochemical integrity and control upon ring closure obtained for the Al$(ClO_4)_3$·9H_2O-mediated IMA reaction was investigated on the *syn*- and *anti*-enone substrate **1k**. The reactions were stirred at room temperature for 3 h (Table 5). The Lewis acid mediated ring closure of *syn*-**1k** occurred in 76% yield, with an excellent level of diastereocontrol. Indeed, both diastereomers formed featured an equatorial 6-methyl group. The *anti*,*anti*-**2k** byproduct was likely the result of an enolisation process occurring either before and/or after cyclisation (Table 5, entry 1). Compound *anti*-**1k** cyclised in the presence of the Lewis acid to give the corresponding THPs *anti*,*syn*-**2k** and *anti*,*anti*-**2k** in 70% overall yield and in a 96:4 ratio. For both diastereomers, the relative stereochemistry of the starting material was faithfully translated into the cyclic products, with the main diastereomer featuring an axial 6-methyl group and the minor diastereomer an equatorial 6-methyl group. A point to note is that the same sense of diastereocontrol upon ring closure was obtained for both the Brønsted and Lewis acid mediated reactions. We also attempted the ring closure of *syn*-**1k** in the presence of the Lewis acid TMSOTf and *i*Pr_2NEt.[17] To prevent decomposition and dehydration, this IMA reaction had to be conducted at low temperature and submolar concentrations. The major all-*syn* **2k** THP product was formed after prolonged reaction times in a lower chemical yield (50%) and with a diastereomeric ratio of 91:9. Subsequent cyclisations were therefore not performed under these conditions.

Table 5. Diastereomeric distribution for Lewis acid mediated IMA.

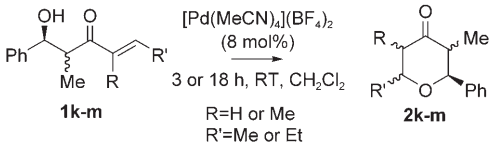


Entry	Starting material	THPs		Yield [%]	*dr*
1	 *syn*-**1k**	 *syn,syn*-**2k**	 *anti,anti*-**2k**	76	95:5
2	 *anti*-**1k**	 *anti,syn*-**2k**	 *anti,anti*-**2k**	70	96:4

Pd^{II}-mediated IMA: The Pd^{II}-mediated nonoxidative cyclisation was carried out on β-hydroxyenone substrates *syn*- and *anti*-**1k–m** by using catalyst **C**. Reactions reached completion after 3 h of stirring for *syn*- and *anti*-**1k** but required overnight stirring for *syn*- and *anti*-**1l–m** (Table 6). All cyclic products **2k–m** were formed in good overall yields, ranging from 60 to 78%. The palladium-mediated ring closure of *syn*-**1k** occurred with a high level of diastereocontrol, with the major diastereomer *syn,syn*-**2k** and minor diastereomer *syn,anti*-**2k** formed in a 96:4 ratio (Table 6, entry 1). The relative *syn*-stereochemistry of the starting material was retained for both diastereomers with the major diastereomer featuring an equatorial 6-methyl group and the minor diastereomer an axial 6-methyl group. The same sense and level of control was observed for the ring closure of *syn*-aldols **1l–m**, with the major diastereomers possessing an equatorial 6-methyl group and the minor diastereomer *syn*, *syn,anti*-**2l–m** featuring an axial 6-methyl group (entries 2–3). The all-*syn* tetrasubstituted **2l–m** THP products were the result of the protonolysis step placing the 5-methyl group axially, instead of its more common equatorial position. In contrast to the Brønsted and Lewis acid mediated IMA reactions, the relative *syn* stereochemistry of the starting aldols was translated faithfully into each of the diastereomeric cyclic products, indicating that no enolisation process occurred for these palladium-mediated reactions. In the *anti* series, the level and sense of diastereocontrol for the ring closure of *anti*-**1k** were similar to the Lewis or Brønsted acid mediated reactions. The major diastereomer *anti,syn*-**2k**, featuring an axial 6-methyl group, and the minor all-equatorial *anti,anti*-**2k** diastereomer were formed in a ratio of 97:3 (entry 4). The cyclisations of *anti*-**1l–m** gave a mixture of three diastereomers formed in equal proportions with an overall yield of 63 and 70%, respectively. Only the all-equatorial *anti,syn,anti*-**2l–m** could be isolated in pure form (entries 5–6). The level of control for the ring closure event of the *anti*-enone precursors containing a trisubstituted alkene group was lower than for that of *anti*-**1k**. The diastereomeric products, featuring an axial 6-methyl group, were formed in a 2:1 ratio with respect to *anti,syn,anti*-**2l–m**, featuring an equatorial 6-methyl group.

Stereochemical stability: To account for the stereochemical outcome of the various ring closures, it was necessary to determine whether these cyclisations were under kinetic or thermodynamic control. We therefore tested the stereochemical stability of the **2k–l** THPs under the reaction conditions upon extended reaction times in the presence of catalysts **A–C** (Table 7). We found that *syn,syn*-**2k** fully epimerised in the presence of **A** or **B** to give the all-equatorial THP *anti,anti*-**2k** (entries 1–2). This suggests that for these two catalysts enolisation proceeded easily at room temperature to give the thermodynamic product. In contrast, we found that *syn,syn*-**2k** was perfectly stable when stirred in the presence of catalyst **C** after three days at room temperature (entry 3). This indicates that this catalyst was not able to coordinate to the carbonyl group to such an extent that enolisation occurred and therefore epimerisation of the stereogenic carbon positioned α to the carbonyl did not occur. Similarly, tetrasubstituted *syn,anti,anti*-**2l** was converted into the all-equatorial *anti,syn,anti*-**2l** (*dr* = 99:1; *dr* = diastereomeric ratio) when resubjected to the reaction conditions in the presence of **A** (entry 4), but was found to be stable in the presence of catalyst **C** (entry 5). When *anti,syn*-**2k** was treated for an extended reaction time in the presence of catalysts **B** and **C**, unchanged starting material was recovered (entry 7–8). However, in the presence of **A**, epimerisation at the C6 carbon occurred after six days (entry 6). As the kinetic product was converted into the more stable all-equatorial product, this result indicates that retrocyclisation can occur under these conditions. Similarly, the mixture of the three diastereomeric tetrahydropyranones **2l** remained unchanged in the presence of catalyst **C**, but in the presence of **A**, it equilibrated after three days at room temperature to exclusively give the more stable all-equatorial *anti,syn,anti*-**2l** (*dr* = 99:1). These experiments allowed us to conclude that the palladium and aluminium-mediated cyclisations are both irreversible under the given reaction conditions. The

Table 6. Diastereomeric distribution for Pd^{II}-mediated IMA.



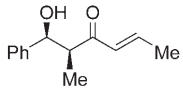
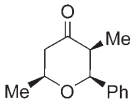
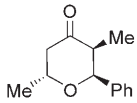
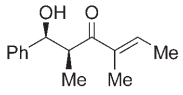
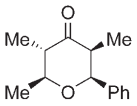
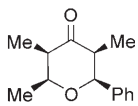
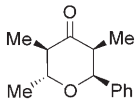
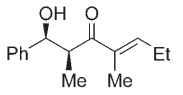
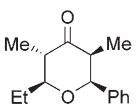
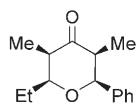
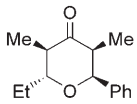
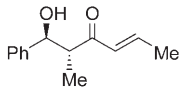
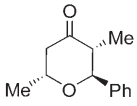
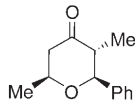
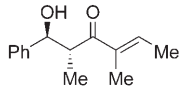
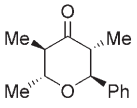
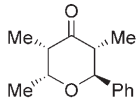
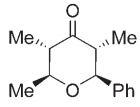
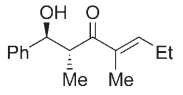
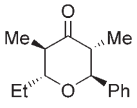
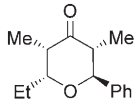
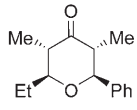
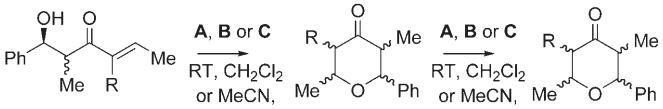
Entry	Starting material	THPs			*dr*	Yield [%]
1	 *syn*-**1k**	 *syn,syn*-**2k**	 *syn,anti*-**2k**	–	96:4	78
2	 *syn*-**1l**	 *syn,anti,anti*-**2l**	 *syn,syn,syn*-**2l**	 *syn,syn,anti*-**2l**	87:10:3	68
3	 *syn*-**1m**	 *syn,anti,anti*-**2m**	 *syn,syn,syn*-**2m**	 *syn,syn,anti*-**2m**	88:10:2	60
4	 *anti*-**1k**	 *anti,syn*-**2k**	 *anti,anti*-**2k**	–	97:3	75
5	 *anti*-**1l**	 *anti,anti,anti*-**2l**	 *anti,syn,syn*-**2l**	 *anti,syn,anti*-**2l**	1:1:1	63
6	 *anti*-**1m**	 *anti,anti,anti*-**2m**	 *anti,syn,syn*-**2m**	 *anti,syn,anti*-**2m**	1:1:1	70

Table 7. Stereochemical stability to reaction conditions.



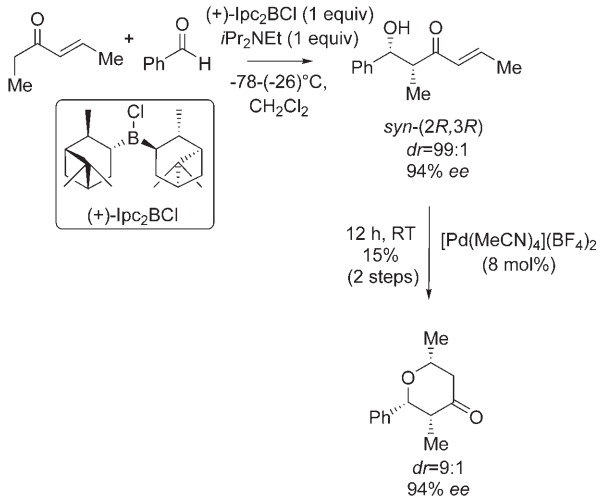
Entry	**1**	Conditions[a] **I**	Product distribution[b]	Major diastereomer	Conditions[a] **II**	*dr*	Major diastereomer
1	*syn*-**1k**	**A**, 5 h, RT	7:3	*syn*,*syn*	**A**, 3 d, RT	99:1	*anti*,*anti*
2		**B**, 3 h, RT	95:5	*syn*,*syn*	**B**, 2 d, RT	99:1	*anti*,*anti*
3		**C**, 3 h, RT	96:4 (99:1)	*syn*,*syn*	**C**, 3 d, RT	99:1	*syn*,*syn*
4	*syn*-**1l**	**A**, 5 h, RT	10:2:3 (9:1)	*syn*,*anti*,*anti*	**A**, 3 d, RT	99:1	*anti*,*syn*,*anti*
5		**C**, 18 h, RT	87:10:3 (99:1)	*syn*,*anti*,*anti*	**C**, 2 d, RT	99:1	*syn*,*anti*,*anti*
6	*anti*-**1k**	**A**, 5 h, RT	93:7 (99:1)	*anti*,*syn*	**A**, 6 d, RT	99:1	*anti*,*anti*
7		**B**, 3 h, RT	96:4 (99:1)	*anti*,*syn*	**B**, 2 d, RT	99:1	*anti*,*syn*
8		**C**, 3 h, RT	97:3 (99:1)	*anti*,*syn*	**C**, 2 d, RT	99:1	*anti*,*syn*
9	*anti*-**1l**	**A**, 18 h, RT	1:1:1	*anti*,*syn*,*anti*	**A**, 3 d, RT	99:1	*anti*,*syn*,*anti*
10		**C**, 18 h, RT	1:1:1	*anti*,*syn*,*anti*	**C**, 3 d, RT	1:1:1	*anti*,*syn*,*anti*

[a] **A** = Amberlyst-15, CH_2Cl_2, RT; **B** = $Al(ClO_4)_3 \cdot 9H_2O$, MeCN, RT; **C** = $[Pd(MeCN)_4](BF_4)_4$, CH_2Cl_2, RT. [b] Number in brackets indicates *dr* with respect to major diastereomer after purification. Subsequent stability tests were carried out on diastereomerically pure cyclic compounds.

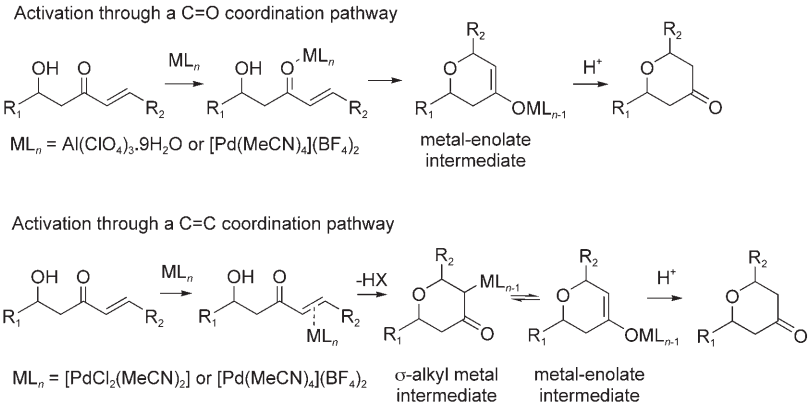
palladium-catalyzed ring closures were sufficiently mild to prevent enolisation and epimerisation at the 3- and 5-positions, which was not the case for $Al(ClO_4)_3 \cdot 9H_2O$. The use of Amberlyst-15, however, was probably narrower in scope, as this catalyst promoted both enolisation and retrocyclisations, consequently leading to the formation of the most stable product upon extended reaction times.

Intramolecular Michael addition of a representative enantiopure β-hydroxyenone: To further probe the synthetic scope of these IMA, we stud-

ied the cyclisation of the enantioenriched aldol precursor *syn*-**1k** (Scheme 4). This compound was prepared in 94% *ee* (*ee* = enantiomeric excess) and *dr* 9:1 by using the chiral boron enolate derived from (+)-Ipc$_2$BCl.[11,17] The aldol *syn*-(*2R,3R*)-**1k** underwent ring closure with the preferential formation of the all-*syn* **2k** product. The enantiomeric excess of the all-*syn* (2*R*,3*R*,6*R*)-**2k** THP was determined to be 94% by HPLC analysis using chiral stationary phases. It therefore mirrored exactly the enantiopurity of the starting material. This information allowed us to conclude that the chemistry outlined herein will be directly applicable to the preparation of enantioenriched targets. The absolute configuration of (2*R*,3*R*,6*R*)-**2k** was assigned by comparison with published α_D values.[3]



Scheme 4. Asymmetric synthesis of (2*R*,3*R*,6*R*)-2-phenyl-3,6-dimethyltetrahydropyran-4-one **2k**.

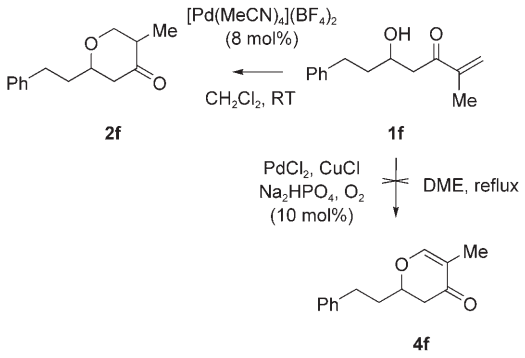


Scheme 5. C=C versus C=O coordination pathways.

Mechanism of the nonoxidative ring closures: The mechanistic pathway of the nonoxidative cyclisations reported herein involves initial activation of the β-hydroxyenone by coordination to the different catalysts. Two modes of activation can operate for these enones with complexation of the catalyst to either the C=O or C=C functional groups (Scheme 5).[18] Both modes of coordination enhance the electrophilicity of the double bond, thereby facilitating nucleophilic attack by the hydroxy group. The C=O mode of activation involves the reversible formation of a transient carbonyl-metal complex or protonated ketone, followed by ring closure and protonolysis of the resulting metal enolate or enol.[19] Amberlyst-15, the oxophilic Lewis acid Al(ClO$_4$)$_3$·9H$_2$O and possibly the cationic palladium catalyst [Pd(MeCN)$_4$](BF$_4$)$_2$ are most likely to operate along this mechanistic pathway. The alternative mechanism, usually more characteristic of palladium-mediated cyclisations involving neutral catalysts of weaker Lewis acidity is initiated by direct coordination of the olefinic double bond to the metal catalyst leading to an activated π-complex. This complex is subsequently subjected to a regioselective 6-*endo*-trig ring closure. The resulting σ-alkyl metal intermediate then undergoes protonolysis to give a tetrahydropyranone product with concomitant regeneration of the palladium(II) catalytic species.[11] It is not clear whether the protonolysis involves direct σ-C–Pd bond cleavage or transits through a Pd–O enolate intermediate.[13] This mechanistic pathway is only possible when the protonolysis of the σ–Pd bond is faster than β-hydride elimination. This competing pathway leads to a dihydropyranone, a product never observed in our crude mixtures. With [Pd(MeCN)$_4$](BF$_4$)$_2$ and [PdCl$_2$(MeCN)$_2$] the undesired β-hydride elimination pathway is probably suppressed due to the presence of acetonitrile ligands for these catalysts. These strongly coordinating ligands assure the unavailability of a vacant or weakly coordinated site *cis* to the Pd-alkyl bond essential for the β-hydride elimination process to take place. It is also possible that the carbonyl group further stabilizes the σ-alkyl palladium intermediate towards elimination by further coordination with the cationic metal.

We have several factual pieces of evidence to support the hypothesis that the cationic palladium catalyst [Pd(MeCN)$_4$](BF$_4$)$_2$ is likely to operate by C=O coordination. The similar sense and level of diastereocontrol observed for the cyclisation with this catalyst and Al(ClO$_4$)$_3$·9H$_2$O suggest similar mechanistic pathways. An additional indication arises from the difference of reactivity of aldol **1f** when using the cationic palladium catalyst [Pd(MeCN)$_4$](BF$_4$)$_2$ under reaction conditions favouring the nonoxidative ring closure pathway or using the neutral catalyst PdCl$_2$ under aerobic conditions leading to the oxidised dihydropyranone. Indeed, aldol **1f** was successfully converted to the tetrahy-

dropyranone **2f** by using $[Pd(MeCN)_4](BF_4)_2$, but did not lead to the desired dihydropyranone **4f** in the presence of $PdCl_2$. The lack of reactivity with $PdCl_2$ indicates that the presence of the methyl group on the nonterminal double bond carbon hampered activation of the substrate by C=C coordination. Also, the ring closure would involve the formation of a highly unfavourable quaternary σ-Pd–C centre. The successful cyclisation observed in the presence of $[Pd(MeCN)_4](BF_4)_2$ might be due to the fact that this catalyst activates the enone by the carbonyl group forming a palladium-enolate intermediate, which could subsequently undergo protonolysis (Scheme 6). Finally, literature data from the

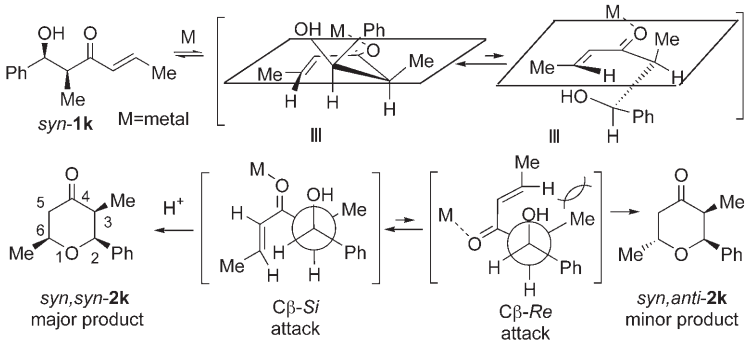


Scheme 6. Difference in reactivity for substrate **1f**.

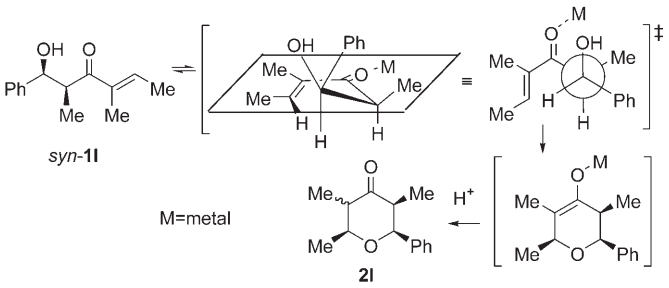
group of Oi et al.[20] suggested a similar C=O mode of activation for the hetero-Diels–Alder reaction of unactivated dienes and aldehydes in the presence of $[Pd(MeCN)_4](BF_4)_2$. They showed that, in contrast, the milder neutral catalyst $[PdCl_2(MeCN)_2]$ was unable to promote these cycloadditions, therefore supporting the hypothesis that this neutral catalyst triggers the nonoxidative cyclisations reported herein by C=C activation. For the palladium(II)-mediated ring closures, we also considered a third coordination mechanism involving intramolecular suprafacial addition of an alkoxy-palladium intermediate.[21] However, this reaction mechanism was discarded due to the highly strained nature of the transition state resulting from an endocyclic ring closure.

The results of Spencer et al.[13] for the intermolecular Michael addition suggest that the mechanism of cationic palladium(II)-mediated intermolecular hetero-Michael additions might take place according to a reaction pathway that involves catalytic activation of the carbonyl group by in situ formed Brønsted acids. Based on our preliminary screening results, we believe that this is probably not the case for the corresponding intramolecular oxy-Michael additions, because the Brønsted acids failed to deliver the cyclised products as efficiently as the palladium(II) catalyst. This was due to the occurrence of competing dehydration, epimerisation and retrocyclisation processes. Further experiments and theoretical calculations are ongoing in our laboratories to establish more clearly the exact mechanism for these novel transformations.

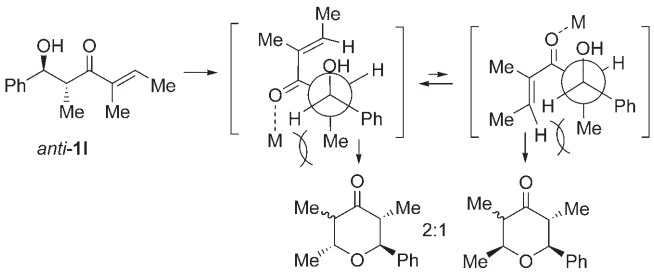
Stereochemical outcome of the nonoxidative ring closures: The overall stereochemical outcome for the intramolecular Michael additions reported herein are the result of two distinct steps, a cyclisation event and a protonolysis which define the stereochemistry at C6 and C5, respectively. The cyclisations initiated with Amberlyst-15 are reversible and susceptible to enolisation. They gave the all-equatorial products after extended reaction times, as anticipated for a thermodynamically controlled reaction. This discussion will hence be solely focused on the kinetically controlled Al- and Pd-mediated cyclisations and will attempt to rationalize the stereochemical outcome of the most successful ring closures. The most distinctive result is the impact of the relative stereochemistry of the starting aldol on the stereochemistry of the cyclisation process catalyzed by $Al(ClO_4)_3 \cdot 9H_2O$ or $[Pd(MeCN)_4](BF_4)_2$. Indeed, we found that the *syn*-aldols led to 2,6-*syn* products with an equatorial substituent at the 6-position. The *anti*-aldols favoured the formation of 2,6-*anti* tetrahydropyranones featuring an *axial* substituent at this same position. For all aldol precursors, the preferential reactive conformation of the enone group is assumed to be s-*trans*, as this conformer enables the electrophilic centre to be proximal to the nucleophile, thereby enabling ring closure.[22] For *syn*-aldol **1k**, activated upon carbonyl complexation by the metal, the major diastereomer results from an attack of the hydroxy group on the Cβ-*Si* face of the enone. The model proposed to account for this result places the methyl and phenyl groups positioned on the stereogenic centres in a preferential staggered gauche or synclinal conformation (Scheme 7). The attack of the hydroxy group on the opposite Cβ-*Re* face generated unfavourable steric interactions between the methyl group positioned α to the carbonyl and the β-hydrogen placed on the terminal double bond carbon. The sense and level of diastereocontrol for the cyclisation event is very similar for *syn*-aldol **1k** featuring an *E*-trisubstituted alkene (Scheme 8). This suggests that the presence of the additional methyl group on the double bond



Scheme 7. Cyclisation of *syn*-aldol **1k**.



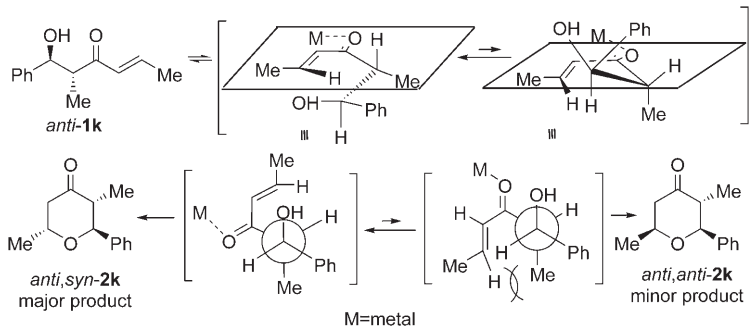
Scheme 8. Cyclisation of *syn*-aldol **1l**.



Scheme 10. Cyclisation of *anti*-aldol **1l**.

has little influence on the stereochemical outcome of the cyclisation. For this substrate, it is likely that the Al- or Pd-based catalyst coordinates to the carbonyl lone pair *anti* to the double bond. The ring closure led to a mixture of three diastereomers in a ratio of 87:10:3, due to additional complications resulting from the directionality of the protonolysis step. The two major diastereomers have their 6-methyl group equatorial but are epimers at C5.

For the *anti*-aldol **1k**, the methyl and phenyl groups placed on the stereogenic centres are also believed to adopt a preferential staggered synclinal conformation, now placing the methyl group axially. Upon cyclisation, the predominant stereoisomer is the result of an attack of the hydroxy group on the Cβ-*Re* face of the enone, as this attack minimizes steric interactions with the methylated stereogenic centre (Scheme 9). This attack leads to the preferential formation



Scheme 9. Cyclisation of *anti*-aldol **1k**.

of tetrahydropyranone *anti*,*syn*-**2k** featuring an axial 6-methyl group. The minor diastereomer resulting from an attack on the opposite face of the enone led to the thermodynamically more stable product with all substituents equatorial. The level of diastereocontrol for the ring closure process drops significantly when an additional methyl group is present on the nonterminal double bond carbon, as illustrated with the cyclisation of aldol *anti*-**1l**. This is likely the result of conflicting steric interactions, that is, whether the attack of the hydroxy group takes place on one or the other face of the enone (Scheme 10). Rigorous theoretical studies are needed to confirm the above proposed models to explain the origin of stereoinduction.

Conclusion

In this report, several issues were under consideration. First was the critical issue as to whether or not an intramolecular Michael addition of β-hydroxyenones was feasible as an entry to the corresponding tetrahydropyranones. Secondly, the possibility of preserving existing stereocentres in the starting enones and controlling simultaneously the diastereoselectivity of the Michael addition had to be determined for the formation of tetrahydropyranones possessing up to four stereocentres. Several catalysts were investigated and this work has clearly identified $Al(ClO_4)_3{\cdot}9H_2O$ and cationic $[Pd(MeCN)_4](BF_4)_2$ as the most effective catalysts for these transformations. They undergo clean ring closure with no detectable side products resulting from dehydration or retroaldolisation. We also found that both catalysts display a similar level and sense of diastereocontrol for the ring closure of both *syn*- and *anti*-aldol precursors. An important difference between the two catalysts is the stereochemical stability of the cyclised product under the reaction conditions: no enolisation occurred for $[Pd(MeCN)_4](BF_4)_2$, but in the presence of $Al(ClO_4)_3{\cdot}9H_2O$ a keto-enolisation process took place. The enolisation led to epimerisation of the centres α to the carbonyl in favour of the thermodynamically more stable product. The data also suggest that when enantiopure aldols are used as precursors for the cyclisation process, no racemisation occurs. The high level diasterocontrol upon ring closure, the mild reaction conditions and the lack of additives and preactivation of the nucleophile are some of the attractive features of the dicationic-palladium-mediated transformation. Two potential mechanisms are outlined, involving either C=O or C=C coordination by the catalyst. A detailed mechanistic investigation remains to be carried out, but the present data have allowed us to hypothesise that carbonyl coordination is likely to take place for the cationic palladium catalyst.

The traditional routes towards trisubstituted THPs, based on HDA, acid-mediated or Prins cyclisations, provide 2,6-*syn*-substituted THP products. The novel palladium(II)-mediated stepwise route reported herein allows for the formation of 2,6-*syn* THPs, when employing *syn*-aldol precursors and of 2,6-*anti* THPs when using *anti*-aldols. Stereochemically stable tetrasubstituted THPs were also formed with high diastereoselectivies when starting from a *syn*-aldol featuring a trisubstituted *E*-alkene functional group.

Experimental Section

General Methods: The infrared spectra were recorded on a Paragon 1000 FTIR spectrometer and only peaks of interest are reported. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DQX400 and DPX400 spectrometers at 400 and 100 MHz, respectively; the chemical shifts are reported in ppm downfield relative to $CDCl_3$ ($\delta = 7.26$ ppm) for ^{1}H spectra and relative to the central $CDCl_3$ ($\delta = 77$ ppm) for ^{13}C NMR spectra. Coupling constants in ^{1}H NMR measurements are in Hz. Mass spectra were recorded on Micromass GCT in Chemical Ionisation (NH_3, CI^+) or on a AutoSpec-oaTof instruments (CI^+). The enantiomeric excess (*ee*) of the products was determined by a Waters HPLC using Chiralcel OD or OJ-H chiral columns with ethanol/hexane as eluent.

Materials: Compounds **1a–b**, **d–f**, **k** and **2b**,**e** have been previously published.[4,9,11,24] The remaining β-hydroxyenones were synthesised according to adapted versions of our previously reported aldol procedures.[9,11] X-ray crystallography data was obtained for compounds **2g** and *anti*,*anti*-**2k**. CCDC-602788 and -602789 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-(4-Bromophenyl)-1-hydroxy-5-methylhex-4-en-3-one (1c): Yellow solid; 73% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.91$ (s, 3H), 2.18 (s, 3H), 2.78 (d, $J = 5.1$ Hz, 2H), 3.88 (d, $J = 3.0$ Hz, 1H), 5.12 (s, 1H), 6.03 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.47 ppm (d, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 27.9 51.9, 69.6, 123.5, 127.4, 128.3, 131.3, 131.5, 142.1, 158.0, 142.0, 157.1, 200.3 ppm; IR (film): $\tilde{\nu} = 1681\,cm^{-1}$.

1-Hydroxy-4-methyl-1-phenyl-hex-4-en-3-one (1g):[23] Colourless oil; 96% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.$ 80 (s, 3H), 1.86 (d, $J = 7.2$ Hz, 3H), 3.04 (d, $J = 8.5$ Hz, 1H), 3.05 (d, $J = 3.7$ Hz, 1H), 5.19 (dd, $J = 8.5$, 3.7 Hz, 1H), 6.76 (q, $J = 6.8$ Hz, 1H), 7.26–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 10.8$, 14.9, 45.8, 70.3, 125.7, 127.5, 128.5, 138.4, 139.2, 143.2, 201.6 ppm; IR (film): $\tilde{\nu} = 1656\,cm^{-1}$.

7-Benzyloxy-6-hydroxy-2,6-dimethylhept-2-en-4-one (1h): Colourless oil; 98% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.26$ (s, 3H), 1.90 (s, 3H), 2.15 (s, 3H), 2.54 (d, $J = 16.4$ Hz, 1H), 2.82 (d, $J = 16.4$ Hz, 1H), 3.35 (d, $J = 9.1$ Hz, 1H), 3.42 (d, $J = 9.1$ Hz, 1H), 4.54 (s, 2H), 7.28–7.37 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 20.9$, 25.2, 27.8, 50.5, 72.0, 73.4, 127.4, 127.6, 128.4, 138.3, 157.0, 201.9 ppm; IR (film): $\tilde{\nu} = 1676$, 1615 cm^{-1}.

1-(1-Hydroxycyclohexyl)-4-pent-3-en-2-one (1i):[4] Colourless oil; 97% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.20$–1.78 (m, 10H), 1.89 (s, 3H), 2.15 (s, 3H), 2.56 (s, 2H), 4.07 (s, 1H), 6.04 ppm (q, $J = 1.26$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 20.9$, 22.0, 25.8, 27.8, 37.7, 52.9, 71.1, 124.8, 157.0, 202.4 ppm; IR (film): $\tilde{\nu} = 1675$, 1614 cm^{-1}; HRMS: *m/z*: calcd for $C_{12}H_{19}O$: 179.1436; found: 179.1429.

7-Hydroxy-9-phenylnon-3-yn-5-one (1j): Colourless oil; 74% yield; ^{1}H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7.4$ Hz, 3H), 1.72 (m, 1H), 1.84 (m, 1H), 2.39 (q, $J = 7.4$ Hz, 2H), 2.67–2.86 (m, 4H), 4.13 (m, 1H), 7.18–7.32 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 12.6$, 12.7, 31.7, 37.9, 52.2, 66.8, 80.3, 96.7, 125.9, 128.4, 128.5, 141.7, 187.7 ppm; IR (film): $\tilde{\nu} = 2210$, 1667, 1603 cm^{-1}; HRMS: *m/z*: calcd for $C_{15}H_{19}O_2$: 231.1385; found: 231.1386.

***syn*-1-Hydroxy-2,4-dimethyl-1-phenylhex-4-en-3-one (*syn*-1l)**: From diisopropylethylamine (1.1 mL, 7.34 mmol), di-*n*-butylborontriflate (5 mL, 5 mmol), (*E*)-4-methylhex-4-en-3-one (0.45 g 4 mmol) and benzaldehyde (1.02 mL, 10 mmol) in anhydrous CH_2Cl_2 (14 mL). Purification by column chromatography (EtOAc/hexane 1:5) gave *syn*-**1l** (0.45 g, 2 mmol) as a colourless oil in 50% yield. *dr* = 99:1; ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ (d, $J = 7.3$ Hz, 3H), 1.78 (s, 3H), 1.88 (d, $J = 6.8$ Hz, 3H), 3.44 (qd, $J = 7.1$, 3.1 Hz, 1H), 3.89 (br s, 1H), 5.05 (d, $J = 3.1$ Hz, 1H), 6.77 (q, $J = 6.8$ Hz, 1H), 7.24–7.37 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 11.0$, 11.5, 15.0, 45.2, 73.4, 126.0, 127.2, 128.1, 137.2, 139.1, 142.0, 207.4 ppm; IR (film): $\tilde{\nu} = 1644\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1313.

***anti*-1-Hydroxy-2,4-dimethyl-1-phenylhex-4-en-3-one (*anti*-1l)**: Colourless oil; 40% yield; *dr* = 9:1; ^{1}H NMR ($CDCl_3$): $\delta = 1.05$ (d, $J = 7.1$ Hz, 3H), 1.82 (s, 3H), 1.91 (d, $J = 6.8$ Hz, 3H), 3.12 (d, $J = 5.0$ Hz, 1H), 3.63 (q, $J = 7.1$ Hz, 1H), 4.91 (dd, $J = 7.3$, 5.0 Hz, 1H), 6.82 (q, $J = 6.8$ Hz, 1H), 7.30–7.42 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 12.2, 16.5, 46.4, 77.1, 126.8, 127.9, 128.6, 138.5, 138.8, 142.8, 206.4 ppm; IR (film): $\tilde{\nu} = 1644\,cm^{-1}$.

***syn*-1-Hydroxy-2,4-dimethyl-1-phenylhept-4-en-3-one (*syn*-1m)**: Colourless oil; 67% yield; *dr* = 99:1; ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ (t, $J = 7.6$ Hz, 3H), 1.08 (d, $J = 7.6$ Hz, 3H), 1.77 (s, 3H), 2.27 (quin, $J = 7.6$ Hz, 2H), 3.45 (qd, $J = 7.1$, 3.0 Hz, 1H), 3.83 (br s, 1H), 5.06 (d, $J = 3.0$ Hz, 1H), 6.62 (t, $J = 7.4$ Hz, 1H), 7.24–7.37 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta =$ 11.2, 11.6, 13.0, 22.6, 45.2, 73.5, 126.0, 127.2, 128.2, 135.6, 142.0, 146.0, 207.7 ppm; IR (film): $\tilde{\nu} = 1652\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1464.

***anti*-1-Hydroxy-2,4-dimethyl-1-phenylhept-4-en-3-one (*anti*-1m)**: Colourless oil; 42% yield; *dr* = 3:1; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (d, $J = 7.3$ Hz, 3H), 1.05 (t, $J = 7.6$ Hz, 3H), 1.77 (s, 3H), 2.24 (quin, $J = 7.4$ Hz, 2H), 3.05 (br s, 1H), 3.59 (quin, $J = 7.2$ Hz, 1H), 4.87 (d, $J = 7.6$ Hz, 1H), 6.60 (t, $J = 7.4$ Hz, 1H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 11.2$, 13.0, 16.4, 22.5, 46.2, 76.8, 126.5, 127.7, 128.4, 136.5, 142.6, 145.6, 206.5 ppm; IR (film): $\tilde{\nu} = 1653\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1463.

Typical procedure for the catalysed intramolecular Michael addition: The substrate dissolved in dry CH_2Cl_2 or MeCN (2 mL mmol^{-1}), respectively, was added to a solution of the catalyst (8 or 10 mol%) in anhydrous CH_2Cl_2 (2 mL mmol^{-1}, for Pd^{II} and Amberlyst-15) or anhydrous MeCN (2 mL mmol^{-1}, for Lewis acids) under an argon atmosphere. The reaction was left to stir until completion at RT, as followed by TLC. The reaction mixture was then diluted with Et_2O and filtered through a pad of silica gel. The solvent was removed in vacuo to give the crude product, which was further purified by column chromatography on silica.

2,2-Dimethyl-6-phenyl-tetrahydropyranone-4-one (2a): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = 1.32$ (s, 3H), 1.48 (s, 3H), 2.39 (dd, $J = 13.6$, 2.0 Hz, 1H), 2.52 (dd, $J = 13.6$, 10.6 Hz, 1H), 2.54–2.60 (m, 2H), 4.91 (dd, $J = 10.6$, 3.5 Hz, 1H), 7.29–7.43 ppm (m, 5H); ^{13}C NMR ($CDCl_3$) $\delta = 24.0$, 31.1, 49.5, 53.2, 73.0, 76.0, 125.8, 128.0, 128.6, 141.4, 207.5 ppm; IR (film): $\tilde{\nu} = 1716\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{13}H_{17}O_2$: 205.1229; found: 205.1233.

6-(4-Bromophenyl)-2,2-dimethyl-tetrahydropyran-4-one (2c): Yellow solid; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (s, 3H), 1.47 (s, 3H), 2.42 (m, 2H), 2.54 (d, $J = 14.2$ Hz, 2H), 4.87 (dd, $J = 11.4$, 3.0 Hz, 1H), 7.28 (d, $J = 8.6$ Hz, 2H), 7.51 ppm (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 24.0$, 31.0, 49.3, 53.0, 72.3, 75.8, 121.7, 127.5, 131.7, 140.4, 206.9 ppm; IR (film): $\tilde{\nu} =$ 1717 cm^{-1}; HRMS: *m/z*: calcd for $C_{13}H_{19}NO_2Br$: 300.0599; found: 300.0542.

2-Methyl-6-phenylethyl-tetrahydropyran-4-one (2d):[24] *syn*-**2d**: ^{1}H NMR ($CDCl_3$): $\delta = 1.37$ (d, $J = 5.8$ Hz, 3H), 1.81 (dddd, $J = 13.7$, 9.2, 7.5, 4.4 Hz, 1H), 2.14 (dtd, $J = 13.9$, 8.8, 5.4 Hz, 1H), 2.20–2.40 (m, 4H), 2.74 (ddd, $J = 14.1$, 8.8, 7.5 Hz, 1H), 2.83 (ddd, $J = 14.0$, 8.2, 5.2 Hz, 1H), 3.52–3.59 (m, 1H), 3.71 (dqd, $J = 12.1$, 5.8, 2.5 Hz, 1H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 22.1$, 31.5, 37.9, 47.5, 49.4, 73.1, 75.8, 126.0, 128.4, 128.5, 141.5, 207.4 ppm; *anti*-**2d**: ^{1}H NMR ($CDCl_3$): $\delta = 1.28$ (d, $J =$ 6.4 Hz, 3H), 1.74 (dddd, $J = 13.9$, 9.2, 7.2, 4.4 Hz, 1H), 1.99 (dtd, $J = 13.9$, 9.2, 5.4 Hz, 1H), 2.23–2.31 (m, 2H), 2.52–2.59 (m, 2H), 2.68 (ddd, $J =$ 14.1, 8.8, 7.5 Hz, 1H), 2.74 (ddd, $J = 14.0$, 8.2, 5.2 Hz, 1H), 4.12 (dtd, $J =$ 14.0, 4.7, 1.3 Hz, 1H), 4.32 (dqd, $J = 11.3$, 6.5, 1.3 Hz, 1H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 20.7$, 31.6, 35.9, 46.9, 48.4, 68.2, 71.1,

126.0, 128.4, 128.5, 141.3, 207.5 ppm; IR (film): $\tilde{\nu}=1723\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{14}H_{19}O_2$: 219.1385; found: 219.1385.

5-Methyl-2-phenylethyl-tetrahydropyran-4-one (2f): Colourless oil; 58% yield; *dr* = 1:1; ^{1}H NMR ($CDCl_3$): $\delta=0.97$ (d, $J=6.8$ Hz, 3H), 1.78–2.04 (m, 2H), 2.36–2.40 (m, 4H), 2.63 (m, 1H), 2.72 (ddd, $J=14.0$, 6.8, 2.0 Hz, 1H), 2.81 (ddd, $J=14.1$, 9.3, 5.1 Hz, 1H), 3.26 (dd, $J=11.4$ Hz, 1H), 3.53–3.60 (m, 1H), 4.24 (dd, $J=11.4$, 7.0 Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=8.9$, 31.7, 38.0, 45.4, 48.2, 73.1, 78.1, 126.0, 128.3, 128.4, 141.4, 208.4 ppm; IR (film[1]): $\tilde{\nu}=1715\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{14}H_{22}NO_2$: 236.1651; found: 236.1648.

***syn*,*anti*-2,3-Dimehthyl-6-methyl-tetrahydropyran-4-one (2g)**: Colourless oil, ^{1}H NMR ($CDCl_3$): $\delta=1.07$ (d, $J=6.5$ Hz, 3H), 1.46 (d, $J=6.0$ Hz, 3H), 4.68 (t, $J=7.2$ Hz, 1H), 7.30–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=9.5$, 20.6, 49.7, 51.7, 79.0, 79.5, 125.7, 128.0, 128.6, 140.9, 208.3 ppm; IR (film): $\tilde{\nu}=1715\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{13}H_{17}O_2$: 205.1229; found: 205.1230.

2-(Benzyloxymethyl)-2,6,6-trimethyl-tetrahydropyran-4-one (2h): Colourless oil, 55% yield; ^{1}H NMR ($CDCl_3$): $\delta=1.28$ (s, 3H), 1.32 (s, 3H), 1.33 (s, 3H), 2.38 (d, $J=16.2$ Hz, 1H), 2.39 (d, $J=16.4$ Hz, 1H), 2.52 (d, $J=16.2$ Hz, 1H), 2.70 (d, $J=16.4$ Hz, 1H), 3.26 (d, $J=9.3$ Hz, 1H), 3.39 (d, $J=9.3$ Hz, 1H), 4.54 (d, $J=12.1$ Hz, 1H), 4.60 (d, $J=12.1$ Hz, 1H), 7.28–7.37 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=27.0$, 30.5, 31.6, 46.4, 51.3, 73.4, 74.5, 76.2, 78.2, 127.4, 127.6, 128.4, 138.2, 208.4 ppm; IR (film): $\tilde{\nu}=1718\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{16}H_{23}O_3$: 263.1647; found: 263.1649.

2,2-Dimethyl-1-oxa-spiro[5.5]undecan-4-one (2i): Yellow oil; 54% yield; ^{1}H NMR ($CDCl_3$): $\delta=1.31$ (s, 6H), 1.32–1.49 (m, 6H), 1.66–1.74 (m, 4H), 2.42 (s, 2H), 2.43 ppm (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta=22.4$, 25.4, 31.5, 39.9, 49.8, 51.9, 74.6, 76.1, 209.0 ppm; IR (film): $\tilde{\nu}=1720\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{12}H_{21}O_2$: 197.1542; found: 197.1536.

6-Ethyl-2-phenylethyl-2,3-dihydropyran-4-one (2j):[11] Pale yellow oil; 60% yield; ^{1}H NMR ($CDCl_3$): $\delta=1.26$ (t, $J=7.6$ Hz, 3H), 1.95 (m, 1H), 2.17 (m, 1H), 2.31 (q, $J=7.6$ Hz, 2H), 2.38 (dd, $J=16.7$, 4.0 Hz, 1H), 2.47 (dd, $J=16.9$, 12.8 Hz, 1H), 2.80 (m, 2H), 4.34 (ddd, $J=12.8$, 8.3, 4.0 Hz, 1H) 5.34 (s, 1H), 7.19–7.35 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=$ 10.6, 28.0, 31.1, 36.0, 41.0, 78.0, 103.2, 126.2, 128.4, 128.6, 140.8, 178.8, 193.0 ppm; IR (film): $\tilde{\nu}=1666\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{15}H_{19}O_2$: 231.1385; found: 231.1392.

***syn*,*syn*-3,6-Dimethyl-2-phenyl-tetrahydropyran-4-one (*syn*,*syn*-2k)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.91$ (d, $J=7.3$ Hz, 3H), 1.45 (d, $J=$ 6.0 Hz, 3H), 2.33 (dd, $J=14.4$, 2.8 Hz, 1H), 2.55 (dd, $J=14.6$, 11.4 Hz, 1H), 2.66 (qdd, $J=7.1$, 2.7, 1.3 Hz, 1H), 3.91 (dqd, $J=11.6$, 6.0, 2.8 Hz, 1H), 4.83 (d, $J=2.7$ Hz, 1H), 7.25–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=11.3$, 22.1, 45.5, 50.7, 73.7, 80.0, 125.5, 127.3, 128.3, 138.7, 211.5 ppm; IR (film): $\tilde{\nu}=1715\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{13}H_{17}O_2$: 205.1229; found 205.1233. Use of (+)-IPc_2BCl gave (2*R*,3*R*,6*R*)-**2k** with *dr* = 99:1 and *ee* = 94%.

***anti*,*anti*-3,6-Dimethyl-2-phenyl-tetrahydropyran-4-one (*anti,anti*-2k)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.81$ (dd, $J=6.6$, 1.5 Hz, 3H), 1.39 (dd, $J=6.3$, 1.7 Hz, 3H), 2.50–2.53 (m, 2H), 2.63 (dq, $J=10.4$, 6.6 Hz, 1H), 3.93 (ddd, $J=14.1$, 11.9, 6.0 Hz, 1H), 4.18 (dd, $J=10.4$, 1.7 Hz, 1H), 7.31–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=9.4$, 22.3, 49.8, 51.2, 74.2, 85.9, 127.2, 128.4, 128.6, 139.8, 208.3 ppm; IR (film): $\tilde{\nu}=1715\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{13}H_{17}O_2$: 205.1229; found: 205.1228.

***anti*,*syn*-3,6-Dimethyl-2-phenyl-tetrahydropyran-4-one (*anti*,*syn*-2k)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.94$ (d, $J=6.8$ Hz, 3H), 1.32 (d, $J=$ 6.6 Hz, 3H), 2.41 (dd, $J=13.9$, 3.5 Hz, 1H), 2.77 (dq, $J=8.8$, 6.8 Hz, 1H), 2.88 (dd, $J=13.9$, 6.1 Hz, 1H), 4.57 (d, $J=8.6$ Hz, 1H), 4.57 (m, 1H), 7.31–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=10.9$, 19.3, 47.1, 50.7, 70.4, 79.7, 127.3, 128.3, 128.6, 137.0, 211.0 ppm; IR (film): $\tilde{\nu}=1716\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{13}H_{17}O_2$: 205.1229; found: 205.1229.

***syn*,*anti*,*anti*-3,5,6-Trimethyl-2-phenyl-tetrahydropyran-4-one (*syn*,*anti*,*anti*-2l)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.93$ (d, $J=7.1$ Hz, 3H), 1.06 (d, $J=6.8$ Hz, 3H), 1.48 (d, $J=6.1$ Hz, 3H), 2.55 (dq, $J=10.1$, 6.6 Hz, 1H), 2.71 (qd, $J=7.1$, 2.2 Hz, 1H), 3.51 (dq, $J=10.4$, 6.1 Hz, 1H), 4.83 (d, $J=2.8$ Hz, 1H), 7.25–7.45 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=$ 9.5, 11.5, 20.6, 47.2, 51.0, 79.5, 80.1, 125.4, 127.2, 128.2, 129.7, 138.8, 212.8 ppm; IR (film) $\tilde{\nu}=1714\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{14}H_{19}O_2$: 219.1385; found: 219.1388.

***anti*,*syn*,*anti*-2-Phenyl-3,5,6-trimethyl-tetrahydropyran-4-one (*anti*,*syn*, *anti*-2l)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.80$ (d, $J=6.6$ Hz, 3H), 1.07 (d, $J=6.6$ Hz, 3H), 1.41 (d, $J=6.0$ Hz, 3H), 2.50 (dq, $J=10.0$, 6.6 Hz, 1H), 2.71 (dq, $J=10.4$, 6.6 Hz, 1H), 3.51 (dq, $J=10.1$, 6.0 Hz, 1H), 4.17 (d, $J=10.4$ Hz, 1H), 7.30–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=9.7$, 9.8, 20.7, 51.0, 51.9, 80.0, 86.1, 127.2, 128.3, 128.6, 139.9, 209.7 ppm; IR (film): $\tilde{\nu}=1713\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{14}H_{19}O_2$: 219.1385; found: 219.1389.

(±)-*syn*,*anti*,*anti*-3,5-Dimethyl-6-ethyl-2-phenyl-tetrahydropyran-4-one (*syn*,*anti*,*anti*-2m): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.91$ (d, $J=$ 7.3 Hz, 3H), 1.04 (d, $J=6.6$ Hz, 3H), 1.13 (t, $J=7.6$ Hz, 3H), 1.70 (qd, $J=7.3$, 7.0 Hz, 1H), 1.91 (qd, $J=7.3$, 3.0 Hz, 1H), 2.65 (dq, $J=10.3$, 6.5 Hz, 1H), 2.74 (qd, $J=7.3$, 2.8 Hz, 1H), 3.34 (ddd, $J=10.3$, 7.0, 3.0 Hz, 1H), 4.80 (d, $J=2.8$ Hz, 1H), 7.26–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=9.3$, 9.4, 11.5, 26.9, 44.8, 51.0, 79.8, 83.8, 125.4, 127.1, 128.2, 139.2, 213.4 ppm; IR (film): $\tilde{\nu}=1714\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{15}H_{21}O_2$: 233.1542; found: 233.1601.

***anti*,*syn*,*anti*-3,5-Dimethyl-6-ethyl-2-phenyl-tetrahydropyran-4-one (*anti*, *syn*,*anti*-2m)**: Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.81$ (d, $J=6.8$ Hz, 3H), 1.02 (t, $J=7.3$ Hz, 3H), 1.04 (d, $J=6.6$ Hz, 3H), 1.64 (qd, $J=7.3$, 7.0 Hz, 1H), 1.85 (qd, $J=7.3$, 3.0 Hz, 1H), 2.59–2.70 (m, 2H), 3.37 (ddd, $J=10.1$, 6.8, 3.0 Hz, 1H), 4.15 (d, $J=10.1$ Hz, 1H), 7.31–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=8.8$, 9.3, 9.8, 26.5, 49.2, 51.6, 84.0, 86.0, 127.1, 128.2, 128.4, 140.2, 210.3 ppm; IR (film): $\tilde{\nu}=1713\,cm^{-1}$; HRMS: *m/z*: calcd for $C_{15}H_{21}O_2$: 233.1542; found: 233.1601.

***(2R,3R,6R)*-3,6-Dimethyl-2-phenyl-tetrahydropyran-4-one ((2*R*,3*R*,6*R*)-2k)**: From (2*R*,3*R*)-**2k** and $[Pd(MeCN)_4](BF_4)_2$ (6 mol%) in CH_2Cl_2. Colourless oil; 15% yield (2 steps); *dr* = 9:1 and *ee* = 94%, as assigned by chiral HPLC with $[\alpha]_D^{25}=+27.1$ (*c* = 1.02 in CH_2Cl_2).

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