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A New Method for Constructing Quaternary Carbon Centres: Tandem Rhodium-Catalysed 1,4-Addition/Intramolecular Cyclisation

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Abstract: The efficient tandem rhodium-catalysed 1,4-addition/cyclisation of 1,1′-alkenes using arylzinc chlorides is described. The simple one-step synthesis of substituted cyclopentanone and cyclohexanone derivatives is performed from acyclic precursors using relatively low catalyst loadings under mild conditions. A new quaternary carbon centre is created during the cyclisation step.

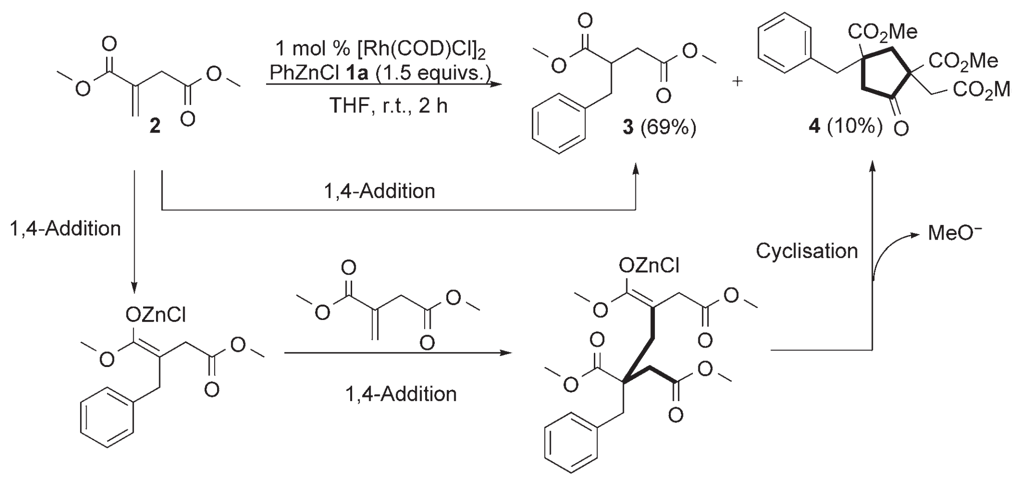
Keywords: alkenes; C–C coupling; conjugate addition; cyclisation; rhodium; zinc

Introduction

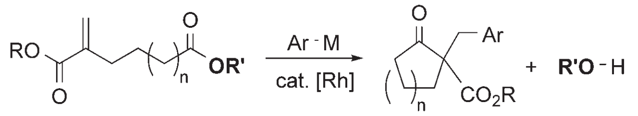
The possibility of combining two or more transformations in a single one-pot reaction has always been of great interest in organic synthesis.[1] Tandem reactions including catalytic processes have become an important methodology for the formation of new chemical bonds in a very efficient way.[2] In recent years, considerable efforts have been made to use a conjugate addition as the initial step of tandem processes.[3] Stoichiometric reactions involving organolithium addition to α,β-unsaturated ketones or esters have been widely used and their association with subsequent intramolecular cyclisation reactions allowed the formation of cyclic products in high yields and good stereoselectivity.[4] Metal-catalysed 1,4-additions have also been used in tandem reactions and combined with different transformations such as electrophilic trapping[5,6] including halogenation,[7] aldol reactions,[8] cyclopropanation,[9] and cyclisation reactions.[10] Conjugate addition reactions allow the addition of different organometallic sources (organoboron, organozinc, organosilane, organoindium, organotitanium, organobismuth,…) using different catalytic species based on rhodium, copper, or palladium and chiral ligands.[11] In the past decade particular attention has been focussed on the rhodium-catalysed 1,4-addition of organoboron derivatives,[11c–e,g,h] and in previous studies, we and others have shown that this reaction can be applied to less reactive substrates such as 1,1′-alkenes, which allows the preparation of 2-alkylsuccinates or α- and β-amino acid compounds[5,6b] and that water can be used as the reaction solvent.[12]

Among the organometallic species used in 1,4-addition reactions, arylzinc chloride derivatives have been relatively rarely employed.[13] However, they present the advantages of an easy preparation from the corresponding aryl halide compound and, thus, access to a wide range of substituted aryl fragments suitable for 1,4-addition reaction. They also possess improved activity in the transmetallation step compared to arylboronic acids in rhodium-catalysed conjugate addition, which allows room temperature reaction conditions. Indeed, in the 1,4-addition of phenylzinc chloride **1a** to dimethyl itaconate **2** using 1 mol% of [Rh(COD)Cl]$_2$, a complete conversion is obtained after stirring for 2 h at room temperature compared with a reaction temperature of 100 °C with phenylboronic acid (Scheme 1). However, in the addition of phenylzinc chloride the 1,4-addition product **3** was isolated in only 69% yield alongside the cyclic compound **4** which was isolated as a minor product in 10% yield. The formation of the cyclopentanone **4** was obtained *via* a consecutive double 1,4-addition/cyclisation process of dimethyl itaconate **2**.

Interestingly, the introduction of chlorotrimethylsilane (1.5 equivalents) in the reaction mixture suppresses the second conjugate addition by forming a more stable enolate than the initial zinc enolate. Thus, side reactions and complex crude reaction mixtures are avoided and the corresponding 1,4-addition



Scheme 1. 1,4-Addition of phenylzinc chloride **1a** to dimethyl itaconate **2** without chlorotrimethylsilane.



Scheme 2. Tandem 1,4-addition/intramolecular cyclisation of aryl organometallic to 1,1′-alkenes.

product **3** was obtained in 94% yield after purification.

The formation of the highly-functionalised cyclopentanone derivative **4** led us to believe that the 1,4-addition of organometallic derivatives to 1,1′-alkenes could be followed with an intramolecular cyclisation of the intermediate enolate to a terminal ester group in a one-pot process. The construction of quaternary stereocentres within the framework of a complex organic molecule remains a significant challenge for organic chemistry.[14] The tandem transformation shown in Scheme 2 leads to the formation of cyclic ketones and a new quaternary carbon centre is created during the cyclisation step.

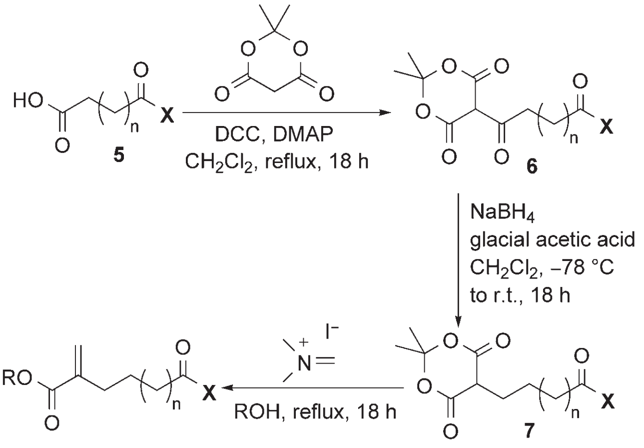
This type of tandem 1,4-addition/cyclisation reactions are known in the literature but involve the use of alkylzinc or boronic acid derivatives as nucleophiles and the subsequent cyclisation occurred *via* the reaction of the intermediate enolate with an aldehyde or a ketone, or addition to another enone fragment.[10] The conjugate addition of an alkylzinc reagent followed by cyclisation reaction onto an ester group has been reported but in a two-step synthesis including the introduction of new reagents.[15]

For that purpose we considered the design of 1,1′-alkene substrates presenting an ester group at the end of an elongated alkyl chain allowing an intramolecular cyclisation of the intermediate enolate prepared *in situ* by the 1,4-addition of an aryl organometallic fragment.

Results and Discussion

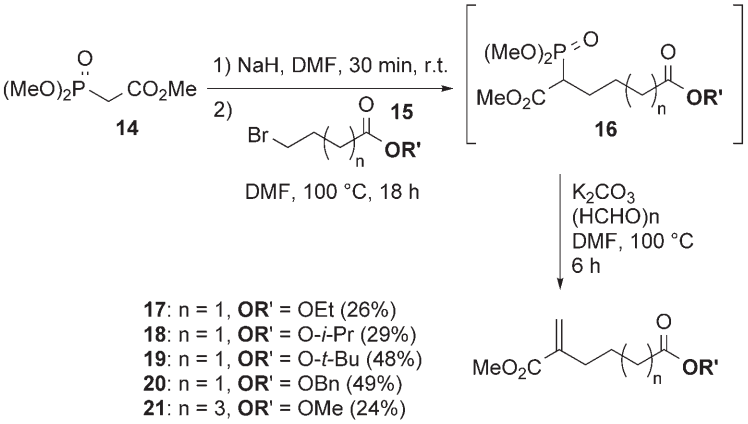
Synthesis of 1,1′-Alkene Substrates

Two methods were investigated for the preparation of 1,1′-alkenes possessing an extended alkyl chain with a terminal ester group. Method **A**, which involves a four-step process, was chosen for its versatility concerning the variation of the nature of the ester group (R) on the acrylate side of the 1,1′-alkene (Scheme 3).[16] Alternatively, method **B** offered a simple two-step synthesis and an easy tuning of the length of the alkyl chain and the nature of the terminal ester (**OR′**) (Scheme 4).[17]



8: n = 0, R = Me, **X** = OMe (42%).
9: n = 1, R = Me, **X** = OMe (50%);
10: n = 1, R = *t*-Bu, **X** = OMe (43%);
11: n = 1, R = Me, **X** = pyrrolidyl (59%).
12: n = 2, R = Me, **X** = OMe (38%);
13: n = 2, R = *t*-Bu, **X** = OMe (36%).

Scheme 3. General procedure for the synthesis of 1,1′-alkenes **8**–**13** following the method **A**.



Scheme 4. General procedure for the synthesis of 1,1′-alkenes **17**–**21** following the method **B**.

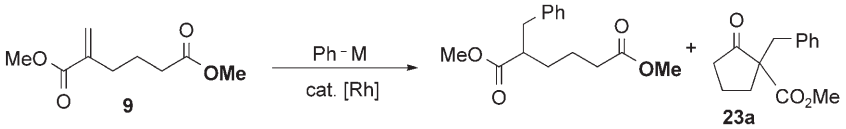
The monoester or monoamide **5** was prepared either from the corresponding diacid or the cyclic anhydride and was then coupled with Meldrum's acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane. The resulting ketone **6** was reduced with sodium borohydride in dichloromethane to give compound **7** and finally the methylenation reaction using Eschenmoser's salt afforded the corresponding 1,1′-alkenes (**8** to **13**), after purification, in good yields over the four steps.

The 1,1′-alkenes **17**–**21** were prepared following a literature procedure in a one-pot two-step reaction starting from trimethyl phosphonoacetate **14**.[17] Unless commercially available, bromo ester compounds **15** were prepared by esterification of the corresponding carboxylic acid using standard methods.[18] Deprotonation with sodium hydride in *N,N*-dimethylformamide followed by the addition of the desired bromo compound led to the formation of the intermediate **16** after 16 h heating at 100 °C. The methylenation step was performed by addition of potassium carbonate and paraformaldehyde to the crude mixture and a further six hours heating at 100 °C afforded the corresponding 1,1′-alkene derivatives **17**–**21** in modest yields after purification (Scheme 4).

Tandem 1,4-Addition/Cyclisation Reactions

Our initial studies examined the preparation of cyclopentanone **23a** from the 1,1′-alkene **9** using different conditions (**A**–**C**) as described in Table 1. The addition of phenylboronic acid using conditions **A** resulted in complete conversion to the 1,4-addition/protonation product, none of the desired cyclopentanone **23a** was obtained (Table 1, Entry 1). This result indicates that protonation of the intermediate enolate is faster than cyclisation onto the ester when water is present in excess (co-solvent). Performing the reac-

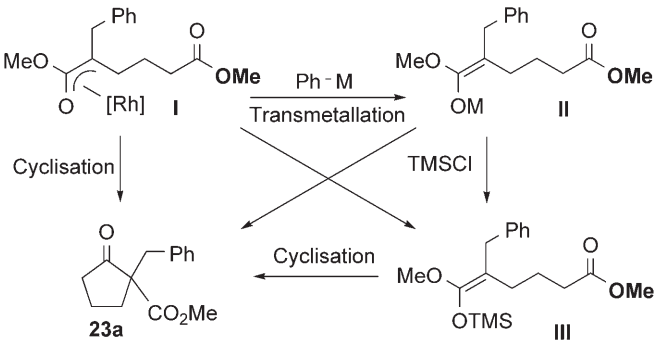
Table 1. Comparison of different protocols for tandem 1,4-addition/cyclisation.



Entry	Organometallic	Conditions[a]	Time [h]	Conversion[b] [%] 1,4-Addition/protonation	 1,4-Addition/cyclisation
1	$PhB(OH)_2$	**A**	20	100	0
2	$PhB(OH)_2$	**B**	20	48	52
3	PhZnCl	**C**	18	0	100
4	PhZnCl	**C**	0.15	13	57
5	PhZnCl	**C**	0.5	18	57
6	PhZnCl	**C**	1	12	73
7	PhZnCl	**C**	2	12	77

[a] *Reaction conditions:* **A** $[Rh(COD)_2][SbF_6]$ (4 mol%), THF/H_2O (10/1), 80 °C; **B** $[Rh(COD)_2][SbF_6]$ (4 mol%), KOH (8 mol%), THF, 80 °C; **C** $[Rh(COD)Cl]_2$ (1 mol%), TMSCl, THF, room temperature.

[b] Determined by ^1H NMR.



Scheme 5. Possible modes of cyclisation.

tion in the absence of water results in low conversions as the catalyst is unable to turnover. However, the addition of potassium hydroxide restores the activity of the catalyst (conditions **B**) and results in complete conversion to a mixture of the 1,4-addition/protonation product and the desired cyclopentanone **23a** (Table 1, Entry 2). In this case, the 1,4-addition/protonation product is likely to arise by a competitive protonation of the intermediate enolate with boric acid (the side product from transmetallation with boronic acids). Using conditions **C** (previously described in Scheme 2 for the addition of phenylzinc chloride **1a** to dimethyl itaconate), a complete conversion into the cyclopentanone **23a** was obtained after 18 h stirring at room temperature (Table 1, Entry 3). No 1,4-addition/protonation product or double 1,4-addition product was observed in the crude reaction mixture indicating that all the intermediate enolate had been consumed in the intramolecular cyclisation process.

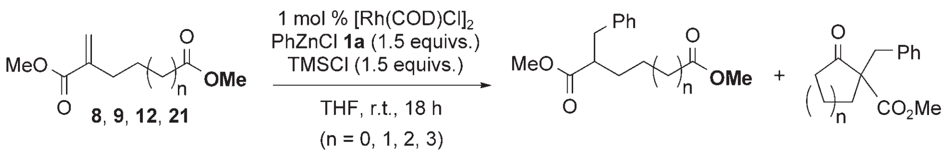
In a separate experiment, the addition of phenylzinc chloride **1a** to 1,1′-alkene **9** using conditions **C** was repeated to follow the product distribution as a function of time. Remarkably, after quenching an aliquot at eight minutes the conversion was 70% and the major product was the cyclopentanone **23a** (Table 1, entry 4). Over the following two hours the reaction proceeds to 90% conversion with a consistent amount of the 1,4-addition/protonation product appearing upon quenching (Table 1, entries 5–7).

The formation of the cyclopentanone **23a** by the 1,4-addition of phenylboronic acid (Table 1, entry 2) suggests that the intramolecular cyclisation can occur *via* the intermediate rhodium enolate species **I** (Scheme 5). This is further supported by the observation that treating a phenyl-rhodium complex (formed by the addition of phenyllithium to $[Rh(COD)Cl]_2$) with one equivalent of 1,1′-alkene **9** in anhydrous THF furnishes the cyclopentanone **23a** as the exclusive product. In the 1,4-addition of phenylzinc chloride **1a**, the intramolecular cyclisation could occur rapidly *via* the intermediate rhodium enolate species **I** or the zinc enolate species **II** (M = ZnCl), formed by a subsequent transmetallation (Scheme 5). In the absence of chlorotrimethylsilane, the cyclopentanone **23a** is observed as the major product but the isolated yields are lower and the ^{1}H NMR of the reaction suggests the formation of side-products. The trapping of either **I** or **II** (prior to cyclisation) with chlorotrimethylsilane affords the enolsilane **III**, and the kinetic experiments suggest that the cyclisation of this species is much slower (observed in ^{1}H NMR). Nevertheless, the reactions proceed to complete conversion. It is possible the presence of zinc chloride in the reaction media facilitates the cyclization of **III** by Lewis acid activation of the carbonyl function of the terminal ester group.

Formation of Different Ring Sizes

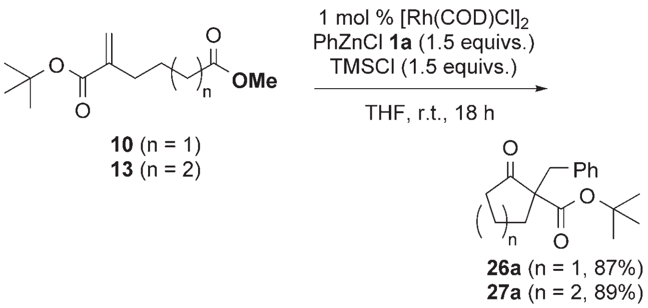
The tandem 1,4-addition/cyclisation of phenyl zinc chloride **1a** was then applied to 1,1′-alkenes presenting the same terminal methyl ester group but possessing different alkyl chain lengths allowing the potential formation of cyclic ketones with 4-, 5-, 6-, or 7-membered rings, respectively (Table 2).

Table 2. Formation of different ring sizes.[a]



Entry	1,1′-Alkene	n	Conversion[b] [%]	
			1,4-Addition/protonation	1,4-Addition/cyclisation
1	**8**	0	100 (**22a**, 93[c])	0
2	**9**	1	0	100 (**23a**, 77[c])
3	**12**	2	0	100 (**24a**, 87[c])
4	**21**	3	100 (**25a**, 90[c])	0

[a] *Reaction conditions:* **C** $[Rh(COD)Cl]_2$ (1 mol%), TMSCl, THF, room temperature.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.



Scheme 6. Tandem 1,4-addition/cyclisation reaction of *tert*-butyl acrylate ester 1,1′-alkene **10** and **13**.

No cyclic product formation was observed during the reaction using the 1,1′-alkene **8** (Table 2, entry 1). It appears that the formation of 4-membered ring ($n=0$) was not possible even by heating the reaction mixture or tuning its concentration, and in each case only the 1,4-addition/protonation product **22a** was obtained and isolated in 93% yield. Applying the same reaction conditions to 1,1′-alkene **12**, a complete conversion to cyclohexanone **24a** ($n=2$) was observed without any traces of the 1,4-addition/protonation product (Table 2, entry 3). Thus, the formation of 6-membered rings can be performed in good yield (87%) and in the same range of activity as for 5-membered ring synthesis (Table 2, entry 2). Using the 1,1′-alkene **21**, no 7-membered ring formation was observed despite the complete conversion of the substrate (Table 2, entry 4). The tuning of the reaction conditions did not improve the selectivity and the 1,4-addition/protonation product **23a** was obtained in 90% yield after column chromatography.

Cyclopentanone and Cyclohexanone Synthesis

The rhodium-catalysed addition of phenylzinc chloride **1a** to the 1,1′-alkenes **9** and **12** allows the preparation of substituted cyclopentanone **23a** and cyclohexanone **24a** in high yield (Table 2, entries 2 and 3). Two analogues **10** and **13** presenting a bulky ester group on the acrylate side of the substrate were prepared following the procedure **A** (Scheme 3) and were submitted to the standard reaction conditions of the tandem 1,4-addition/cyclisation reaction (Scheme 6).

In both cases the presence of a *tert*-butyl group on the acrylate ester of the substrate did not hinder either the 1,4-addition or the cyclisation step. Indeed, the addition of phenylzinc chloride **1a** followed by the intramolecular cyclisation of the intermediate enolate reached completion and the corresponding cyclopentanone **26a** and cyclohexanone **27a** were obtained in 87% and 89% yield, respectively.

To demonstrate the scope of the process, a variety of arylzinc chloride derivatives were prepared from their corresponding aryl halides (or directed lithiation) and these organozinc chloride compounds were then used in the tandem 1,4-addition/cyclisation reaction on 1,1′-alkenes presenting at the same time a methyl or a *tert*-butyl group as their acrylate ester, and possessing different alkyl chain lengths to obtain 5- and 6-membered ring ketones (Table 3).

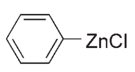
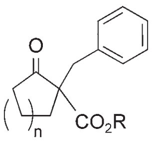
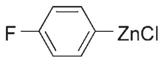
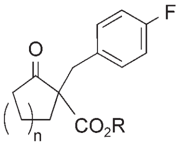
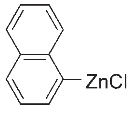
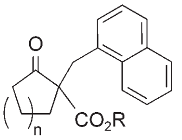
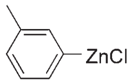
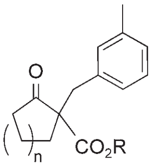
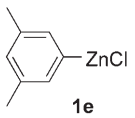
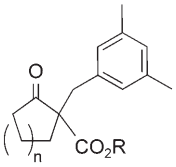
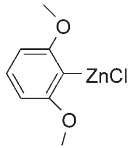
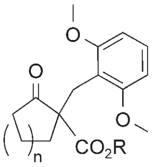
With either the methyl or the *tert*-butyl ester group, a range of cyclopentanones with different aryl groups was obtained in high yields after purification ($n=1$, 75% to 92% yield). The formation of substituted cyclohexanones occurred in the same range of activity and in good yields ($n=2$, 62% to 93% yield). A high level of steric tolerance is apparent in the reaction as evidenced by the efficient 1,4-addition/cyclisation with the *ortho*-disubstituted arylzinc reagent **1f** (Table 3, entry 6, product **23f**). Thus, a useful variety of substituted cyclopentanone and cyclohexanone products was prepared under mild conditions in high yield by changing the nature of the aromatic group of the arylzinc chloride nucleophiles.

Effect of the Nature of the Terminal Ester Group

Finally we investigated the versatility of our catalytic 1,4-addition/cyclisation procedure by using a variety of 1,1′-alkenes with different terminal ester/amide groups (compounds **9**, **17**–**20**, Scheme 4; compound **11**, Scheme 3). Thus, the efficiency of the intramolecular cyclisation of the intermediate enolate would be tested. The substrates were employed in the standard reaction conditions using phenyl zinc chloride **1a** as the organometallic nucleophile (Table 4).

Interestingly, the presence of a benzyl group on the terminal ester did not hinder the cyclisation step and a complete conversion into the cyclopentanone **23a** was observed after 18 h at room temperature using the 1,1′-alkene **20** (Table 4, entry 1). A similar observation was made with an ethoxy fragment as leaving group, the cyclopentanone **23a** was isolated in 87% yield with no 1,4-addition product being observed in the reaction mixture (Table 4, entry 3). Moving from ethyl to isopropyl, the conversion was complete but a mixture of 1,4-addition product **28** and cyclopentanone **23a** was observed, with the cyclisation product observed as the major product (80%) (Table 4, entry 4). However, this ratio was reversed by the use of a terminal *tert*-butyl group (Table 4, entry 5). Indeed, 10% conversion into the cyclopentanone **23a** was observed and 1,4-addition product **29** was obtained in 88% yield after purification. Finally, the cyclisation reaction was completely shut down by the introduction of an amide group at the end of the alkyl chain. In this case, the corresponding 1,4-addition

Table 3. Synthesis of substituted cyclopentanones and cyclohexanones.[a]

Entry	Alkene	ArZnCl[b]	Cyclic Products	n	R	Products (Yield) [%]
1	**9** **10** **12** **13**	 **1a**		1 2 	Me *t*-Bu Me *t*-Bu	**23a** (77) **26a** (87) **24a** (87) **27a** (89)
2	**9** **10** **12** **13**	 **1b**		1 2 	Me *t*-Bu Me *t*-Bu	**23b** (90) **26b** (82) **24b** (74) **27b** (62)
3	**9** **10** **12** **13**	 **1c**		1 2 	Me *t*-Bu Me *t*-Bu	**23c** (87) **26c** (82) **24c** (93) **27c** (63)
4	**9** **10**	 **1d**		1	Me *t*-Bu	**23d** (92) **26d** (89)
5	**9** **10**	 **1e**		1	Me *t*-Bu	**23e** (85) **26e** (79)
6	**9**	 **1f**		1	Me	**23f** (75)

[a] *Reaction conditions:* alkene (0.5 mmol), $[Rh(COD)Cl]_2$ (1 mol%), arylzinc chloride (0.75 mmol), chlorotrimethylsilane (0.75 mmol), tetrahydrofuran (1 mL), 18 h, room temperature.

[b] Prepared from the corresponding aryl halide or in the case of **1f** by directed lithiation (see Experimental Section).

product **30** was isolated in 90% yield after chromatography (Table 4, entry 6).

Conclusions

The above results show that aryl zinc chloride derivatives are useful reagents for the tandem rhodium-catalysed 1,4-addition/cyclisation reaction of 1,1′-alkenes presenting an extended alkyl chain with a terminal ester group. This transformation leads to the facile preparation of substituted cyclopentanones and cyclohexanones with adjacent quaternary carbon centres under mild conditions and in high yields from acyclic precursors. The high reactivity of the system allows the use of bulky aryl nucleophiles and the cyclisation step can occur on different ester group such as methyl, ethyl or benzyl. The selectivity of the tandem reaction can be tuned by employing a terminal amide function on the alkyl chain of the 1,1′-alkene, which inhibits any cyclisation and leads exclusively to the 1,4-addition product.

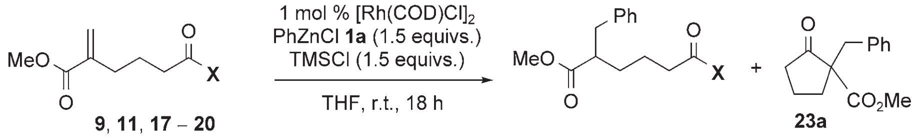
Studies on the application of this tandem 1,4-addition/cyclisation of aryl zinc chlorides in total synthesis are currently under investigation, as is its potential transposition into an asymmetric process by the mean of chiral catalyst or chiral auxiliaries.

Experimental Section

General Remarks

All reactions were performed under nitrogen atmosphere in pre-dried glassware. All solvents were purified by passing through a neutral alumina column under argon (Pure-Solv™

Table 4. Effect of the nature of the terminal ester group in the tandem 1,4-addition/cyclisation reaction.[a]



Entry	1,1′-Alkene	X	Conversion[b] [%]	
			1,4-Addition/protonation	1,4-Addition/cyclisation
1	**20**	OBn	0	100 (**23a**, 83[c])
2	**9**	OMe	0	100 (**23a**, 77[c])
3	**17**	OEt	0	100 (**23a**, 87[c])
4	**18**	O-*i*-Pr	20 (**28**[d])	80
5	**19**	O-*t*-Bu	90 (**29**, 88[c])	10
6	**11**	pyrrolidine	100 (**30**, 90[c])	0

[a] *Reaction conditions:* alkene (0.5 mmol), $[Rh(COD)Cl]_2$ (1 mol%), phenylzinc chloride (0.75 mmol), chlorotrimethylsilane (0.75 mmol), tetrahydrofuran (1 mL), 18 h, room temperature.

[b] Determined by ^{1}H NMR.

[c] Isolated Yield.

[d] The 1,4-addition product **28** cannot be separated from the cyclopentanone **23a** by chromatography.

by Innovative Technology). All chemicals were purchased from Fisher Scientific (Acros), Lancaster or Aldrich and used as received. $[Rh(COD)Cl]_2$ was synthesised following the literature procedure.[19] Flash chromatography was carried out using Fisher silica 60 A (35–70 micron). TLC was performed using Alugram® silica G/UV$_{254}$ coated plates. Mass spectra were carried out by the EPSRC mass spectrometry service, Swansea. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM 300 instrument at 300 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ as an internal reference. Coupling constants are measured in Hertz. ^{13}C NMR spectra were recorded in $CDCl_3$ on the same instrument at 75 MHz. The bromo ester compounds **15** were prepared following standard esterification protocols from the literature.[17] Characterisation data of all the products are reported in the Supporting Information.

General Procedure for the Preparation of Arylzinc Chloride Derivatives (1a–e)

t-BuLi (20.0 mL, 30.0 mmol; 1.5 M solution in pentane) was added dropwise to a solution of aryl bromide or iodide (15 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, and then for 15 min at room temperature. The aryllithium solution was then added to a dry solution of $ZnCl_2$ (31.5 mL, 15.75 mmol; 0.5 M solution in THF) at 0 °C and the resulting solution was stirred for 30 min at this temperature before removing the ice bath and the stirring was continued for 1 h at room temperature. The pale yellow solution was concentrated under vacuum to reach a final volume of 30 mL to afford a 0.5 M solution of arylzinc chloride in tetrahydrofuran (**1a**–**e**).

Procedure for the Preparation of 2,6-Dimethoxybenzylzinc Chloride (1f)

n-BuLi (3.13 mL, 5.0 mmol; 1.6 M solution in hexane) was added dropwise to a solution of 1,3-dimethoxybenzene (0.69 g, 5 mmol) in tetrahydrofuran (12 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then for 3.5 h at room temperature. The aryllithium solution was then added to a dry solution of $ZnCl_2$ (10.5 mL, 5.25 mmol; 0.5 M solution in THF) at 0 °C and the resulting solution was stirred for 30 min at this temperature before removing the ice bath and the stirring was continued for 1 h at room temperature. The pale yellow solution was concentrated under vacuum to reach a final volume of 10 mL to afford a 0.5 M solution of 2,6-dimethoxybenzylzinc chloride in tetrahydrofuran (**1f**).

General Procedure for the Preparation of 1,1′-Alkenes

Method A, alkenes 8–13:[15] Cyclic anhydride (dihydrofuran-2,5-dione or dihydro-3*H*-pyran-2,6-dione) was stirred overnight at room temperature either in methanol or in a solution of pyrrolidine (1 equiv.) in acetonitrile to afford the corresponding ester or amide, respectively, in quantitative conversion after evaporation to dryness. The resulting solid was then added to a mixture of dicyclohexylcarbodiimide (DCC) (1.1 equivs.) and 4-dimethylaminopyridine (DMAP) (1.6 equivs.) in dichloromethane at 0 °C and stirred overnight at room temperature. To ensure the complete removal of all the dicyclohexylurea (DCU) the reaction mixture was concentrated under vacuum, the resulting product was treated with an ethyl acetate/petroleum ether mixture (1/1) and filtrated. The filtrate was washed twice with a 10% $KHSO_4$ aqueous solution and brine, dried over $MgSO_4$ and evaporated to dryness to afford a yellow solid, which was used in the next step without any further purification. To a solution of glacial acetic acid (10 equivs.) in dichloromethane at 0 °C were added the resulting yellow solid followed by sodium borohydride (2.5 equivs.) portionwise over 1 hour. The mixture was allowed to warm up to room temperature and stirred overnight. The resulting mixture was extracted twice with brine and twice with water, dried over $MgSO_4$ and concentrated under vacuum to afford a yellow solid used as it is for the next step. This solid was refluxed overnight with dimethylmethyleneimmonium iodide (Eschenmoser's salt) (2.5 equivs.) in the required alcohol. After cooling down evaporation afforded a residue, which was dissolved in ethyl acetate and washed with a saturated $NaHCO_3$ aqueous solution, followed with a 10% $KHSO_4$ aqueous solution and brine. Drying over $MgSO_4$ and concentration under vacuum afforded the crude mixture which was purified by flash column chromatography over silica gel using ethyl acetate/petroleum ether as elution mixture (1/20 except where specified) to give the desired 1,1′-alkene as a colourless oil.

Method B, alkenes 17–21:[16] To a solution of sodium hydride (60% in mineral oil, 1.3 equivs.) in *N,N*-dimethylformamide (5 mL per mmol of phosphonoacetate) was slowly added trimethyl phosphonoacetate (1 equiv.) at room temperature. The mixture was stirred for 30 min at this temperature before the addition of the bromo ester (1.3 equivs.). After 30 min stirring at room temperature, the mixture was heated at 100 °C for 16 h. After cooling down to room temperature, potassium carbonate (3 equivs.) and paraformaldehyde (2 equivs.) were added and the mixture was heated at 100 °C for 6 h. After cooling down to room temperature, the mixture was quenched with brine and extracted with ethyl acetate. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed three times with water, then with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by silica gel chromatography using ethyl acetate/petroleum ether (1/20) as eluent.

General Procedures for the Tandem 1,4-Addition/Cyclisation Reaction

Conditions A: The 1,1′-alkene (0.5 mmol, 1 equiv.) and phenylboronic acid (2.0 mmol, 4 equivs.) were added to a solution of $[Rh(COD)_2][SbF_6]$ (11.1 mg, 4 mol%) in a mixture of tetrahydrofuran (2 mL) and water (0.2 mL). The resulting solution was stirred for 20 h at 80 °C. After cooling down to room temperature brine was added and the solution was extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography using ethyl acetate/petroleum ether (1/10) as eluent to afford the 1,4-addition product or the corresponding cyclic product.

Conditions B: The 1,1′-alkene (0.5 mmol, 1 equiv.) and phenylboronic acid (2.0 mmol, 4 equivs.) were added to a solution of potassium hydroxide (22.4 mg, 8 mol%) and $[Rh(COD)_2][SbF_6]$ (11.1 mg, 4 mol%) in tetrahydrofuran (2 mL). The resulting solution was stirred for 20 h at 80 °C. After cooling down to room temperature brine was added and the solution was extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography using ethyl acetate/petroleum ether (1/10) as eluent to afford the 1,4-addition product or the corresponding cyclic product.

Conditions C: To a solution of $[RhCl(COD)]_2$ (2.5 mg, 1 mol%), 1,1′-alkene (0.5 mmol, 1 equiv.), chlorotrimethylsilane (0.095 mL, 0.75 mmol, 1.5 equivs.) in tetrahydrofuran (1 mL) was added the arylzinc chloride solution (1.5 mL, 0.75 mmol, 0.5 M in tetrahydrofuran, 1.5 equiv) at room temperature. The reaction mixture was stirred overnight (18 h) at room temperature. The reaction was quenched with brine, extracted twice with ethyl acetate and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography using ethyl acetate/petroleum ether (1/10) as eluent to afford the 1,4-addition product or the corresponding cyclic product.

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References

[1] a) T. L. Ho, *Tandem Organic Reactions*, Wiley, New York, **1992**; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–165; d) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206; e) M. Malacria, *Chem. Rev.* **1996**, *96*, 289–306.

[2] a) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365–2379; b) A. Ajamian, J. L. Gleason, *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760; c) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, 105, 1001–1020; d) P. Eilbracht, L. Barfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3365.

[3] H. C. Guo, J. A. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366, and references cited therein.

[4] a) R. D. Little, J. R. Dawson, *Tetrahedron Lett.* **1980**, *21*, 2609–2612; b) S. Saito, Y. Hirohara, O. Narahara, T. Moriwake, *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535; c) C. Thebtaranonth, Y. Thebtaranonth, *Tetrahedron* **1990**, *46*, 1385–1389; d) T. Uyehara, N. Shida, Y. Yamamoto, *J. Org. Chem.* **1992**, *57*, 3139–3145; e) H. Inoue, Y. Nagaoka, M. Tomioka, *J. Org. Chem.* **2002**, *67*, 5864–5867; f) Y. Nagaoka, H. Inoue, N. El-Koussi, K. Tomioka, *Chem. Commun.* **2002**, 122–123; g) L. C. Wang, A. L. Luis, K. Agaplou, H. Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403; h) S. G. Davies, D. Diez, S. H. Dominguez, N. M. Garrido, D. Kruchinin, P. D. Price, A. D. Smith, *Org. & Biomol. Chem.* **2005**, *3*, 1284–1301.

[5] a) R. J. Moss, K. J. Wadsworth, C. J. Chapman, C. G. Frost, *Chem. Commun.* **2004**, 1984–1985; b) C. J. Chapman, K. J. Wadsworth, C. G. Frost, *J. Organomet. Chem.* **2003**, *680*, 206–211; c) M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083–4085; d) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571–2573; e) J. D. Hargrave, G. Bish, C. G. Frost, *Chem. Commun.* **2006**, 4389–4391; f) J. D. Hargrave, J. Herbert, G. Bish, C. G. Frost, *Org. & Biomol. Chem.* **2006**, *4*, 3235–3241.

[6] a) K. Yoshida, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2003**, *68*, 1901–1905; b) L. Navarre, S. Darses, J. P. Genêt, *Angew. Chem. Int. Ed.* **2004**, *43*, 719–723.

[7] K. Y. Li, A. Alexakis, *Tetrahedron Lett.* **2005**, *46*, 5823–5826.

[8] a) A. Mandoli, L. A. Arnold, A. H. M. de Vries, P. Salvadori, B. L. Feringa, *Tetrahedron: Asymmetry* **2001**, *12*, 1929–1937; b) L. A. Arnold, R. Naasz, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2002**, *67*, 7244–7254; c) K. Yoshida, M. Ogasawara, T. Hayashi, *J. Am. Chem. Soc.* **2002**, *124*, 10984–10985.

[9] H. Y. Kim, A. E. Lurain, P. Garcia-Garcia, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139.

[10] a) D. F. Cauble, J. D. Gipson, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111; b) K. Y. Li, A. Alexakis, *Tetrahedron Lett.* **2005**, *46*, 8019–8022.

[11] a) K. Tomioka, Y. Nagaoka, *Conjugate Addition of Organometallic Reagents in Comprehensive Asymmetric Catalysis*, (Eds.: A. Pfaltz, H. Yamamoto), Vols. 1–3, Springer, Berlin, **1999**; b) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry, Ser. 9, Pergamon, Oxford, **1992**; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196; d) T. Hayashi, *Synlett* **2001**, 879–887; e) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; f) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236; g) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; h) S. Darses, J. P. Genêt, *Eur. J. Org. Chem.* **2003**, 4313–4327; i) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196.

[12] a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; b) K. J. Wadsworth, F. K. Wood, C. J. Chapman, C. G. Frost, *Synlett* **2004**, 2022–2024; c) C. J. Chapman, C. G. Frost, *Adv. Synth. Catal.* **2003**, *345*, 353–355.

[13] a) R. Shintani, N. Tokunaga, H. Doi, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 6240–6241; b) R. Shintani, T. Yamagami, T. Kimura, T. Hayashi, *Org. Lett.* **2005**, *7*, 5317–5319; c) A. Kina, K. Ueyama, T. Hayashi, *Org. Lett.* **2005**, *7*, 5889–5892; d) S. K. Brayshaw, T. M. Douglas, J. Le Nôtre, C. G. Frost, A. S. Weller, *Chem. Commun.* **2006**, 3408–3410.

[14] a) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690; b) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482.

[15] C. L. Hill, M. McGrath, T. Hunt, G. Grogan, *Synlett* **2006**, 309–311.

[16] B. Hin, P. Majer, T. Tsukamoto, *J. Org. Chem.* **2002**, *67*, 7365–7368.

[17] A. A. Vasil'ev, L. Engman, E. P. Serebryakov, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2211–2216.

[18] a) V. Chaleix, V. Sol, Y. M. Huang, M. Guilloton, R. Granet, J. C. Blais, P. Krausz, *Eur. J. Org. Chem.* **2003**, 1486–1493; b) M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, *J. Org. Chem.* **2005**, *70*, 1227–1236.

[19] R. Uson, L. A. Oro, J. A. Cabeza, *Inorg. Synth.* **1985**, *23*, 126–130.