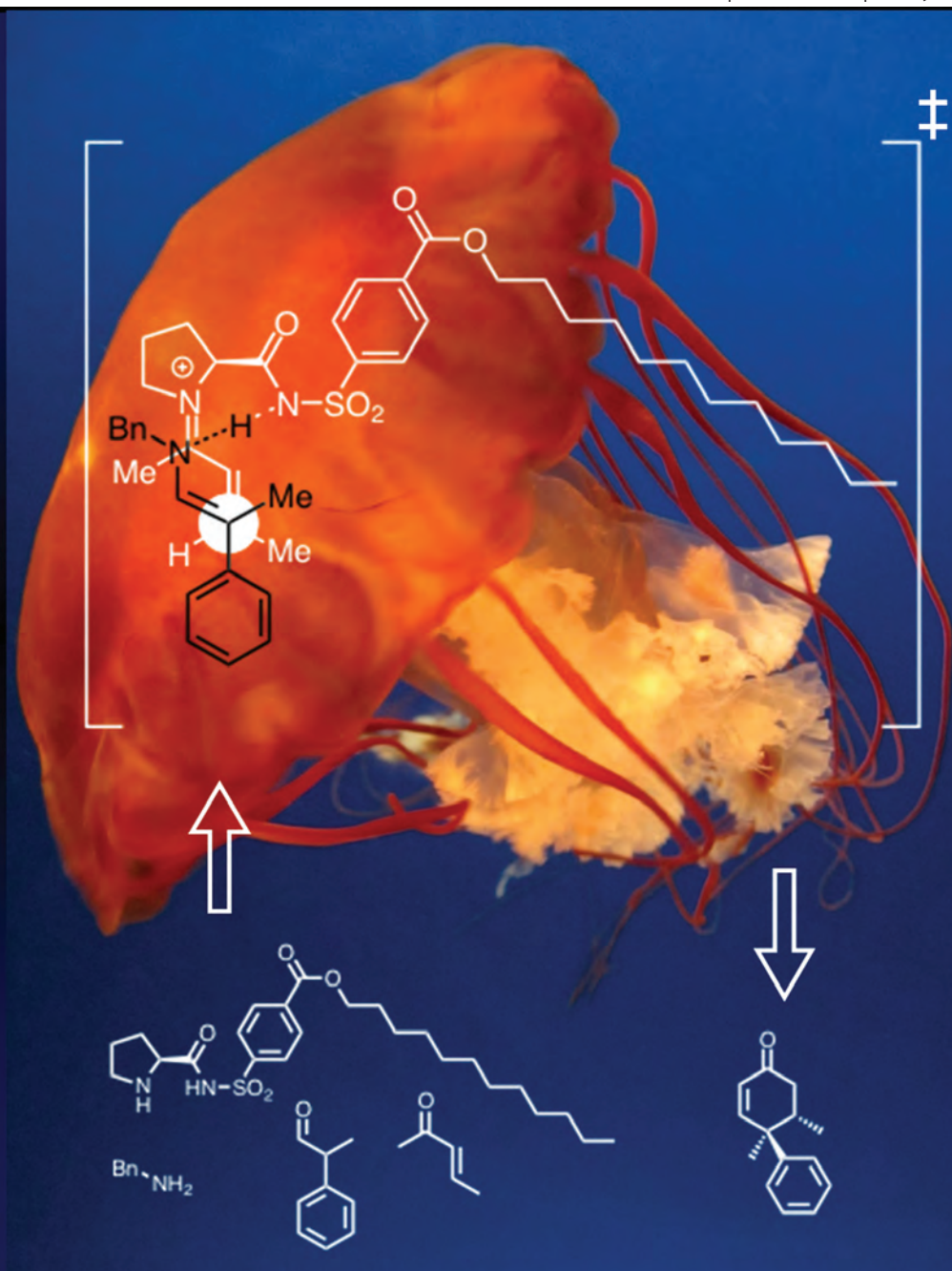


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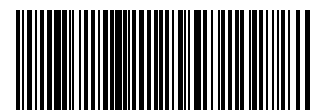
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**PAPER**Rich G. Carter *et al.*

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PAPER

## Proline sulphonamide-catalysed Yamada–Otani condensation: reaction development, substrate scope and scaffold reactivity†‡

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The development of a proline sulphonamide-catalysed method for enantioselective and diastereoselective construction of functionalized cyclohexenones is described. Impact of catalyst structure as well as solvent effects and additives are explored. A significant substrate scope is demonstrated by variation of both the aldehyde and the enone components. Diastereoselective derivatization of the cyclohexenone scaffold illustrates its utility as a building block for chemical synthesis.

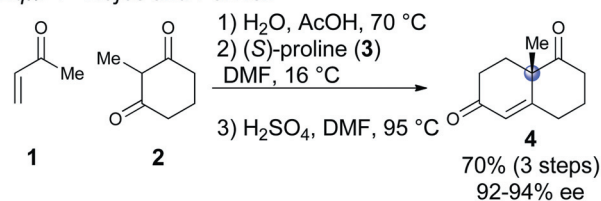
### Introduction and background

Stereogenic quaternary centres are widely present in natural products and new methods for their construction continue to be needed to address this challenge.<sup>1</sup> The efficient construction of all-carbon quaternary centres is a central focus of organic chemistry.<sup>1a,2</sup> More specifically, stereogenic,  $\gamma,\gamma$ -disubstituted cycloalkenones embody a potentially powerful building block in natural product synthesis. An important method for accessing this structural motif is the Hajos–Parrish reaction,<sup>3</sup> which typically generates bicyclic enone systems and employs a cyclic  $\beta$ -di-ketone starting material (Scheme 1, eqn (1)). Recent examples from several laboratories have utilized the Michael addition itself as the enantiodetermining step *via* transition metal,<sup>4</sup> Brønsted acid<sup>5</sup> or phase-transfer catalysis.<sup>6</sup> In order to access stereogenic,  $\gamma,\gamma$ -disubstituted cycloalkenones, aldehyde-based nucleophiles are needed; however, this functional group has not been widely used to date. Yamada and Otani reported a traceless auxiliary-based approach in this area in the late 1960s and early 1970s (Scheme 1, eqn (2)).<sup>7</sup> This concept has essentially laid dormant over the next four decades<sup>8</sup> – likely due to the difficulty related to catalytic turnover and the disappointing levels of enantioselectivity. Recent advances by our laboratory<sup>9</sup> as well as others<sup>8,10</sup> in methods for controlling stereochemistry

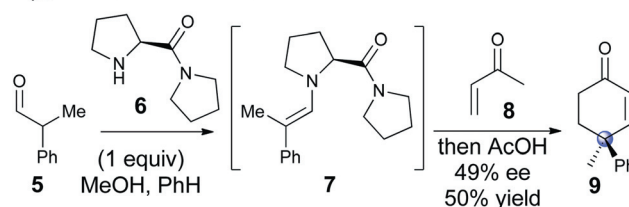
using  $\alpha,\alpha$ -disubstituted aldehydes prompted us to reinvestigate the Yamada–Otani reaction.

In a preliminary communication, we disclosed our development of an organocatalysed method facilitating Yamada–Otani-type reactivity on systems containing  $\beta$ -substitution on the enone moiety.<sup>11</sup> Concurrently to our discoveries, the Kotsuki laboratory reported a dual catalysis method using enone moiety not containing  $\beta$ -substitution.<sup>8</sup> We view this work as a perfect complement to our protocols for systems containing  $\beta$ -substitution. Herein, we disclose a full account of our development of proline sulphonamide-catalysed method for facilitating the annulation of  $\alpha$ -aryl,  $\alpha$ -alkyl-disubstituted aldehydes with acyclic enones to generate highly functionalized cyclohexenones in excellent levels of diastereoselectivity and enantioselectivity.

#### Eqn. 1 - Hajos and Parrish



#### Eqn. 2 - Yamada and Otani



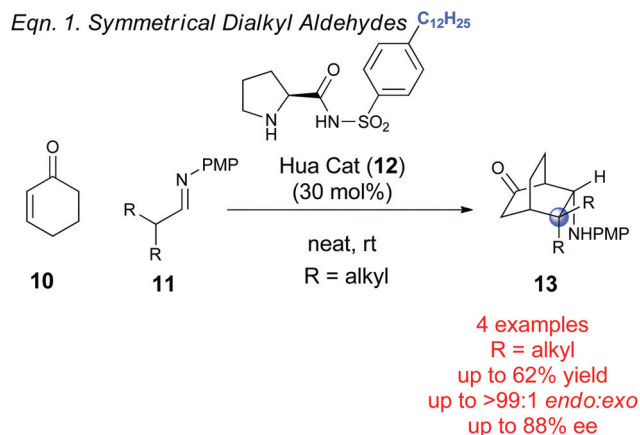
**Scheme 1** Pioneering work in synthesis of  $\gamma,\gamma$ -disubstituted cycloalkenones.

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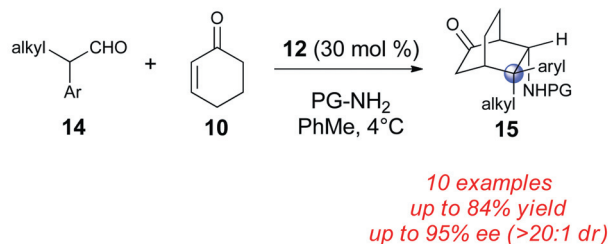
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†Electronic supplementary information (ESI) available: Remaining experimental procedures and copies of NMR spectra and CIF data are provided. CCDC reference numbers 753483, 753484, 869713 and 869714. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25400j

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**Eqn. 2 - Aryl, Alkyl Disubstituted Aldehyde**

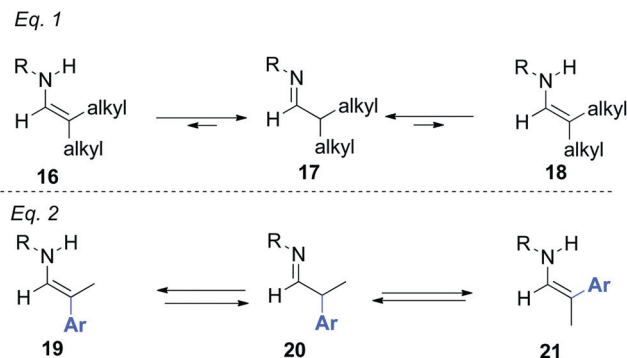


**Scheme 2** Prior work from our laboratory using  $\alpha,\alpha$ -disubstituted aldehydes/imines.

## Results and discussion

We based our initial forays into this area on prior work with cyclic enones (primarily cyclohexenone) as shown in Scheme 2.<sup>9</sup> In these reactions, we were able to develop conditions for facilitating the enantioselectivity construction of [2.2.2] bicyclic systems using a proline sulphonamide<sup>12</sup> organocatalyst (nicknamed Hua Cat-®) developed in our laboratory.<sup>13</sup> Both enantiomers of this catalyst have now been commercialized through Sigma and Synthetech, Inc. In eqn (1), we first studied the utility of symmetrical aldehydes where  $R = \text{alkyl}$  using a pre-formed imine (*e.g.* **11**). These transformations were performed neat using excess (5 equiv.) of the enone to provide the bicyclic ketone products in excellent *endo/exo* selectivity but in modest chemical yield (eqn (1)).<sup>9a</sup> The reactivity of this system could be greatly improved by substitution of one of the two alkyl substitutions on the aldehyde or imine for an aryl moiety (eqn (2)).<sup>9b</sup> This modification also allowed us to change to a multi-component coupling process in which the pre-formed enamine was not isolated prior to addition of the enone and proline sulphonamide organocatalyst.

The rationale behind the replacement of one of the two alkyl substituents for an aryl moiety can be found in imine–enamine equilibria (Scheme 3). We hypothesize that replacement of the alkyl moiety for an aryl group likely improves the concentration of enamine relative to imine in solution by a lowering of the  $pK_a$  of the  $\alpha$ -hydrogen through added conjugation in resultant enamine **19/21**. d'Angelo and co-workers hypothesized decades earlier that the rate of conjugate addition of enamines to suitable electrophiles was directly correlated to the concentration of the



**Scheme 3** Likely equilibria between imine and enamines depending on substitution patterns.

enamine in solution.<sup>14</sup> Interestingly, we have found <sup>1</sup>H NMR analysis of a premixed solution of benzyl amine and 2-phenylpropanal in CDCl<sub>3</sub> does yield the imine **20** ( $R = \text{Bn}$ ,  $\text{Ar} = \text{Ph}$ ) as the major product [<sup>1</sup>H NMR spectra:  $\delta$  7.82 (d,  $J = 4.4$  Hz, 1H), 7.1–7.5 (m, 10H), 4.59 (s, 2H), 3.70 (dq,  $J = 4.4, 6.8$  Hz, 1H), 1.49 (d,  $J = 6.8$  Hz, 3H) ppm] and shows essentially complete consumption of the aldehyde signal at 9.7 ppm. It should be noted, however, that the spectra is complex (containing additional signals between 4.5–5.0 ppm as well as at 2.6 ppm) which we attribute to the dynamic enamine–imine equilibria.

Using the knowledge gained from these cyclic enone systems, we next sought out to apply our work to acyclic enones. We were well-aware of the added complexity that acyclic enones introduced into the system – primarily due to the added rotational flexibility surrounding the C–C  $\sigma$ -bond separating the carbonyl and alkene moieties of the enone. We were encouraged by the pioneering work by other groups in this area;<sup>15</sup> however, we recognized that acyclic enone substrates were noticeable more challenging than acyclic enal systems. We chose to study the reactivity of 2-phenyl propanal with 3-pentenone as the initial model system. It should be noted that 2-pentenone is sold as only an approximately 70% pure solution with the remaining mass balance being 4-methyl-3-pentenone (also known as mesityl oxide). We did not ever observe reactivity with the mesityl oxide under the reaction conditions and made no attempt to purify the 3-pentenone prior to use.

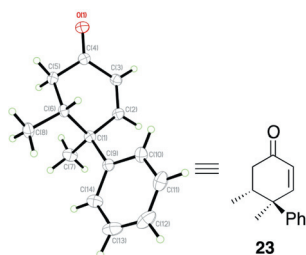
The initial exploration of this transformation on acyclic enones is shown in Table 1. We were pleased to see that our original conditions<sup>9b</sup> did provide the desired product – albeit in modest chemical yield and dr (entry 1). The relative stereochemistry of the cyclohexenone product was conclusively established by X-ray crystallographic analysis (Fig. 1). For optimization, we first focused on the impact of the amine and other additives to the reaction process. Interestingly, addition of molecular sieves to the reaction mixture led to a dramatic acceleration in the reaction rate and enantioselectivity of the process (entry 2). This additive effect would appear at first glance to be counter-intuitive as the removal of water from the reaction system greatly complicates any feasible mechanism for catalyst turnover. We also probed if alternate amines would prove beneficial in the transformation. Consequently, we screened a series of amines – all of which proved inferior to the parent benzyl amine. Addition of *ortho*-substitution on the benzyl ring led to



**Table 1** Additive effects on annulation reaction<sup>a</sup>

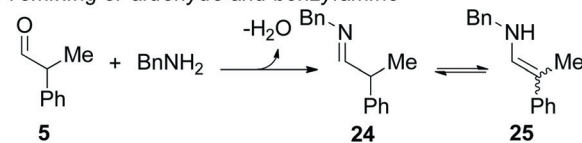
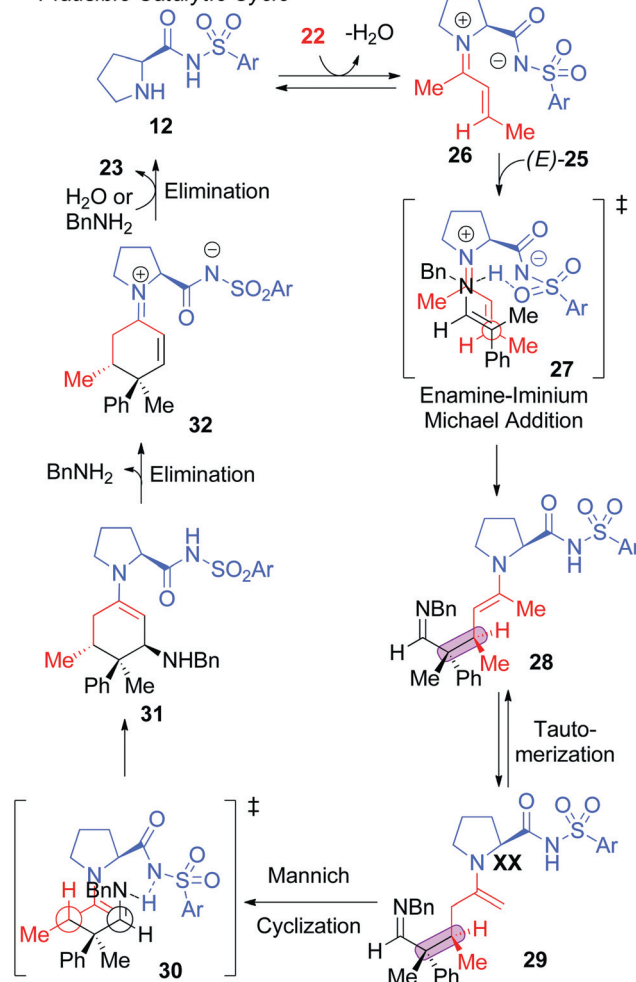
Entry	Amine	Additive	Yield (%)	er (dr)
1 <sup>b</sup>	BnNH <sub>2</sub>	None	30	77 : 23 (>20 : 1)
2	BnNH <sub>2</sub>	Mol. sieves	66	91 : 9 (>20 : 1)
3	2-Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> NH <sub>2</sub>	Mol. sieves	20	79.5 : 21.5 (>20 : 1)
4	2-Me-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> NH <sub>2</sub>	Mol. sieves	39	78 : 22 (>20 : 1)
5	2,6-Cl-C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub> NH <sub>2</sub>	Mol. sieves	0	n/a
6	2,4,6-Me-C <sub>6</sub> H <sub>2</sub> -CH <sub>2</sub> NH <sub>2</sub>	Mol. sieves	0	n/a
7	( <i>R</i> )-PhCH(Me)NH <sub>2</sub>	Mol. sieves	0	n/a
8	( <i>R</i> )-PhCH(Me)NH <sub>2</sub>	Mol. sieves	0	n/a
9	Allylamine	Mol. sieves	36	90.5 : 9.5 (>20 : 1)

<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis. <sup>b</sup> This reaction was performed for 24 h.

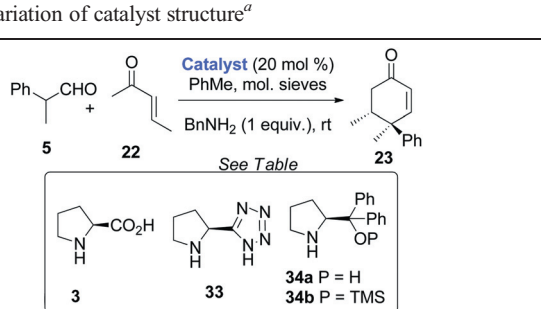
**Fig. 1** ORTEP representation of enone **23**.

reduction of chemical efficiency as shown by both 2-methyl- and 2-chlorobenzyl amine (entries 3 and 4). Not surprisingly, *ortho*, *ortho*-disubstitution on the benzyl amine was also deleterious to the reaction – leading to no product formation (entries 5 and 6). Use of a chiral amine ( $\alpha$ -methyl benzylamine) could potentially provide an added stereocontrolling element; however, the increased steric bulk using either (*R*)- or (*S*)- $\alpha$ -methyl benzylamine led to no product formation (entries 7 and 8). Less hindered amines such as allyl amine did produce the desired product, but in reduced chemical yield (entry 9).

A likely mechanism for this transformation is illustrated in Scheme 4. An in-depth computational analysis of this process can be found elsewhere.<sup>16</sup> The experimental procedure premixes the aldehyde and benzylamine prior to addition of the enone or catalyst. Consequently, we hypothesize that the imine–enamine mixture **24–25** is preformed and the presumed enamine (*E*)-**25** is the reactive nucleophile in the enamine–iminium ion, dual-catalysed<sup>10*h*,17</sup> Michael addition to form the key quaternary stereogenic centre and the vicinal stereocenter. Additional support for

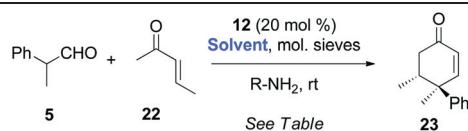
**Premixing of aldehyde and benzylamine****Plausible Catalytic Cycle****Scheme 4** Possible mechanism for catalytic cycle.

this hypothesis can be found in the products derived from the cyclohexenone series **15** described in Scheme 2 in which the benzyl amine moiety is incorporated in the product **15** where subsequent elimination is not viable. The important role of the molecular sieves in the reaction is likely to remove the water from the reaction media, which would possibly disrupt the key hydrogen bonding network present in transition state **28**. After enamine tautomerization, an intramolecular Mannich cyclization followed by elimination of benzyl amine would yield zwitterion **32**. The presence of molecular sieves in the reaction complicates any mechanistic explanation for the proline sulphonamide hydrolysis step. If water is not the nucleophile for catalyst cleavage, it is possible that the by-product benzylamine could undergo iminium ion–imine exchange with **32** after its elimination from intermediate **31**. If this iminium ion–imine exchange is operative, it would require that a subsequent imine hydrolysis step occur to reveal the enone product **23**.

**Table 2** Variation of catalyst structure<sup>a</sup>

Entry	Catalyst	Time (h)	Yield	er (dr)
1	<b>12</b>	36	66%	90.7 : 9.3 (>20 : 1)
2	<b>3</b>	60	32%	84.4 : 15.6 (>20 : 1)
3	<b>32</b>	60	11%	62 : 38 (20 : 1)
4	<b>33</b>	60	Trace	n/a
5	<b>34</b>	60	Trace	n/a

<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis.

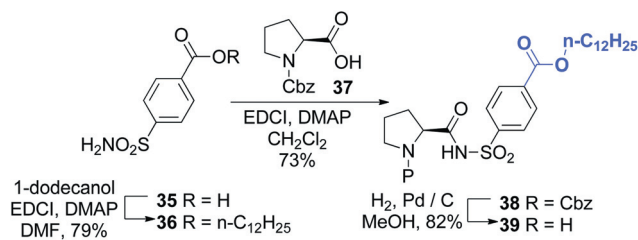
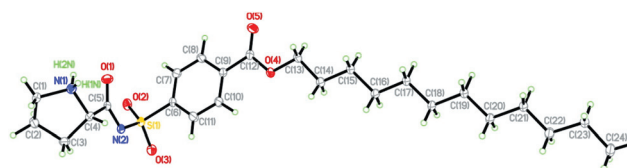
**Table 3** Solvent effects on annulation reaction<sup>a</sup>

Entry	Solvent	Time (h)	Yield (%)	er (dr)
1	Toluene	36	66	90.7 : 9.3 (>20 : 1)
2	MTBE	36	52	73.5 : 26.5 (18 : 1)
3	2-Me-THF	36	52	78 : 22 (>20 : 1)
4	CH <sub>2</sub> Cl <sub>2</sub>	36	67	87 : 13 (>20 : 1)
5	CHCl <sub>3</sub>	36	63	85.5 : 14.5 (>20 : 1)
6	Cyclohexane	60	62	83.5 : 15.5 (19 : 1)
7	CF <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	60	71	92 : 8 (20 : 1)
8	1,2-DCE	60	67	92.1 : 7.9 (>20 : 1)

<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis.

Given the early success of this transformation, we wanted to explore if the sulphonamide scaffold was unique in providing this reactivity (Table 2). Consequently, we screened proline as well as other proline derivatives to gain a fair comparison with the proline sulphonamide **12**. Both proline (**3**) and the proline tetrazole **33** proved inferior – providing noticeably lower levels of chemical yield and stereoselectivity *versus* the proline sulphonamide **12** (entries 2 and 3). Use of prolinol derivatives **34a** and **34b** led to only trace amounts of product formation – even after extended reaction times (entries 4 and 5).

We next explored the impact of solvent on the transformation (Table 3). Use of MTBE or 2-methyl-THF led to notable decreases in enantioselectivity (entries 2–3). The poor performance of 2-methyl-THF was surprising as we had previously used this solvent in proline sulphonamide-catalysed aldol reactions with considerable success.<sup>18</sup> Dichloromethane and chloroform proved more effective than oxygenated solvents (entries 4–5),

**Scheme 5** Synthesis of second generation catalyst.**Fig. 2** ORTEP representation of catalyst **39**.

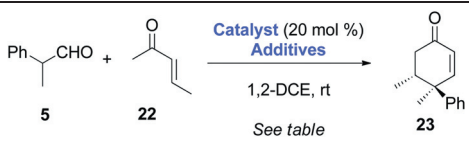
but the level of enantioselectivities was lower than the parent toluene conditions (entry 1). Cyclohexane also performed with reduced levels of stereoselectivity (entry 6). Fortunately, trifluorotoluene and 1,2-dichloroethane both proved to be useful solvents – with the later providing superior levels of diastereoselectivity (entry 8).

We also became intrigued by the possibility that we could augment the enantioselectivity in this process by tuning the sulphonamide pK<sub>a</sub> (Scheme 5). In support of this hypothesis, we synthesized the *p*-dodecyl ester version of our parent catalyst. This catalyst was readily available from commercial sulphonamide carboxylic acid **35** which was esterified and coupled with Cbz-proline followed by hydrogenation to afford proline sulphonamide **39** in high yield. The product **39** was crystalline and its structure was unambiguously determined by X-ray analysis (Fig. 2).

We were pleased to find that this catalyst did appear to provide slightly higher enantioselectivities under otherwise identical conditions (Table 4, entries 1–2). In addition, the requirement of molecular sieves for this reaction continued to be prevalent (entry 3). We also explored if less than one equivalent of the amine could be used with comparable efficiency. If 0.8 equivalent of benzyl amine was added, a reduced chemical yield was observed (entry 4). Interestingly, reduction of the equivalency of benzyl amine could be tolerated (0.5 equiv. BnNH<sub>2</sub>) if an acid additive was used (1 mol% 4-fluorobenzoic acid) (entry 5).

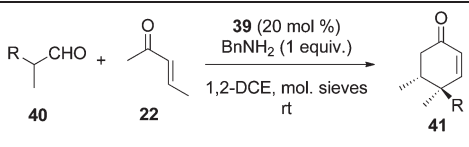
With the optimization complete, we turned our focus to briefly screening the scope of the aldehyde component (Table 5). We were pleased to find that *p*-methyl, *p*-bromo and *p*-chloro moieties were all tolerated on the aromatic ring (entries a–c). X-ray crystallographic analysis of enone **22b** allowed for the assignment of absolute configuration (Fig. 3). Interestingly, replacement of the aromatic ring for a methyl ester (entry d) led to a dramatic drop in diastereoselectivity under the reaction conditions.

An in-depth analysis of scope on the enone component is described in Table 6. We were pleased to see that both the replacement of the β-methyl moiety with a longer alkyl chain (butyl)

**Table 4** Utilization of an improved proline sulphonamide catalyst<sup>a</sup>


Entry	Catalyst (20 mol %)	Additives	Yield (%)	er (dr)
1	Hua Cat	BnNH <sub>2</sub> (1 equiv.), mol. sieves, 60 h	67	92 : 8 (>20 : 1)
2	Hua Cat II	BnNH <sub>2</sub> (1 equiv.), mol. sieves, 60 h	74	94.5 : 5.5 (>20 : 1)
3	Hua Cat II	BnNH <sub>2</sub> (1 equiv.), 48 h	66	85.5 : 14.5 (20 : 1)
4	Hua Cat II	BnNH <sub>2</sub> (0.8 equiv.), mol. sieves, 60 h	56	91.5 : 8.5 (>20 : 1)
5	Hua Cat II	BnNH <sub>2</sub> (0.5 equiv.), ( <i>p</i> -C <sub>6</sub> H <sub>4</sub> F)CO <sub>2</sub> H (1 mol%), mol. sieves, 60 h	70	90.5 : 9.5 (>20 : 1)

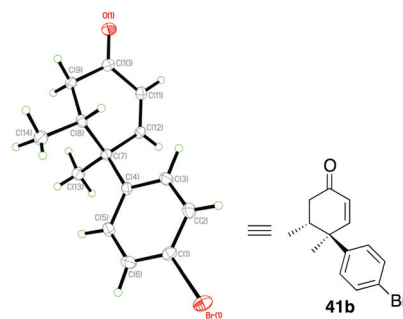
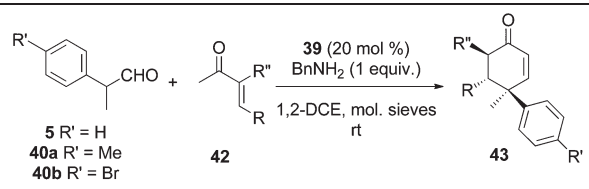
<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis.

**Table 5** Scope of aldehyde component<sup>a</sup>


Entry	R	Yield (%)	er (dr)
A	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -	56	94.4 : 5.6 (>20 : 1)
B	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> -	54	93.6 : 6.4 (>20 : 1)
C	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	52	93.6 : 6.4 (20 : 1)
D	MeO <sub>2</sub> C-	72	n/d (1.5 : 1)

<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis.

was tolerated with a variety of aldehyde nucleophiles (entries a–c) as well as additional substitution on the alkene (entry d); however,  $\alpha$ -branching at this position appeared to be too sterically demanding (entry e). Aromatic substitution in the  $\beta$ -position does lead to enantioenriched products **43f** and **43g** in modest chemical yield (entries f–g). Product **43g** produced crystals that were suitable for X-ray crystallographic analysis (Fig. 4).<sup>19</sup> We also studied the placement of functional groups on the  $\beta$ -position of the enone. Using of propyl halides (*e.g.* **42h** and **42i**) led to modest chemical yield and greatly reduced enantioselectivity (entries h and i). Interestingly, this effect appears to be limited to the propyl halides (entries h and i) as propyl tosylate (entry j) as well as butyl and pentyl iodides (entries o–p) give more reasonable enantioselectivities. Alkenes, benzyl ethers, silyloxy moieties and azides are all tolerated on the alkyl chain (entries k–n). We were also pleased to see that phenyl sulfone and phthalamide moieties could also be incorporated with good levels of enantioselectivity (entries q–r).

**Fig. 3** ORTEP representation of cyclohexenone **41b**.**Table 6** Scope of enone component<sup>a</sup>


Entry	R	R'	R''	Yield (%)	er (dr)
a	Bu	H	H	84	95.7 : 4.3 (>20 : 1)
b	Bu	Me	H	76	91.5 : 8.5 (>20 : 1)
c	Bu	Br	H	68	95.9 : 4.1 (>20 : 1)
d	Me	H	Me	33	89 : 11 (>20 : 1)
e	<i>i</i> -Pr	H	H	0	n/a
f	Ph	H	H	48	97.5 : 2.5 (>20 : 1)
g	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	H	43	87.8 : 12.2 (>20 : 1)
h	Br(CH <sub>2</sub> ) <sub>3</sub> -	H	H	55	63.8 : 36.2 (>20 : 1)
i	I(CH <sub>2</sub> ) <sub>3</sub> -	H	H	65	56.6 : 43.4 (>20 : 1)
j	TsO(CH <sub>2</sub> ) <sub>3</sub> -	H	H	32	88.3 : 11.7 (16 : 1)
k	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>3</sub> -	H	H	79	92.6 : 7.4 (>20 : 1)
l	BnO(CH <sub>2</sub> ) <sub>4</sub> -	H	H	68	92.7 : 7.3 (>20 : 1)
m	TBSO(CH <sub>2</sub> ) <sub>4</sub> -	H	H	68	89.7 : 10.3 (>20 : 1)
n	N <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> -	H	H	54	91.4 : 8.6 (>20 : 1)
o	I(CH <sub>2</sub> ) <sub>4</sub> -	H	H	62	81.6 : 18.4 (>20 : 1)
p	I(CH <sub>2</sub> ) <sub>5</sub> -	H	H	55	92.8 : 7.2 (15 : 1)
q	PhSO <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -	H	H	39	98.8 : 1.2 (>20 : 1)
r	PhthN(CH <sub>2</sub> ) <sub>5</sub> -	H	H	61	96.9 : 3.1 (8 : 1)

<sup>a</sup> Enantiomeric ratios (er) determined by chiral HPLC analysis and diastereomeric ratios (dr) determined by <sup>1</sup>H NMR analysis. <sup>b</sup> This reaction was run using catalyst **12**. Use of catalyst **39** gave lower levels of enantioselectivity (80 : 20 er).

The stereochemically rich cyclohexenone scaffold can be further derivatized with high levels of diastereoselectivity (Scheme 6). Enolization using LDA and DMPU followed by the addition of a suitable electrophile produced the  $\alpha$ -functionalized products **44** and **45**. Nucleophilic addition to the enone scaffolds was possible in both a 1,2- and a 1,4-pathway. Addition of methyl or phenyllithium provided the 3° alcohol products **46** and **47** in high selectivity and chemical yield. We were unable to determine the relative stereochemistry of the newly formed 3° alcohol moiety. The conjugate addition<sup>20</sup> proceeded equally well – with again high levels of diastereoselectivity being observed in products **48** and **49**.

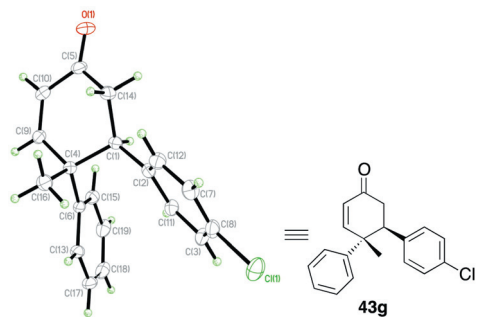
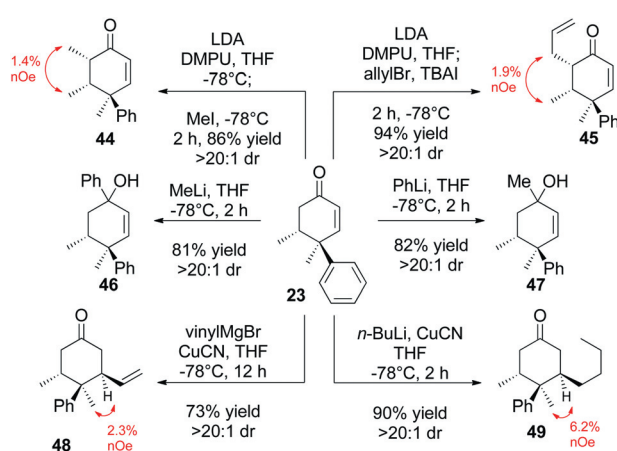


Fig. 4 ORTEP representation of cyclohexenone **43g**.

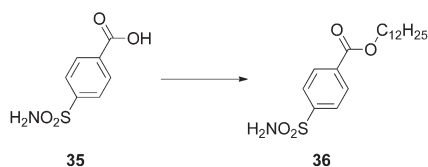


Scheme 6 Derivatization of cyclohexenone scaffold.

## Conclusion

In conclusion, the extension of the Hajos–Parrish reaction<sup>3</sup> to include aldehyde components with acyclic enones represents one of first major advances to since its discovery nearly forty years ago. This proline sulphonamide-catalysed protocol generates useful cyclohexenone building blocks in a highly stereoselective process. The scope of this transformation has been extensively explored and subsequent derivatization of the product enone scaffold has been demonstrated. A plausible mechanism is outlined for this transformation. Further application of this chemistry in natural product synthesis will be disclosed in due course.

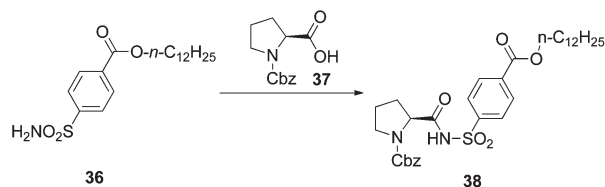
## Experimental section



### Sulphonamide 36

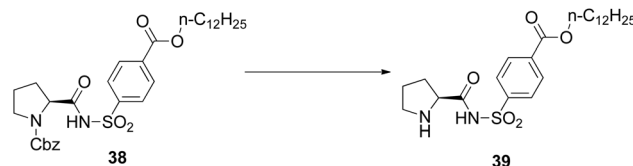
To a solution of 1-dodecanol (9.30 g, 50 mmol) in DMF (100 mL) was added sulphonamide **35** (5.03 g, 25 mmol), DMAP (1.53 g, 12.5 mmol) and EDCI (4.80 g, 25 mmol) respectively. The reaction mixture was stirred at room temperature for 48 h before being partitioned between EtOAc (150 mL)

and aq. HCl (50 mL, 1 N). The organic layer was washed with brine (3 × 100 mL). The dried (Na<sub>2</sub>SO<sub>4</sub>) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5–25% EtOAc–CH<sub>2</sub>Cl<sub>2</sub>, to give sulphonamide **36** (7.26 g, 19.7 mmol, 79%) as a white solid. Mp: 105–106 °C; IR (neat) 3330, 2916, 2845, 1713, 1282, 1157, 1124, 765, 738, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 4.99 (br s, 2H), 4.38 (t, *J* = 6.8 Hz, 2H), 1.79–1.83 (m, 2H), 1.29–1.46 (m, 18H), 0.90 (t, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 165.2, 145.6, 134.4, 130.4, 126.5, 66.0, 31.9, 29.64, 29.58, 29.53, 29.4, 29.3, 28.6, 26.0, 22.7, 14.1; HRMS (EI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>31</sub>NO<sub>4</sub>S (M<sup>+</sup>), 369.1974 found 369.1971.



### Z-L-Sulphonamide 38

To a solution of Z-L-proline **37** (2.88 g, 11.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (58 mL) was added sulphonamide **36** (4.27 g, 11.6 mmol), DMAP (1.41 g, 11.6 mmol) and EDCI (2.22 g, 11.6 mmol) respectively. The reaction mixture was stirred at room temperature for 4 d before being partitioned between DCM (50 mL) and aq. HCl (50 mL, 1 N). The organic layer was washed with half-saturated brine (3 × 80 mL). The dried (Na<sub>2</sub>SO<sub>4</sub>) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10–60% EtOAc–CH<sub>2</sub>Cl<sub>2</sub>, to give Z-L-sulphonamide **38** (5.06 g, 8.42 mmol, 73%) as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -94.0° (*c* = 3.1, CHCl<sub>3</sub>); IR (neat) 3477, 2922, 2851, 1718, 1691, 1615, 1435, 1266, 1092, 863, 770, 700, 618 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.19–7.29 (m, 5H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.91 (d, *J* = 12.4 Hz, 1H), 4.23–4.31 (m, 3H), 3.35–3.39 (m, 2H), 1.69–2.01 (m, 6H), 1.29–1.43 (m, 19H), 0.90 (t, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 165.4, 156.2, 146.1, 136.3, 133.2, 129.6, 128.4, 127.9, 127.7, 127.0, 67.3, 65.5, 62.8, 46.9, 31.9, 29.7, 29.6, 29.4, 28.7, 26.0, 24.3, 22.7, 14.1; HRMS (CI<sup>+</sup>) calcd for C<sub>32</sub>H<sub>45</sub>N<sub>2</sub>O<sub>7</sub>S (M + 1), 601.2947 found 601.2921.



### Sulphonamide 39

To a solution of Z-L-sulphonamide **38** (3.72 g, 6.20 mmol) in MeOH (100 mL) was added Pd/C (0.37 g, 10%). The mixture was stirred at rt for under an atmosphere of hydrogen. After 20 h, the reaction was filtered through Celite and silica gel pad, and the filtrate was concentrated *in vacuo* to give white solid.

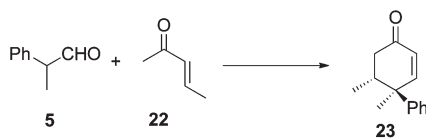


The crude product was purified by chromatography over silica gel, eluting with 1–20% MeOH–CH<sub>2</sub>Cl<sub>2</sub>, to give sulphonamide **39** (2.37 g, 5.08 mmol, 82%) as a white solid. Mp: 166–168 °C;  $[\alpha]_{\text{D}}^{23} = -88.1^\circ$  ( $c = 0.7$ , CHCl<sub>3</sub>); IR (neat) 3129, 3074, 2922, 1729, 1620, 1560, 1391, 1266, 857, 732, 618 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.69 (br s, 1H), 8.12 (d,  $J = 8.4$  Hz, 2H), 8.00 (d,  $J = 8.4$  Hz, 2H), 4.33–4.38 (m, 3H), 3.37–3.51 (m, 2H), 2.35–2.38 (m, 1H), 1.75–2.05 (m, 5H), 1.29–1.45 (m, 19H), 0.90 (t,  $J = 6.4$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.2, 165.6, 146.9, 133.3, 129.8, 126.5, 65.7, 63.0, 46.8, 31.9, 29.9, 29.63, 29.55, 29.4, 29.3, 28.7, 26.0, 24.6, 22.7, 14.1; HRMS (CI<sup>+</sup>) calcd for C<sub>24</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub>S (M + 1), 467.2580 found 467.2566.



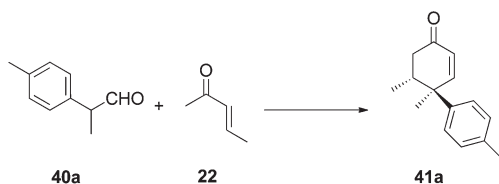
#### General procedure for three-component reaction with acyclic enone (20 mol% catalyst)

The aldehyde (0.25 mmol), benzyl amine (0.25 mmol) and 4 Å MS (0.1 g) were added to dichloroethane solution (0.25 mL) in a vial. After stirring at room temperature for 30 min, the corresponding enone (0.75 mmol, 3 equiv.) and sulphonamide **39** (23.3 mg, 0.05 mmol) were added to it at room temperature. After stirring at same temperature, reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 1–5% EtOAc–hexanes, to give the corresponding product.



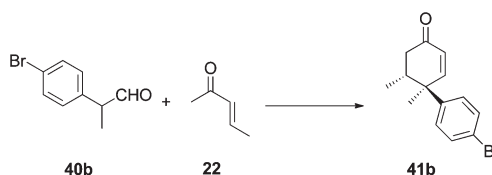
#### 4,5-Dimethyl-4-phenyl-2-cyclohexen-1-one (**23**)

Reaction time 60 h. Purified by chromatography over silica gel, eluting with 1–4% EtOAc–hexanes, to give enone **23** (37.3 mg, 75%, 94.6 : 5.4 er, >20 : 1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99 : 1 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 13.3 min (major) and 16.1 min (minor)] to be 94.6 : 5.4 er: Mp: 48–50 °C;  $[\alpha]_{\text{D}}^{23} = -63.4^\circ$  ( $c = 1.2$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.27–7.40 (m, 5H), 6.84 (d,  $J = 10.0$  Hz, 1H), 6.10 (d,  $J = 10.0$  Hz, 1H), 2.36–2.45 (m, 3H), 1.47 (s, 3H), 0.84–0.86 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.9, 159.1, 146.2, 128.4, 127.4, 126.8, 126.7, 44.2, 42.6, 40.6, 16.9, 15.8; HRMS (CI<sup>+</sup>) calcd for C<sub>14</sub>H<sub>17</sub>O (M + 1), 201.1279 found 201.1269.



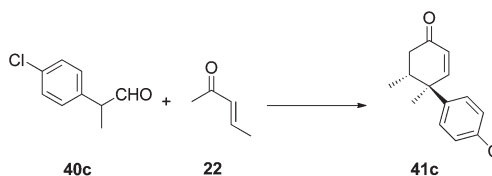
#### 4,5-Dimethyl-4-(4-methylphenyl)-2-cyclohexen-1-one **41a**

Reaction time 60 h. Purified by chromatography over silica gel, eluting with 1–4% EtOAc–hexanes, to give enone **41a** (30.1 mg, 56%, 94.4 : 5.6 er, >20 : 1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OJ column, 95 : 5 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 9.89 min (major) and 18.5 min (minor)] to be 94.4 : 5.6 er: Mp: 64–66 °C;  $[\alpha]_{\text{D}}^{23} = -90.4^\circ$  ( $c = 1.2$ , CHCl<sub>3</sub>); IR (neat) 2961, 1680, 1455, 1385, 1276, 1116, 816, 778 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.18–7.22 (m, 4H), 6.83 (d,  $J = 10.0$  Hz, 1H), 6.09 (d,  $J = 10.0$  Hz, 1H), 2.36–2.46 (m, 6H), 1.45 (s, 3H), 0.86–0.87 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  200.0, 159.4, 143.3, 136.4, 129.1, 127.3, 126.7, 43.9, 42.6, 40.6, 20.9, 16.9, 15.8; HRMS (CI<sup>+</sup>) calcd for C<sub>15</sub>H<sub>19</sub>O (M + 1), 215.1436 found 215.1435.



#### 4-(4-Bromophenyl)-4,5-dimethyl-2-cyclohexen-1-one **41b**<sup>21</sup>

Reaction time 60 h. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **41b** (37.4 mg, 54%, 93.6 : 6.4 er, >20 : 1 dr, colorless crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OJ column, 98 : 2 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 16.6 min (major) and 20.3 min (minor)] to be 93.6 : 6.4 er: Mp: 144–146 °C;  $[\alpha]_{\text{D}}^{23} = -101.6^\circ$  ( $c = 1.3$ , CHCl<sub>3</sub>); IR (neat) 2976, 1685, 1457, 1081, 808, 792, 716 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.47–7.51 (m, 1H), 7.17–7.20 (m, 1H), 6.78 (d,  $J = 10.0$  Hz, 1H), 6.10 (d,  $J = 10.4$  Hz, 1H), 2.34–2.44 (m, 3H), 1.44 (s, 3H), 0.84 (d,  $J = 6.0$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.5, 158.1, 145.4, 131.5, 128.7, 127.8, 120.8, 44.0, 42.4, 40.6, 16.9, 15.7; HRMS (CI<sup>+</sup>) calcd for C<sub>14</sub>H<sub>16</sub>OBr (M + 1), 279.0385 found 279.0382.

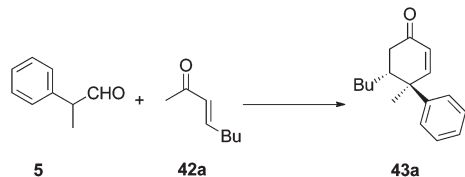


#### 4-(4-Chlorophenyl)-4,5-dimethyl-2-cyclohexen-1-one **41c**

Reaction time 60 h. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **41c** (30.6 mg, 52%, 93.6 : 6.4 er, >20 : 1 dr, light yellow crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OJ column, 95 : 5 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 11.6 min (major) and 14.2 min (minor)] to be 93.6 : 6.4 er: Mp: 133–135 °C;  $[\alpha]_{\text{D}}^{23} = -97.6^\circ$  ( $c = 1.3$ , CHCl<sub>3</sub>); IR (neat) 2965, 2927, 1685, 1484, 1457, 1271, 1005, 814, 732, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.36 (m, 2H), 7.23–7.28 (m, 2H), 6.79 (d,  $J = 10.4$  Hz, 1H), 6.10 (d,  $J = 10.0$  Hz, 1H),

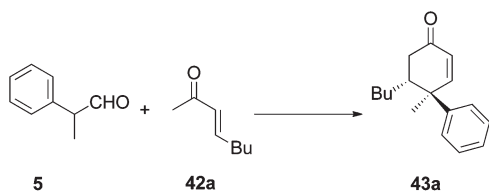


2.33–2.47 (m, 3H), 1.44 (s, 3H), 0.84 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.5, 158.3, 144.8, 132.7, 128.5, 128.3, 127.7, 44.0, 42.5, 40.6, 16.9, 15.7; HRMS (CI<sup>+</sup>) calcd for  $\text{C}_{14}\text{H}_{16}\text{OCl}$  ( $M + 1$ ), 235.0890 found 235.0883.



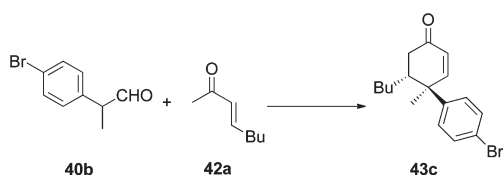
#### 5-Butyl-4-methyl-4-phenyl-2-cyclohexen-1-one (43a)

Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–3% EtOAc–hexanes, to give enone **43a** (50.9 mg, 84%, 95.7 : 4.3 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99.5 : 0.5 hexanes–i-PrOH, 0.8 mL min<sup>-1</sup>, retention times 17.0 min (major) and 12.6 min (minor)] to be 95.7 : 4.3 er.  $[\alpha]_{\text{D}}^{23} = -100.9^\circ$  ( $c = 2.0$ ,  $\text{CHCl}_3$ ); IR (neat) 2253, 2930, 1680, 1498, 1373, 1272, 1023, 762, 704 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26–7.39 (m, 4H), 6.80 (d,  $J = 10.0$  Hz, 1H), 6.07 (d,  $J = 10.0$  Hz, 1H), 2.61 (dd,  $J = 16.0$ , 3.2 Hz, 1H), 2.18–2.34 (m, 2H), 1.46 (s, 3H), 0.92–1.30 (m, 7H), 0.73 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 159.5, 146.3, 128.4, 127.2, 127.0, 126.7, 45.4, 44.4, 39.6, 29.2, 29.1, 22.4, 16.9, 13.8; HRMS (CI<sup>+</sup>) calcd for  $\text{C}_{17}\text{H}_{23}\text{O}$  ( $M + 1$ ), 243.1749 found 243.1748.



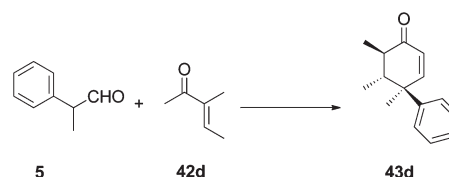
#### 5-Butyl-4-methyl-4-(4-methylphenyl)-2-cyclohexen-1-one (43b)

Reaction time 3 d. Purified by chromatography over silica gel, eluting with 1–4% EtOAc–hexanes, to give enone **35e** (48.9 mg, 76%, 91.5 : 8.5 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel AS-H column, 98 : 2 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 33.9 min (major) and 38.1 min (minor)] to be 91.5 : 8.5 er.  $[\alpha]_{\text{D}}^{23} = -97.4^\circ$  ( $c = 2.0$ ,  $\text{CHCl}_3$ ); IR (neat) 2954, 2927, 1685, 1457, 1266, 1124, 1021, 814, 776, 721 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17–7.22 (m, 4H), 6.78 (d,  $J = 10.0$  Hz, 1H), 6.06 (d,  $J = 10.0$  Hz, 1H), 2.61 (dd,  $J = 16.4$ , 3.6 Hz, 1H), 2.38 (s, 3H), 2.17–2.34 (m, 2H), 1.45 (s, 3H), 0.94–1.29 (m, 6H), 0.77 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.1, 159.8, 143.3, 136.3, 129.1, 127.0, 126.8, 45.3, 44.1, 39.6, 29.3, 29.1, 22.5, 20.9, 17.0, 13.8; HRMS (CI<sup>+</sup>) calcd for  $\text{C}_{18}\text{H}_{25}\text{O}$  ( $M + 1$ ), 257.1905 found 257.1910.



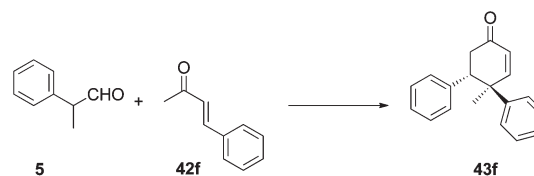
#### 4-(4-Bromophenyl)-5-butyl-4-methyl-2-cyclohexen-1-one (43c)

Reaction time 3 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43c** (54.5 mg, 68%, 95.9 : 4.1 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel AS-H column, 90 : 10 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 36.8 min (major) and 28.2 min (minor)] to be 95.9 : 4.1 er.  $[\alpha]_{\text{D}}^{23} = -125^\circ$  ( $c = 1.5$ ,  $\text{CHCl}_3$ ); IR (neat) 2953, 2930, 1680, 1490, 1077, 1003, 816, 723 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.52 (m, 2H), 7.18–7.21 (m, 2H), 6.74 (d,  $J = 10.0$  Hz, 1H), 6.08 (d,  $J = 10.0$  Hz, 1H), 2.62 (dd,  $J = 16.8$ , 4.0 Hz, 1H), 2.14–2.33 (m, 2H), 1.45 (s, 3H), 0.89–1.31 (m, 6H), 0.77 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.6, 158.6, 145.4, 131.5, 128.8, 127.5, 120.8, 45.4, 44.3, 39.5, 29.3, 29.1, 22.4, 16.9, 13.8; HRMS (CI<sup>+</sup>) calcd for  $\text{C}_{17}\text{H}_{22}\text{OBr}$  ( $M + 1$ ), 321.0854 found 321.0860.



#### 4,5,6-Trimethyl-4-phenyl-2-cyclohexen-1-one (43d)

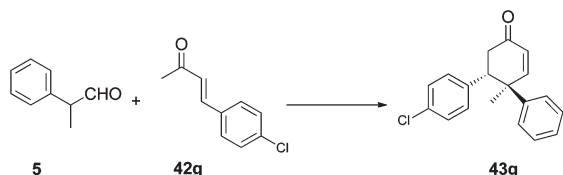
Reaction time 7 d. Purified by chromatography over silica gel, eluting with 1–4% EtOAc–hexanes, to give enone **43d** (17.6 mg, 33%, 89 : 11 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel AS-H column, 99 : 1 hexanes–i-PrOH, 0.9 mL min<sup>-1</sup>, 254 nm, retention times 13.5 min (major) and 11.1 min (minor)] to be 89 : 11 er.  $[\alpha]_{\text{D}}^{23} = -32.1^\circ$  ( $c = 1.4$ ,  $\text{CHCl}_3$ ); IR (neat) 2969, 2922, 1673, 1459, 1365, 1116, 1019, 735, 700 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26–7.39 (m, 6H), 6.60 (q,  $J = 1.2$  Hz, 1H), 2.36–2.46 (m, 2H), 1.87 (d,  $J = 1.6$  Hz, 3H), 1.44 (s, 3H), 0.82–0.84 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 154.4, 147.0, 133.4, 128.3, 126.9, 126.6, 44.5, 42.6, 40.8, 17.2, 15.8, 15.7; HRMS (CI<sup>+</sup>) calcd for  $\text{C}_{15}\text{H}_{19}\text{O}$  ( $M + 1$ ), 215.1436 found 215.1442.



#### 4,5-Diphenyl-4-methyl-2-cyclohexen-1-one (43f)

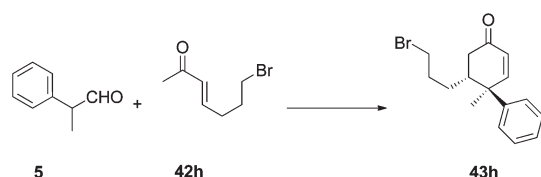
Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–4% EtOAc–hexanes, to give enone **43f** (31.1 mg, 47%, 97.5 : 2.5 er, >20 : 1 dr, white solid). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99 : 1 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 29.1 min (major) and 23.8 min (minor)] to be 97.5 : 2.5 er. Mp: 104–106 °C;  $[\alpha]_{\text{D}}^{23} = -102.9^\circ$  ( $c = 1.4$ ,  $\text{CHCl}_3$ ); IR (neat) 3020, 2971, 1669, 1495, 1446, 1266, 798, 770, 700 cm<sup>-1</sup>;  $^1\text{H}$  NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.32 (m, 4H), 7.12–7.21 (m, 3H), 7.05 (dd,  $J$  = 8.0, 2.4 Hz, 1H), 6.97 (d,  $J$  = 10.0 Hz, 1H), 6.64 (d,  $J$  = 7.2 Hz, 2H), 6.22 (d,  $J$  = 10.0 Hz, 1H), 3.57 (dd,  $J$  = 14.0, 3.6 Hz, 1H), 3.11 (dd,  $J$  = 16.8, 14.2 Hz, 1H), 2.63 (dd,  $J$  = 16.8, 4.0 Hz, 1H), 1.40 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.9, 158.8, 145.5, 138.9, 129.0, 128.2, 127.6, 127.19, 127.17, 127.0, 126.9, 52.2, 45.4, 40.1, 17.3; HRMS (CI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>19</sub>O (M + 1), 263.1436 found 263.1437.



#### 5-(4-Chlorophenyl)-4-phenyl-4-methyl-2-cyclohexen-1-one (43g)

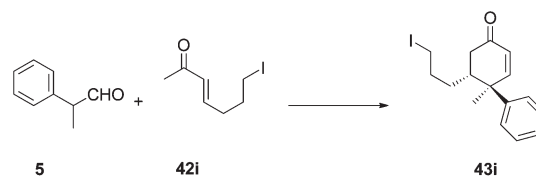
Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43g** (32.2 mg, 43%, 87.8 : 12.2 er, >20 : 1 dr, light yellow crystal). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel AS-H column, 90 : 10 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 44.5 min (major) and 37.6 min (minor)] to be 87.8 : 12.2 er: Mp: 106–108 °C; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = –150.2° ( $c$  = 1.1, CHCl<sub>3</sub>); IR (neat) 3031, 2976, 1685, 1495, 1255, 1097, 1015, 830, 759, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.34 (m, 3H), 7.11 (d,  $J$  = 8.4 Hz, 2H), 7.04 (dd,  $J$  = 8.0, 2.0 Hz, 2H), 6.96 (d,  $J$  = 10.4 Hz, 1H), 6.54 (d,  $J$  = 8.4 Hz, 2H), 6.22 (d,  $J$  = 10.4 Hz, 1H), 3.54 (dd,  $J$  = 14.4, 3.6 Hz, 1H), 3.06 (dd,  $J$  = 16.8, 14.8 Hz, 1H), 2.60 (dd,  $J$  = 16.4, 3.6 Hz, 1H), 1.38 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.4, 158.6, 145.1, 137.4, 132.9, 130.2, 128.3, 127.8, 127.2, 127.1, 51.6, 45.2, 39.9, 17.1; HRMS (CI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>18</sub>OCl (M + 1), 297.1046 found 297.1044.



#### 5-(3-Bromopropyl)-4-phenyl-4-methyl-2-cyclohexen-1-one (43h)

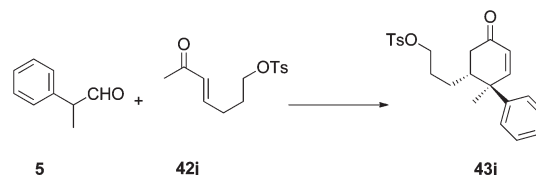
Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43h** (42.2 mg, 55%, 63.8 : 36.2 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 98 : 2 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 20.0 min (major) and 24.0 min (minor)] to be 63.8 : 36.2 er: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = –26.7° ( $c$  = 1.1, CHCl<sub>3</sub>); IR (neat) 2926, 1684, 1660, 1501, 770, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.41 (m, 5H), 6.81 (d,  $J$  = 10.4 Hz, 1H), 6.09 (d,  $J$  = 10.0 Hz, 1H), 3.13–3.29 (m, 2H), 2.58 (dd,  $J$  = 16.4, 3.6 Hz, 1H), 2.21–2.39 (m, 2H), 1.77–1.89 (m, 1H), 1.24–1.57 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.3, 159.2, 145.8, 128.6, 127.2, 127.0, 126.9, 45.1, 44.4, 39.7, 33.2, 30.3, 28.5, 16.9;

HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>19</sub>OBr (M<sup>+</sup>), 306.0619 found 306.0618.



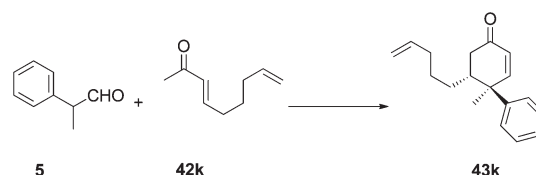
#### 5-(3-Iodopropyl)-4-methyl-4-phenyl-2-cyclohexen-1-one (43i)

Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–3% EtOAc–hexanes, to give enone **43i** (57.6 mg, 65%, 56.6 : 43.4 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99 : 1 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 23.9 min (major) and 19.8 min (minor)] to be 56.6 : 43.4 er; IR (neat) 2957, 2918, 2848, 1680, 1455, 1369, 1276, 1023, 781, 766, 704 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.41 (m, 5H), 6.81 (d,  $J$  = 10.0 Hz, 1H), 6.09 (d,  $J$  = 10.0 Hz, 1H), 2.91–3.07 (m, 2H), 2.57 (dd,  $J$  = 16.4, 3.6 Hz, 1H), 2.24–2.38 (m, 2H), 1.71–1.89 (m, 1H), 1.24–1.57 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.3, 159.2, 145.8, 128.6, 127.2, 127.0, 126.9, 44.8, 44.3, 39.7, 31.0, 30.8, 16.9, 6.0; HRMS (CI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>19</sub>OI (M<sup>+</sup>), 354.0481 found 354.0478.



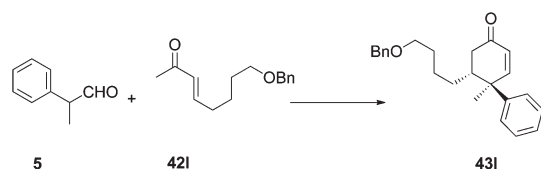
#### 4-Methyl-4-phenyl-5-(3-tosyloxybutyl)-2-cyclohexen-1-one (43j)

Reaction time 4 d. Purified by chromatography over silica gel, eluting with 2–20% EtOAc–hexanes, to give enone **43j** (31.8 mg, 32%, 88.3 : 11.7 er, 16 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel AD column, 90 : 10 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 36.7 min (major) and 30.2 min (minor)] to be 88.3 : 11.7 er: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = –24.6° ( $c$  = 1.1, CHCl<sub>3</sub>); IR (neat) 2957, 2926, 1677, 1357, 1178, 953, 918, 816, 762, 704, 661 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8.0 Hz, 2H), 7.26–7.40 (m, 7H), 6.78 (d,  $J$  = 10.0 Hz, 1H), 6.07 (d,  $J$  = 10.0 Hz, 1H), 3.82–3.88 (m, 2H), 2.47–2.52 (m, 4H), 2.14–2.31 (m, 2H), 1.61–1.62 (m, 1H), 1.44 (s, 3H), 1.23–1.29 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.1, 159.1, 145.8, 144.8, 133.1, 129.8, 128.6, 127.9, 127.1, 127.0, 126.8, 70.1, 45.2, 44.3, 39.4, 26.5, 25.9, 21.7, 17.0; HRMS (CI<sup>+</sup>) calcd for C<sub>23</sub>H<sub>26</sub>O<sub>4</sub>S (M<sup>+</sup>), 398.1552 found 398.1543.



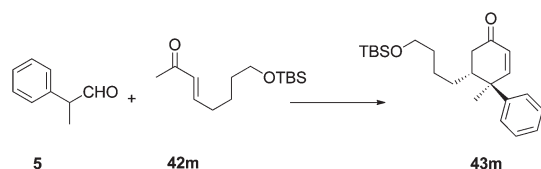
#### 4-Methyl-5-(4-pentenyl)-4-phenyl-2-cyclohexen-1-one (43k)

Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–3% EtOAc–hexanes, to give enone **43k** (50.2 mg, 79%, 92.6 : 7.4 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99.5 : 0.5 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 13.5 min (major) and 17.6 min (minor)] to be 92.6 : 7.4 er;  $[\alpha]_D^{23} = -78.5^\circ$  ( $c = 1.2$ , CHCl<sub>3</sub>); IR (neat) 3058, 3023, 2926, 2852, 1684, 1498, 1459, 1264, 1023, 992, 914, 789, 762, 704 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.27–7.40 (m, 5H), 6.80 (d,  $J = 10.0$  Hz, 1H), 6.08 (d,  $J = 10.0$  Hz, 1H), 5.58–5.66 (m, 1H), 4.81–4.86 (m, 2H), 2.61 (dd,  $J = 16.4$ , 2.8 Hz, 1H), 2.19–2.35 (m, 2H), 1.76–1.95 (m, 2H), 1.46 (s, 3H), 1.05–1.46 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.8, 159.4, 146.2, 138.2, 128.4, 127.2, 127.0, 126.8, 114.6, 45.3, 44.4, 39.6, 33.3, 29.0, 26.1, 16.9; HRMS (CI<sup>+</sup>) calcd for C<sub>18</sub>H<sub>22</sub>O (M<sup>+</sup>), 254.1671 found 254.1663.



#### 4-Methyl-4-phenyl-5-(4-phenylmethoxybutyl)-2-cyclohexen-1-one (43i)

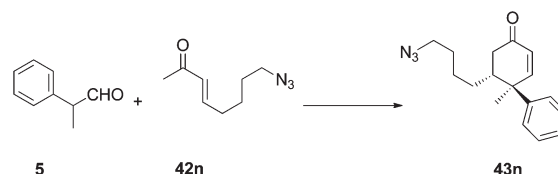
Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43i** (59.2 mg, 68%, 92.7 : 7.3 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OJ column, 85 : 15 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 20.9 min (major) and 29.2 min (minor)] to be 92.7 : 7.3 er;  $[\alpha]_D^{23} = -51.3^\circ$  ( $c = 1.6$ , CHCl<sub>3</sub>); IR (neat) 2926, 2852, 1680, 1451, 1097, 758, 735, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26–7.39 (m, 10H), 6.80 (d,  $J = 10.0$  Hz, 1H), 6.08 (d,  $J = 10.0$  Hz, 1H), 4.41 (s, 2H), 3.28–3.31 (m, 2H), 2.62 (dd,  $J = 16.0$ , 2.8 Hz, 1H), 2.19–2.34 (m, 2H), 1.02–1.46 (m, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.8, 159.4, 146.2, 138.5, 128.43, 128.35, 127.6, 127.5, 127.2, 127.0, 126.8, 72.9, 69.9, 45.4, 44.4, 39.6, 29.5, 29.4, 23.6, 16.9; HRMS (EI<sup>+</sup>) calcd for C<sub>24</sub>H<sub>28</sub>O<sub>2</sub> (M<sup>+</sup>), 348.2089 found 348.2085.



#### 5-[4-[(1,1-Dimethylethyl)dimethylsilyl]oxybutyl]-4-methyl-4-phenyl-2-cyclohexen-1-one (43m)

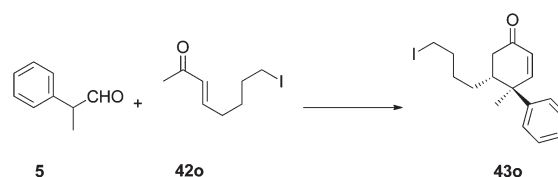
Reaction time 5 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43m** (62.9 mg, 68%, 89.7 : 10.3 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm

Daicel OJ column, 85 : 15 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 11.8 min (major) and 14.7 min (minor)] to be 89.7 : 10.3 er;  $[\alpha]_D^{23} = -59.0^\circ$  ( $c = 2.0$ , CHCl<sub>3</sub>); IR (neat) 2949, 2930, 2852, 1684, 1470, 1385, 1252, 1101, 1027, 836, 774, 704, 665 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26–7.39 (m, 5H), 6.80 (d,  $J = 10.4$  Hz, 1H), 6.07 (d,  $J = 10.0$  Hz, 1H), 3.44 (t,  $J = 6.4$  Hz, 2H), 2.61 (dd,  $J = 16.0$ , 3.2 Hz, 1H), 2.23–2.34 (m, 2H), 1.46 (s, 3H), 1.37 (m, 7H), 0.86 (s, 9H), -0.005 (s, 3H), -0.008 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.8, 159.5, 146.2, 128.4, 127.2, 126.9, 126.8, 62.7, 45.5, 44.4, 39.6, 32.5, 29.4, 26.0, 23.2, 18.3, 16.9, -5.32; HRMS (CI<sup>+</sup>) calcd for C<sub>23</sub>H<sub>37</sub>O<sub>2</sub>Si (M + 1), 373.2563 found 373.2549.



#### 5-(4-Azidobutyl)-4-methyl-4-phenyl-2-cyclohexen-1-one (43n)

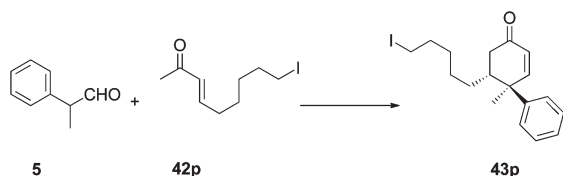
Reaction time 4 d (no light). Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43n** (38.2 mg, 54%, 91.4 : 8.6 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 98 : 2 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 20.0 min (major) and 25.8 min (minor)] to be 91.4 : 8.6 er;  $[\alpha]_D^{23} = -67.9^\circ$  ( $c = 1.2$ , CHCl<sub>3</sub>); IR (neat) 2934, 2860, 2093, 1684, 1260, 766, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.41 (m, 5H), 6.81 (d,  $J = 10.0$  Hz, 1H), 6.08 (d,  $J = 10.0$  Hz, 1H), 3.07 (t,  $J = 6.4$  Hz, 2H), 2.60 (dd,  $J = 16.4$ , 3.2 Hz, 1H), 2.18–2.36 (m, 2H), 1.46 (s, 3H), 1.05–1.45 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.5, 159.3, 146.0, 128.5, 127.2, 126.9, 51.0, 45.3, 44.4, 39.6, 29.0, 28.5, 24.0, 16.8; HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O (M<sup>+</sup>), 283.1685 found 283.1677.



#### 5-(4-Iodobutyl)-4-methyl-4-phenyl-2-cyclohexen-1-one (43o)

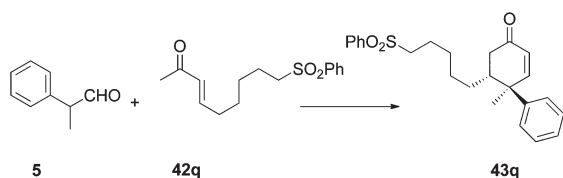
Reaction time 4 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43o** (57.1 mg, 62%, 81.6 : 18.4 er, >20 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99 : 1 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 18.1 min (major) and 23.5 min (minor)] to be 81.6 : 18.4 er;  $[\alpha]_D^{23} = -27.3^\circ$  ( $c = 1.6$ , CHCl<sub>3</sub>); IR (neat) 2926, 2856, 1680, 1498, 1459, 1369, 1101, 1027, 766, 707 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.29–7.42 (m, 5H), 6.82 (d,  $J = 10.4$  Hz, 1H), 6.09 (d,  $J = 10.0$  Hz, 1H), 2.96–3.02 (m, 2H), 2.63 (dd,  $J = 16.4$ , 3.6 Hz, 1H), 2.23–2.37 (m, 2H), 1.09–1.65 (m, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.6, 159.3, 146.0, 128.5,

127.2, 126.9, 45.2, 44.4, 39.6, 32.9, 28.4, 27.8, 16.8, 6.23; HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>21</sub>OI (M<sup>+</sup>), 368.0638 found 368.0625.



#### 5-(5-Iodopentyl)-4-methyl-4-phenyl-2-cyclohexen-1-one (43p)

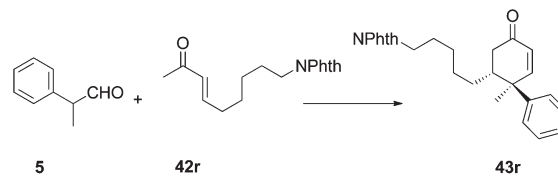
Reaction time 5 d. Purified by chromatography over silica gel, eluting with 1–5% EtOAc–hexanes, to give enone **43p** (52.6 mg, 55%, 92.8 : 7.2 er, 16 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 99 : 1 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 16.9 min (major) and 21.9 min (minor)] to be 92.8 : 7.2 er: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -64.2° (*c* = 2.1, CHCl<sub>3</sub>); IR (neat) 2922, 2851, 1685, 1451, 1364, 1260, 1168, 1026, 787, 765, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.40 (m, 5H), 6.80 (d, *J* = 10.0 Hz, 1H), 6.08 (dd, *J* = 10.4, 0.8 Hz, 1H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.59 (dd, *J* = 16.8, 2.8 Hz, 1H), 1.59–1.66 (m, 2H), 1.46 (s, 3H), 1.12–1.33 (m, 8H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.7, 159.4, 146.1, 128.5, 127.2, 126.94, 126.86, 45.3, 44.4, 39.6, 33.0, 30.1, 20.3, 25.8, 16.9, 6.84; HRMS (EI<sup>+</sup>) calcd for C<sub>18</sub>H<sub>23</sub>OI (M<sup>+</sup>), 382.0794 found 382.0809.



#### 4-Methyl-4-phenyl-5-(4-phenylsulfonyl)-2-cyclohexen-1-one (43q)

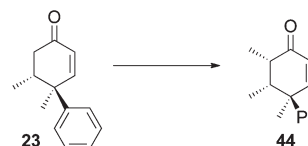
Reaction time 5 d. Purified by chromatography over silica gel, eluting with 5–20% EtOAc–hexanes, to give enone **43q** (37.2 mg, 39%, 98.8 : 1.2 er, 15 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 90 : 10 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 37.2 min (major) and 28.2 min (minor)] to be 98.8 : 1.2 er: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -55.9° (*c* = 1.8, CHCl<sub>3</sub>); IR (neat) 2922, 2867, 1677, 1447, 1307, 1143, 1085, 766, 707, 684, 598 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.83–7.85 (m, 2H), 7.54–7.68 (m, 4H), 7.26–7.39 (m, 4H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.06 (d, *J* = 10.4 Hz, 1H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.51 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.14–2.30 (m, 2H), 1.02–1.60 (m, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.3, 159.2, 145.9, 139.1, 133.7, 129.3, 128.6, 128.0, 127.2, 127.0, 126.9, 55.8, 45.1, 44.3, 39.5, 29.0, 25.6, 22.3, 16.8; HRMS (EI<sup>+</sup>) calcd for C<sub>23</sub>H<sub>26</sub>O<sub>3</sub>S (M<sup>+</sup>),

382.1603 found 382.1584.



#### 4-Methyl-4-phenyl-5-(6-phthalimidohexyl)-2-cyclohexen-1-one (43r)

Reaction time 5 d. Purified by chromatography over silica gel, eluting with 1–6% EtOAc–hexanes, to give enone **43r** (61.3 mg, 61%, 96.9 : 3.1 er, 8 : 1 dr, colorless oil). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 90 : 10 hexanes–i-PrOH, 1.0 mL min<sup>-1</sup>, retention times 26.4 min (major) and 24.5 min (minor)] to be 96.9 : 3.1 er: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -38.3° (*c* = 1.0, CHCl<sub>3</sub>); IR (neat) 2933, 2851, 1767, 1718, 1680, 1467, 1391, 1369, 1064, 765, 721, 705 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.70–7.86 (m, 4H), 7.22–7.37 (m, 5H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 2H), 2.59 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.00–2.33 (m, 3H), 1.10–1.64 (m, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  199.8, 168.4, 159.4, 146.2, 133.9, 132.2, 128.4, 128.3, 127.9, 127.1, 126.9, 126.8, 123.2, 45.4, 44.4, 39.6, 37.8, 29.5, 28.3, 26.63, 26.56, 16.9; HRMS (EI<sup>+</sup>) calcd for C<sub>26</sub>H<sub>27</sub>NO<sub>3</sub> (M<sup>+</sup>), 401.1991 found 401.183.



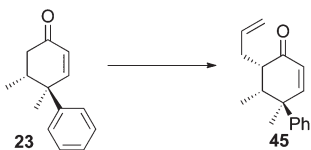
#### 4,5,6-Trimethyl-4-phenyl-2-cyclohexen-1-one (44)

To a solution of **23** (20 mg, 0.1 mmol) in THF (0.2 mL) at -78 °C was added sequentially LDA§ (0.15 mL, 0.15 mmol, 1.0 M in THF–hexanes) and freshly distilled DMPU (0.05 mL, 0.4 mmol). The reaction was gradually warmed to 0 °C over a period of 20 min. After recooling the system to -78 °C, MeI (182.4 mg, 80  $\mu$ L, 1.0 mmol) was added. After 2 h, the reaction was quenched with sat. aq. NH<sub>4</sub>Cl (0.2 mL), warmed to rt and partitioned between Et<sub>2</sub>O (5 mL) and water (5 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 5 mL) and the combined organic layer was dried with anhydrous MgSO<sub>4</sub>, concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **44** (17 mg, 0.08 mmol, 86%, >20 : 1 dr) as a thick oil: [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -38.0°; IR (neat) 2971, 2927, 2878, 1712, 1680 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26–7.39 (m, 5H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.08 (d, *J* = 10.0 Hz, 1H), 2.35–2.43 (m, 1H), 2.03–2.10 (m, 1H), 1.48

§ *Preparation of LDA Solution (1 M in THF–hexanes)*: To a solution of diisopropylamine (0.607 g, 0.85 mmol) in THF (2.63 mL) at -78 °C, was added n-BuLi (2.52 mL, 6.3 mmol, 2.5 M in hexanes). After 5 min, the white slurry was warmed to -10 °C and stirred for 15 min prior to use.

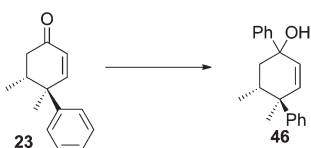


(s, 3H), 1.19 (d,  $J = 6.8$  Hz, 3H), 0.96–1.00 (m, 1H), 0.828 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  201.6, 158.2, 146.8, 128.4, 127.0, 126.7, 126.6, 46.5, 44.9, 44.1, 30.9, 16.1, 13.7, 12.1; HRMS (CI+) calcd for  $\text{C}_{15}\text{H}_{18}\text{O}$  (M+) 215.1436, found 215.1442.



#### 6-Allyl-4,5-dimethyl-4-phenyl-2-cyclohexen-1-one (45)

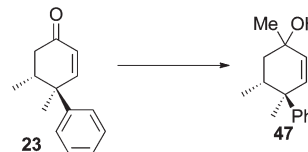
To a solution of **23** (20 mg, 0.1 mmol) in THF (0.2 mL) at  $-78$  °C was added sequentially LDA§ (0.15 mL, 0.15 mmol, 1.0 M in THF–hexanes) and freshly distilled DMPU (0.05 mL, 0.4 mmol). The reaction was gradually warmed to  $0$  °C over a period of 20 min. After recooling the system to  $-78$  °C, allyl bromide (125.1 mg, 90  $\mu\text{L}$ , 1.0 mmol) and TBAI (0.37 g, 1.0 mmol) were added. After 2 h, the reaction was then with sat. aq.  $\text{NH}_4\text{Cl}$  (0.2 mL), warmed to rt and partitioned between  $\text{Et}_2\text{O}$  (5 mL) and water (5 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL) and the combined organic layer was dried with anhydrous  $\text{MgSO}_4$ , concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **45** (0.019 g, 0.08 mmol, 94%,  $>20:1$  dr) as a thick oil:  $[\alpha]_{\text{D}}^{23} = -109.1^\circ$ ; IR (neat) 2973, 1675, 761, 702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26–7.39 (m, 5H), 6.78 (d,  $J = 10.0$  Hz, 1H), 6.09 (d,  $J = 10.0$  Hz, 1H), 5.68–5.80 (m, 1H), 5.00–5.09 (m, 2H), 2.91–2.95 (m, 1H), 2.43–2.47 (m, 1H), 2.22–2.35 (m, 2H), 1.48 (s, 3H), 0.83 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 158.48, 146.7, 135.0, 128.4, 127.1, 127.1, 126.7, 117.1, 48.43, 44.71, 42.6, 30.1, 16.5, 13.2; HRMS (CI+) calcd for  $\text{C}_{17}\text{H}_{20}\text{O}$  (M+) 241.1592, found 241.1584.



#### 4,5-Dimethyl-1,4-diphenyl-2-cyclohexen-1-ol (46)

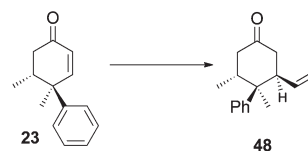
To a solution of **23** (20 mg, 0.1 mmol) in THF (0.2 mL) at  $-78$  °C was added  $\text{PhLi}$  (0.25 mL, 0.4 mmol, 1.7 M in  $\text{Bu}_2\text{O}$ ). After 2 h, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (0.2 mL), warmed to rt and partitioned between  $\text{Et}_2\text{O}$  (5 mL) and water (5 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL) and the combined organic layer was dried with anhydrous  $\text{MgSO}_4$ , concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **46** (23 mg, 0.08 mmol, 82%,  $>20:1$  dr) as a thick oil:  $[\alpha]_{\text{D}}^{23} = -13.8^\circ$ ; IR (neat) 3374, 3085, 3020, 2965, 2867  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 1.2$  Hz, 2H), 7.22–7.46 (m, 8H), 5.93 (d,  $J = 10.0$  Hz, 1H), 5.87 (d,  $J = 11.2$  Hz, 1H), 2.06–2.16 (m, 3H), 1.80–1.86 (m, 1H), 1.42 (s, 3H), 0.70 (d,  $J =$

7.2 Hz, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  148.2, 147.0, 140.1, 130.0, 128.3, 128.1, 127.5, 127.0, 126.3, 126.1, 44.4, 43.6, 37.1, 18.0, 15.8; HRMS (CI+) calcd for  $\text{C}_{20}\text{H}_{22}\text{O}$  (M+) 278.1671, found 278.1664.



#### 1,4,5-Trimethyl-4-phenyl-2-cyclohexen-1-ol (47)

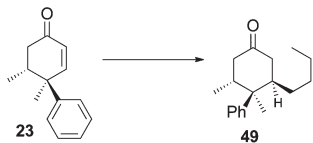
To a solution of **23** (0.02 g, 0.1 mmol) in THF (0.2 mL) at  $-78$  °C was added  $\text{MeLi}$  (0.25 mL, 0.4 mmol, 1.6 M in  $\text{Et}_2\text{O}$ ). After 2 h, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (0.2 mL), warmed to rt and partitioned between  $\text{Et}_2\text{O}$  (5 mL) and water (5 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 3.5$  mL) and the combined organic layer was dried with anhydrous  $\text{MgSO}_4$ , concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **47** (17 mg, 0.08 mmol, 81%,  $>20:1$  dr) as a thick oil:  $[\alpha]_{\text{D}}^{23} = -16.8^\circ$ ; IR (neat) 3281, 3058, 3009, 2971, 2867  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21–7.35 (m, 5H), 5.68 (d,  $J = 10.0$  Hz, 1H), 5.54 (d,  $J = 10.0$  Hz, 1H), 1.93–1.97 (m, 1H), 1.75 (d,  $J = 8.0$  Hz, 2H), 1.58 (s, 2H), 1.44 (s, 3H), 1.32 (s, 3H), 0.79 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  137.5, 132.4, 128.0, 127.0, 125.9, 70.7, 43.9, 43.6, 39.2, 28.8, 17.9, 16.0; HRMS (CI+) calcd for  $\text{C}_{15}\text{H}_{20}\text{O}$  (M+) 216.1514, found 216.1511.



#### 3-Vinyl-4,5-dimethyl-4-phenyl-1-cyclohexanone (48)

To a suspension of  $\text{CuCN}$  (18 mg, 0.2 mmol) in THF (0.2 mL) at  $-78$  °C was added vinyl magnesium bromide (0.6 mL, 0.4 mmol, 0.7 M in THF). The reaction mixture was gradually warmed to  $0$  °C over a period of 30 min. After recooling the system to  $-78$  °C, a solution of **23** (20 mg, 0.1 mmol) in THF (0.3 mL) was added. After 12 h, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (0.2 mL), warmed to rt and partitioned between  $\text{Et}_2\text{O}$  (5 mL) and water (5 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL) and the combined organic layer was dried with anhydrous  $\text{MgSO}_4$ , concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of EtOAc–hexanes to give **48** (16 mg, 0.07 mmol, 73%,  $12:1$  dr) as a thick oil:  $[\alpha]_{\text{D}}^{23} = -29.5^\circ$ ; IR (neat) 3080, 2971, 1707  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22–7.35 (m, 5H), 5.39–5.43 (m, 1H), 4.87 (d,  $J = 10.8$  Hz, 1H), 4.72 (d,  $J = 14.8$  Hz, 1H), 2.80–2.86 (m, 2H), 2.65–2.66 (m, 1H), 2.35–2.56 (m, 3H), 1.61 (s, 3H), 0.95 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  211.0, 145.6, 137.9, 128.0, 127.1, 126.0, 116.7, 52.4, 45.8, 43.3, 42.3, 32.9, 20.4, 17.0; HRMS (CI+) calcd for  $\text{C}_{16}\text{H}_{20}\text{O}$  (M+)

229.1592, found 229.1599.



### 3-Butyl-4,5-dimethyl-4-phenyl-1-cyclohexanone (49)

To a suspension of CuCN (30 mg, 0.33 mmol) in THF (0.2 mL), cooled at  $-78\text{ }^{\circ}\text{C}$ , was added n-BuLi (0.42 mL, 0.67 mmol, 1.6 M in hexanes) and the reaction mixture was gradually warmed to  $0\text{ }^{\circ}\text{C}$ . After recooling the system to  $-78\text{ }^{\circ}\text{C}$ , a solution of **23** (50 mg, 0.25 mmol) in THF (0.3 mL) was added. After 2 h, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (0.2 mL), warmed to rt and partitioned between  $\text{Et}_2\text{O}$  (5 mL) and water (5 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5\text{ mL}$ ) and the combined organic layer was dried with anhydrous  $\text{MgSO}_4$ , concentrated *in vacuo* and purified by chromatography over silica gel eluting with 1–4% of  $\text{EtOAc}$ –hexanes to give **49** (0.060 g, 0.23 mmol, 90%, >20 : 1 dr) as a thick oil:  $[\alpha]_{\text{D}}^{23} = -57.8^{\circ}$ ; IR (neat) 3085, 3052, 2954, 2873, 1718  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.35 (m, 5H), 2.82–2.85 (m, 1H), 2.72–2.77 (m, 1H), 2.33–2.43 (m, 3H), 1.84–1.86 (m, 1H), 1.56 (s, 3H), 1.02–1.18 (m, 1H), 1.00–1.02 (m, 2H), 0.98 (d,  $J = 6.4\text{ Hz}$ , 3H), 0.86–0.94 (m, 2H), 0.78–0.86 (m, 1H), 0.66 (t,  $J = 7.2\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  211.8, 146.3, 128.0, 127.1, 126.8, 125.8, 49.4, 45.8, 43.5, 41.5, 32.9, 29.7, 28.6, 22.2, 21.0, 17.3, 13.7; HRMS (CI+) calcd for  $\text{C}_{18}\text{H}_{26}\text{O}$  ( $\text{M}^+$ ) 259.2062, found 259.2070.

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