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Catalytic asymmetric carbon–carbon bond formation using alkenes as alkylmetal equivalents

Rebecca M. Maksymowicz, Philippe M. C. Roth and Stephen P. Fletcher*

Catalytic asymmetric conjugate addition reactions with organometallic reagents are powerful reactions in synthetic chemistry. Procedures that use non-stabilized carbanions have been developed extensively, but these suffer from a number of limitations that prevent their use in many situations. Here, we report that alkylmetal species generated *in situ* from alkenes can be used in highly enantioselective 1,4-addition initiated by a copper catalyst. Using alkenes as starting materials is desirable because they are readily available and have favourable properties when compared to pre-made organometallics. High levels of enantioselectivity are observed at room temperature in a range of solvents, and the reaction tolerates functional groups that are not compatible with comparable methods—a necessary prerequisite for efficient and protecting-group-free strategies for synthesis.

The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most powerful tools for C–C bond formation and is frequently used as a key step in syntheses[1–3]. Copper-catalysed asymmetric 1,4-addition of organometallic reagents has been viewed as an important solution to the problem of asymmetric C–C bond formation for over twenty years[4–7]. Tremendous advances in the catalytic enantioselective addition of unstabilized organometallic nucleophiles such as Grignard reagents[8–11], dialkylzincs[12–14], alkyl aluminiums[15–17] and alkyl lithiums[18] have recently been achieved.

In these reactions, the use of Grignard reagents is considered particularly attractive because they are readily available, easy to handle and are able to transfer all of the alkyl groups of the organometallic compound[6,7]. Furthermore, very useful complementary reactivity with alkyl aluminium and dialkyzinc reagents[4,7] is observed. Procedures involving the addition of a pre-made organometallic are inherently limited by the availability and reactivity profiles of the reagent itself. As previously noted, sensitivity to solvent, temperature, concentration, method of addition and the presence of additives is the rule, rather than the exception, in copper-catalysed Grignard reagent addition[6], and this can limit the options available in reaction design. In the synthesis of complex molecules, functional groups are often present that are incompatible with organometallic reagents, and the sensitivity of many asymmetric procedures to reaction conditions can make even the use of protecting group strategies ineffective[19]. The reactivity of organometallic reagents presents challenges in the use of functionalized reagents[6,20], and is associated with safety issues that can restrict implementation in industrial processes[21]. Perhaps most importantly, the asymmetric addition of these reagents often requires the use of cryogenic temperatures to obtain high levels of selectivity. This is difficult in industry and is a limitation of these methods[21]. A principle of green chemistry is that synthetic methods should be conducted at ambient temperature[22], and the need to develop new methods for copper-catalysed conjugate addition reactions that are effective at room temperature is well recognized[7].

Results and discussion

We decided to evaluate the use of alkenes as alkylmetal equivalents in catalytic asymmetric conjugate addition (ACA). These reactions would be strategically important because they would accomplish transformations that are not currently possible. As well as offering new synthetic strategies, it was anticipated that, by replacing pre-made organometallic reagents, the procedures might overcome some of the limitations of current methods (Fig. 1).

Grignard reagents, dialkylzincs and alkylaluminiums are generally formed (Fig. 1b) from the corresponding halide, which is either reacted directly with a metal in an oxidative process or is involved in a transmetallation reaction with a stoichiometric amount of a different pre-formed organometallic reagent[23–25]. The oxidative processes are limited in their functional group compatibility, and transmetallation procedures contribute to excessive waste generation. As noted by Krische, many of these processes actually

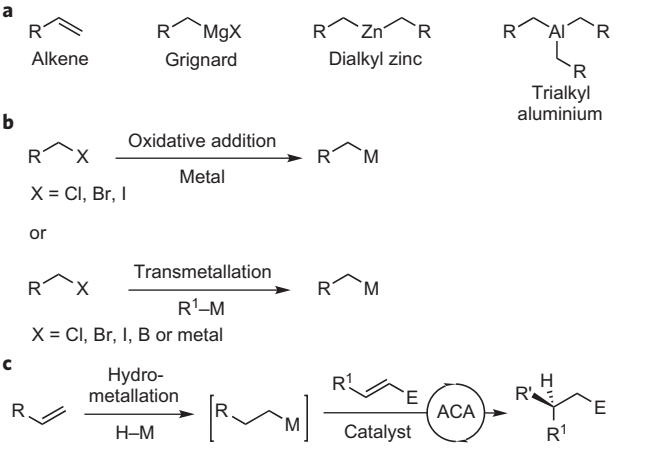
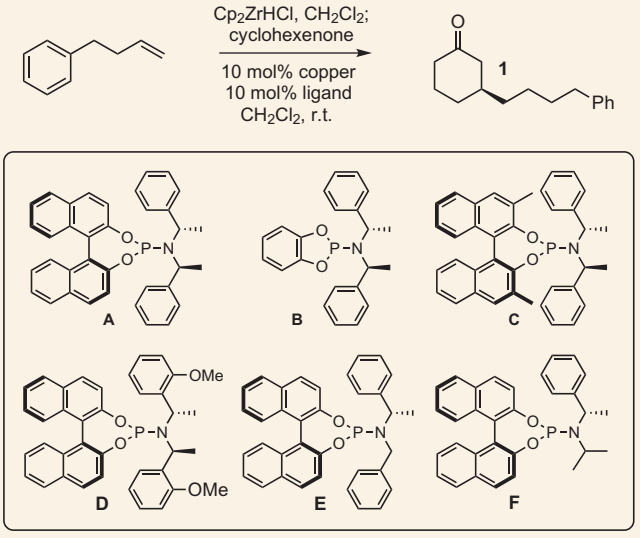


Figure 1 | Comparing alkenes and the organometallics typically used in catalytic asymmetric addition reactions. a, Structure of alkenes, dialkyl zincs, Grignard reagents and trialkyl aluminiums. Alkenes are more readily available and less reactive than organometallic reagents. **b**, Typical preparation of alkylmetal reagents for use in asymmetric conjugate addition reactions. **c**, Generating an organometallic reagent from an alkene by reductive hydrometallation. Here we show that this approach allows alkenes to be used as alkylmetal equivalents in asymmetric catalysis (E = electron-withdrawing group).

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK.
*e-mail: stephen.fletcher@chem.ox.ac.uk

Table 1 | Copper and ligand screen for the HM-ACA reaction.



Entry	Copper source	Ligand	e.e.*,†
1	CuCl	**A**	Racemic
2	CuBr·Me_2S	**A**	Racemic
3	Cu(TC)	**A**	Racemic
4	CuI	**A**	Racemic
5	$Cu(OTf)_2$	**A**	12%
6	$[Cu(MeCN)_4]PF_6$	**A**	55%
7	$(CuOTf)_2$·PhH	**A**	80%
8	$(CuOTf)_2$·PhH	**B**	17%
9	$(CuOTf)_2$·PhH	**C**	20%
10	$(CuOTf)_2$·PhH	**D**	7%
11	$(CuOTf)_2$·PhH	**E**	30%
12	$(CuOTf)_2$·PhH	**F**	8%

Conditions: alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), cyclohexenone (1 equiv.), copper (10 mol%), ligand (10 mol%); room temperature. *Absolute configuration determined by circular dichroism spectroscopy. †Enantiomeric excess determined by HPLC.

use multiple pre-formed organometallic reagents, giving rise to super-stoichiometric amounts of by-products and requiring the use of multiple air- and moisture-sensitive materials[26].

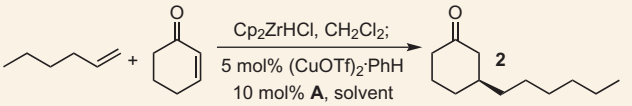
The direct use of organometallics generated by the reductive hydrometallation (Fig. 1c) of alkenes as nucleophiles in enantioselective catalysis would offer many powerful opportunities. However, to the best of our knowledge, the hydrometallation or hydroboration of olefins followed by direct asymmetric 1,4-addition is unknown[2,27], even though hydrometallation of alkynes followed by transmetallation[7,26,28] and direct stoichiometric[29,30] and catalytic[31] alkyne reduction followed by asymmetric C–C bond formation has been reported. The ability to use simple and readily available starting materials in C–C bond formation is extremely important. In this respect, the work of Krische, who has developed asymmetric C–C bond-forming reductive hydrogenation[26] and redox-neutral transfer hydrogenation[32] reactions with alkynes and other π-bond-containing starting materials, is especially noteworthy. Alkenes are particularly desirable as starting materials as they are abundant and commonly used feedstocks in industrial processes. Methods that convert alkenes into functionalized compounds are among the most useful processes known[33,34], and the asymmetric oxidation and hydrogenation of olefins has revolutionized synthesis[35].

To test the feasibility of a hydrometallation–ACA (HM–ACA) process with alkenes (Fig. 1c), we chose to examine the readily prepared[36] and commercially available Schwartz reagent[37]. Hydrometallation with this reagent produces zirconium species that can undergo C–C bond-forming processes, a fruitful area of research pioneered by Schwartz and extensively developed by Wipf and others[28,38–45].

The key to developing a successful asymmetric procedure is finding a suitable catalyst system, and our initial experiments involved examining combinations of copper sources and chiral non-racemic ligands. Using 4-phenyl-1-butene and cyclohexenone as HM–ACA coupling partners, we conducted a series of experiments as described in Table 1. We evaluated a variety of copper salts in combination with the easily accessible and commercially available ligand **A** (ref. 46), in CH_2Cl_2 at room temperature (Table 1, entries 1–7). Here, the nature of the counterion was found to have a stunning effect on enantioselectivity and only strongly electron-deficient copper salts were found to provide asymmetric induction. The enantioselectivity was improved dramatically, from racemic in most cases to 80% enantiomeric excess (e.e.), by using freshly prepared copper(I) triflate benzene complex. When the HM–ACA was examined with other phosphoramidite ligands and $(CuOTf)_2$·PhH (Table 1, entries 8–12) a striking dependence of ligand structure on enantioselectivity was observed: ligands **B**–**F** gave vastly inferior levels of selectivity, despite the appearance of only subtle structural differences compared to **A**.

We were delighted that the above experiments led to reaction conditions where high levels of enantioselectivity could be observed at room temperature, and next examined the effect of solvent on the enantioselectivity of the reaction. For these experiments we chose 1-hexene and cyclohexenone as asymmetric reductive coupling partners (Table 2). Remarkably, and in contrast to other catalytic asymmetric addition procedures[6,7,11,18], we found the selectivity to be highly tolerant of the solvent used. The reactions in Table 2 gave full conversion of the starting material overnight, but the resulting enolate underwent further reaction with unreacted cyclohexenone at a rate comparable to 1,4-addition[47], which tended to lower the yields of **2** and made the reactions difficult to reproduce. In four cases (using CH_2Cl_2, diglyme, tetrahydrofuran (THF) and 2-Me-THF as solvent) we attempted to optimize the reaction temperature to obtain higher levels of selectivity. With CH_2Cl_2 and diglyme, room temperature was optimal, but cooling reactions with THF and 2-Me-THF (to 5 and 10 °C, respectively) increased the

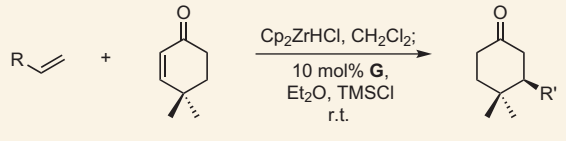
Table 2 | Effect of solvent on enantioselectivity.

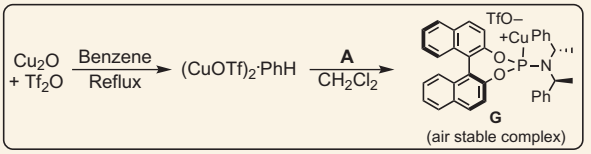


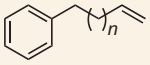
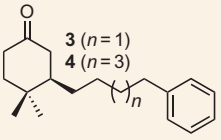
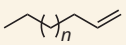
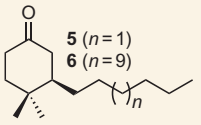
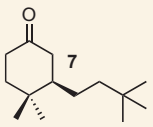
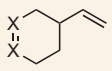
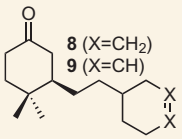
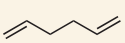
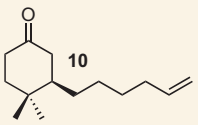
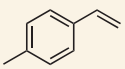
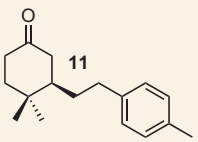
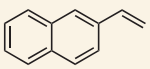
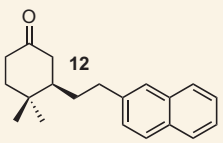
Entry	Solvent	e.e.*,†
1	CH_2Cl_2	89%
2	1,2-Dichloroethane	75%
3	$CHCl_3$	80%
4	Et_2O	85%
5	*t*-BuOMe	84%
6	*i*-Pr_2O	84%
7	2,2-Dimethoxypropane	86%
8	THF	80%
		92%‡
9	2-Me-THF	88%
		94%§
10	Diglyme	89%
11	1,4-Dioxane	75%
12	Hexane	75%
13	Toluene	83%
14	*m*-Xylene	75%
15	Bromobenzene	50%

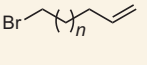
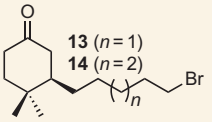
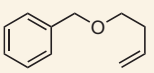
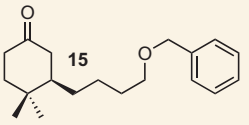
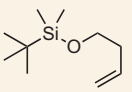
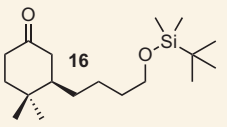
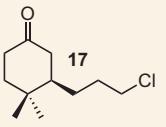
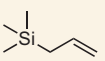
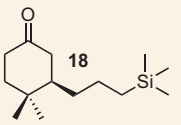
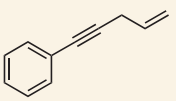
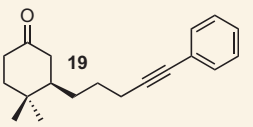
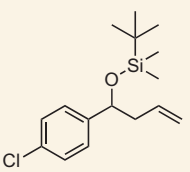
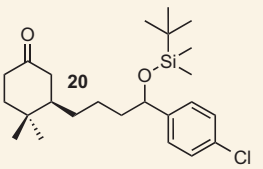
Conditions: 1-hexene (2.5 equiv.), Cp_2ZrHCl (2.0 equiv.), cyclohexenone (1.0 equiv.), $(CuOTf)_2$·PhH (5 mol%), ligand A (10 mol%); room temperature unless specified, full conversion overnight. *Absolute configuration determined by circular dichroism spectroscopy. †Enantiomeric excess determined by derivatization and ^{13}C NMR spectroscopy, see Supplementary Information. ‡Reaction peformed at 5 °C. §Reaction performed at 10 °C.

Table 3 | Scope of alkenes.





Entry	Substrate	Product	Yield*	e.e.†
1 ($n=1$) **2** ($n=3$)			74% 65%	89%‡,§ 89%‡
3 ($n=1$) **4** ($n=9$)			67% 70%	89%§ 89%§
5‖			65%	84%§
6 (X = CH^2) **7** (X = CH)			74% 60%¶	93%§ 87%§
8#			71%	78%§
9			56%	82%‡
10			52%	71%‡

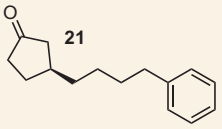
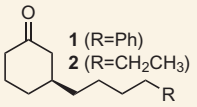
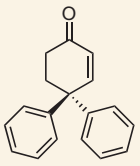
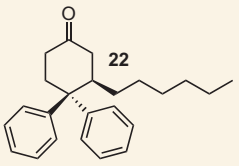
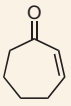
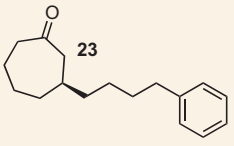
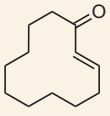
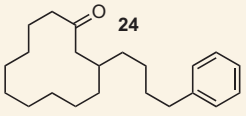
Entry	Substrate	Product	Yield*	e.e.†
11 **12**			66% 58%	76%‡,§ 76%‡,§
13			54%	80%‡
14			49%	94%§
15			19%	71%§
16**			53%	96%§
17‖			62%	72%‡
18 **19**			62%¶ 93%¶	85%§,†† 70%††,‡‡

Conditions: alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), enone (1 equiv.), **G** (0.1 equiv.). *Isolated yield. †Absolute configurations known, determined or assigned by analogy (see Supplementary Information). ‡e.e. determined by HPLC. §e.e. determined by derivatization and ^{13}C NMR spectroscopy. ‖Reaction heated at hydrometallation stage. ¶Isolated as a 1:1 mixture of diastereomers. #10 equiv. of the alkene was used. **Reaction performed at 0 °C. ††e.e. determined by removal of the silyl group and HPLC. ‡‡Conditions: alkene (2.0 equiv.), Cp_2ZrHCl (1.7 equiv.), **G** (0.05 equiv.), 1.90 g of product isolated.

enantioselectivity to 92 and 94% e.e., respectively (Table 2, entries 8 and 9). The ability to use a wide variety of solvents allows for variations in conditions and is advantageous for many reasons. Different starting materials, for example, may demonstrate different solubility behaviour. The reaction was even found to tolerate bromobenzene as a solvent (Table 2, entry 15).

We then explored the possibility of evaluating the scope of the alkene reagent in the HM–ACA process. It was decided to perform all reactions at room temperature, and we chose and optimized conditions for a sterically hindered and challenging[48] α,β-unsaturated carbonyl compound—4,4-dimethyl-cyclohexenone—as Michael acceptor, with 4-phenyl-1-butene as starting alkene (Table 3, entry 1). As copper triflate benzene complex is air-sensitive, we found it convenient to use pre-formed catalyst complex **G** (Table 3) in these experiments. Complex **G** can be weighed and handled in air and is stable for at least a month when stored at ambient temperature under an inert gas. No step in the process requires a glovebox and no special procedures (such as a slow addition of the reagents[49] over time) are necessary. We found that using diethyl ether as a co-solvent and trimethylsilyl chloride (TMSCl)[49] as an additive increased the e.e. of **3** by ~5–10%. Under these conditions, the reaction shown in Table 3, entry 1,

Table 4 | Scope of enones.

Entry	Enone	Product	Yield*	e.e.†
1a		 **21**	23%	75%‡
1b§			29%	85%‡
2 R=Ph		 **1** (R=Ph) **2** (R=CH_2CH_3)	59%	90%‡‖
3 R=CH_2CH_3			59%	93%‖
4		 **22**	75%	90%‡
5		 **23**	73%	91%‡
6		 **24**	50%	60%‡,¶

Conditions: alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), enone (1 equiv.), **G** (0.1 equiv.). *Isolated yield. †Absolute configurations known, determined or assigned by analogy (see Supplementary Information). ‡e.e. determined by HPLC. §Reaction performed at 0 °C. ‖e.e. determined by derivatization and ^{13}C NMR spectroscopy. ¶Absolute configuration not determined.

proceeds to full conversion in ~2.5 h. With the exception of Table 3, entries 8 (which required an excess of the alkene to statistically favour mono-hydrometallation) and 16 (carried out at 0 °C to minimize by-product formation) all further reactions were performed using these conditions without further optimization.

Examination of a variety of alkenes illustrated that these conditions are remarkably general. High levels of e.e. were observed with linear alkenes (Table 3, entries 1–4) and sterically hindered tert-butyl and cyclohexyl substituted olefins (entries 5 and 6). We were able to access products **9** and **10** containing internal and terminal alkenes in the HM–ACA sequence (entries 7 and 8). The method was also successful with styrenyl substrates (entries 9 and 10). The ability to add a naphthyl-containing unit and access products such as **12** may be useful, as this functional group frequently appears in material science and ligand design because of its steric bulk and ability to induce π-stacking interactions.

The presence of an alkyl bromide substituent, a functional group incompatible with the Grignard formation step[25], was tolerated in our method (entries 11 and 12). These products (**13** and **14**) are directly suitable for further synthetic elaboration. The ease of this reaction, using conditions optimized for a different substrate, is in direct contrast to the extensive efforts that have been made to develop useful methods for generating functionalized organometallics. There are still major challenges involved in such procedures, and alkyl-magnesium reagents are particularly problematic[6,7,20]. The presence of benzyl ether and silyl ether groups is also tolerated (entries 13 and 14), demonstrating that protected alcohols such as **15** and **16** can be obtained in very high enantiopurity.

We next examined the HM–ACA procedure with two highly challenging activated alkenes, allyl chloride and allylsilane, both of which gave products with high levels of enantiopurity (Table 3, entries 15 and 16). Although the yield is poor, any tolerance for allyl chloride in this procedure is surprising as the organometallic nucleophile is necessarily generated in the presence of unreacted allyl chloride, an electrophile. Curiously, the major by-product of the reaction is a material where the chloride in **17** has been replaced with a hydrogen atom to give the product of simple *n*-propyl addition, and no cyclized product is observed. In the case of electron-rich allylsilane, excellent enantioselectivity was obtained. The reaction was performed at 0 °C to minimize competitive 1,2-reduction of the carbonyl, which we speculate arises from retro-hydrometallation to regenerate Schwartz reagent, which can then reduce the carbonyl.

We were also delighted to observe that a substrate featuring an internal alkyne (Table 3, entry 17) and an alkene bearing multiple functional groups (entry 18) could undergo HM–ACA. These experiments clearly demonstrate that the HM–ACA procedure is compatible with common functional groups, suggesting that (i) very high levels of chemoselectivity may be possible when these processes are fully developed and (ii) useful tandem reaction sequences for the rapid synthesis of complex materials may be initiated with this methodology.

To examine the potential for scaling up these reactions[21], we performed a single experiment on a preparative scale (Table 3, entry 19) in which we decided to lower the catalyst loading to 5% and reduce the amount of alkene and Schwartz reagent used in our normal screening reactions. On a gram scale, at room temperature, using 5% catalyst complex **G**, we were able to obtain 1.90 g of product **20** (93%) with only a moderate loss of enantioselectivity (70% e.e.). Although more work is needed to fully optimize these procedures, this result suggests that these room-temperature HM–ACA reactions will be much more amenable to scale than the ACA reactions that have been reported using pre-made organometallic nucleophiles[21].

The scope of the reaction with respect to the enone coupling partner was also briefly examined, using the conditions optimized above, as shown in Table 4. Cyclopentenone, a notoriously difficult substrate for catalytic asymmetric 1,4-addition[7,13,49], was found to give only modest yields. Slightly better enantioselectivity was observed when the reaction was performed at 0 °C (Table 4, entry 1b). Cyclohexenone (entries 2 and 3), 4,4-diphenyl-cyclohexenone (entry 4) and cycloheptenone (entry 5) are all suitable substrates without reoptimization of the reaction conditions. In one case (Table 4, entry 6) we examined a macrocyclic ring bearing a *trans*-enone moiety. The results obtained (50% yield, 60% e.e.) using our standard conditions demonstrate that additional optimization will be required to achieve high levels of selectivity for this class of substrates.

Conclusions

We have demonstrated that alkylmetal species generated *in situ* from alkenes can be used as nucleophiles in highly enantioselective 1,4-addition initiated by a copper-based catalyst. The process is formally an asymmetric reductive coupling of an alkene to an enone. The approach of hydrometallating an alkene for use in asymmetric catalysis has tremendous potential as a strategy in synthesis and can overcome some of the limitations of methods using pre-made organometallics. It is anticipated that the tolerance of the reaction to solvents, temperature and additives will allow optimization of the yield and selectivity for many other substrates, and there are many additional possibilities in alternative catalysts, ligands and hydrometallating agents that could also be examined. The robustness, tolerance of functional groups and the ability to use mild conditions may allow the future development of more scalable

and industrially friendly catalytic asymmetric C–C bond-forming methods involving organometallics.

Methods

Preparation of complex G. To a flame-dried Schlenk flask containing $(CuOTf)_2(C_6H_6)$ (239 mg, 0.48 mmol, 0.5 equiv.), at room temperature under an argon atmosphere, was added the phosphoramidite ligand (513 mg, 0.95 mmol, 1.0 equiv.) then CH_2Cl_2 (10 ml). This mixture was stirred for 1 h before canula-filtering the resulting clear colourless solution into another Schlenk flask. The solvent was then gently removed using an oil-pump vacuum (with liquid nitrogen trapping). The resulting off-white solid was dried for at least one extra hour under oil-pump vacuum before storing the catalyst complex under argon.

Procedure for catalytic asymmetric conjugate addition of alkenes. Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 equiv.) was added to a stirred, room-temperature solution of alkene (1.0 mmol, 2.5 equiv.) in CH_2Cl_2 (0.40 ml) under an argon atmosphere. After stirring for ~40 min, the resulting clear yellow solution was transferred via syringe over ~1 min to a clear colourless stirred solution of **G** (30.0 mg, 0.040 mmol, 0.10 equiv.) in Et_2O (2.0 ml) under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclic enone (0.40 mmol, 1.0 equiv.) and then TMSCl (0.25 ml, 2.0 mmol, 5.0 equiv.) were added dropwise via syringe. The reaction was stirred until complete (TLC control; EtOAc/petrol 1:9). The reaction was quenched by the addition of Et_2O (~3 ml) then NH_4Cl (1 M, aq., ~1.5 ml). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (3 × 10 ml). The combined organic phase was washed with $NaHCO_3$ (aq. sat., ~10 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic ketone.

Materials and methods, all procedures, characterization data and spectra are available in the Supplementary Information.

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Author contributions

R.M.M. and P.M.C.R. performed the experiments. All authors contributed to designing the experiments, analysing the data and editing the manuscript. S.P.F. guided the research and wrote the manuscript.

Additional information

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