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Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminium Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers

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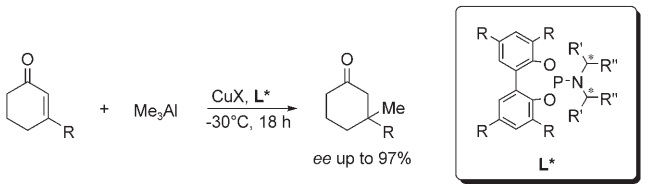
Dedicated to the memory of Professor Yoshihiko Ito

Abstract: Me_3Al, Et_3Al, and vinylalane species undergo enantioselective conjugate addition to a wide range of 2- or 3-substituted enones (cyclopent-2-enones, cyclohex-2-enones, 3-methyl cyclohept-2-enone) in the presence of catalytic amount of copper salt (copper thiophene carboxylate, $[Cu(CH_3CN)_4]BF_4$ or $[CuOTf]_2{\cdot}C_6H_6$) and tropos-phosphoramidite-based ligand. Thus, chiral quaternary centers can be built, with up to 98% *ee* after rigorous optimization of experimental conditions. It was shown that the main important parameter was the order of the introduction of the reagents. Then, the generated enantioenriched aluminium enolates and the chiral conjugate adducts were functionalized and used for subsequent reactions.

Keywords: aluminium · asymmetric catalysis · conjugate addition · copper · phosphoramidite ligands

Introduction

The creation of enantioenriched all-carbon quaternary centers is still a synthetic challenge.[1] Solutions to this problem through the asymmetric conjugate addition (A.C.A.)[2] have been recently disclosed. We have found that the enhanced Lewis acidity of trialkylaluminium species allows the copper-catalyzed conjugate addition to proceed on simple 2- or 3-substituted cyclic enones (Scheme 1).[3] On the other hand, more reactive substrates, such as nitroalkenes,[4] or doubly activated enones[5,6] are able to react with dialkylzinc species. Recently, the use of chiral bidentate *N*-heterocyclic carbenes was developed for the copper-catalyzed asymmetric conjugate addition (A.C.A.) of zinc species to 3-substituted cyclohex-2-en-1-ones[7] and γ-keto esters,[8] and for the Cu-catalyzed A.C.A. of Grignard reagents to several 3-substituted cyclohex-2-en-1-ones.[9] Finally, the asymmetric synthesis of quaternary stereocenters was successfully achieved through copper-catalyzed 1,6-asymmetric addition of dialkylzinc reagents to Meldrum's acid derivatives in the presence of phosphoramidite ligands with good enantioselectivities.[10] We report here our focused efforts to find the right chiral ligand to copper salt, and experimental conditions, that could induce high levels of enantioselectivities in good yields, for a large range of trisubstituted substrates. Moreover, the use of the enantioenriched aluminium enolates will be detailed as the further use of the chiral conjugate adducts.



Scheme 1. Copper-catalyzed A.C.A. of Me_3Al to 3-substituted cyclohex-2-enones.

Results and Discussion

Tri- and tetrasubstituted α,β-unsaturated ketones used for this study are compiled in Figure 1. Some of them were commercially available (**1**, **12**, **13**, **14**, and **18**) or were a generous gift from the industry (**20**). The remaining compounds were prepared according to general procedures (see Experimental Section).[11–14]

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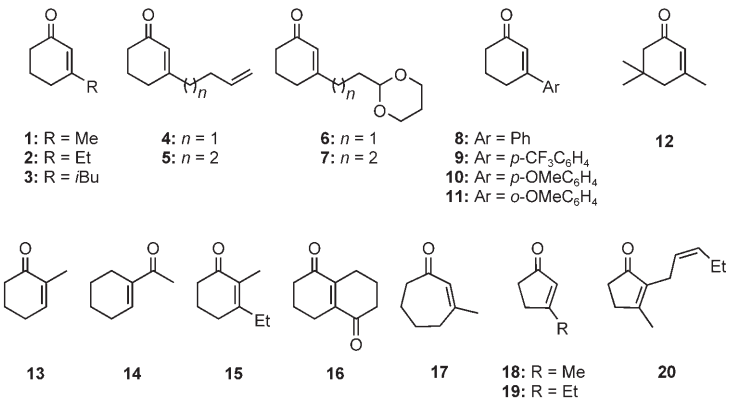


Figure 1. Tri- and tetrasubstituted α,β-unsaturated ketones studied.

Copper-catalyzed A.C.A. optimization of experimental conditions: We first extensively optimized the experimental conditions for the conjugate addition of triethylaluminium species to 3-methylcyclohex-2-en-1-one (**1**) and found that the reaction proceeded to completion after 18 h at −30 °C, and more rapidly at higher temperatures. Two sets of conditions were found, the choice of which depends on the copper salt used (diethyl ether was best with copper thiophene carboxylate (CuTC), whereas tetrahydrofuran was better with $[Cu(CH_3CN)_4]BF_4$). Although the addition of Me_3SiCl has been reported to increase the chemical yield,[15] we found that it was detrimental in the presence of phosphorous ligands. Some attempts to reduce selectively the double bond, with a chiral induction, by adding DiBAl-H (iBu_2AlH) to **1**, as described by Saegusa in stoichiometric version,[16] were unfruitful since the corresponding α,β-unsaturated alcohol was mainly generated in a very complex mixture. Similarly, use of triisobutylaluminium (iBu_3Al), as organometallic species, led to a complex mixture whereas the conjugate adduct was not formed.

In a second step, we screened several biphenol- and binaphthol-based phosphoramidite ligands (Figure 2) for the copper-catalyzed asymmetric conjugate addition of Et_3Al species to **1** (Table 1).

The biphenol ligands **L4** (Table 1, entries 4 and 17) and, particularly, **L7** (Table 1, entry 10) afforded the best results in terms of enantioselectivity, whatever the solvent (up to 97% *ee*). In general, the conversions were higher in diethyl ether than in THF, although the enantioselectivity was unaffected. Raising the reaction temperature increased the conversion at the cost of a small drop in enantioselectivity (Table 1, entries 4, 5 and 6) from 94% *ee* to 88% *ee*, at −15 °C. The binaphthol ligands (**L8**–**L11**) were less efficient. It should be noticed that there was a strong matched/mismatched effect (Table 1, entries 13 vs 14 and 20 vs 21), and that the absolute configuration of the conjugate adduct was dictated by the binaphthol part of the ligand.

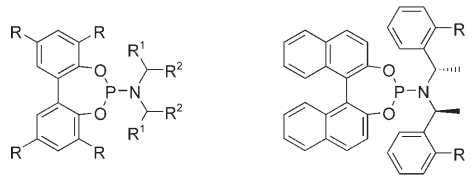
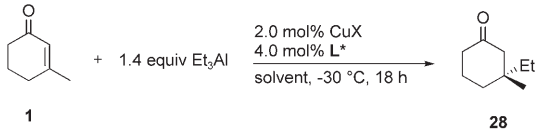


Figure 2. Ligands used in this study.

Table 1. Cu-catalyzed A.C.A. of Et_3Al to **1**.



1 28

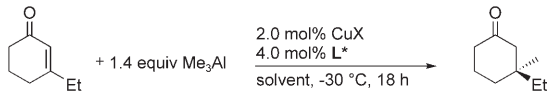
Entry	CuX	Ligand	Solvent	Conv.[a] [%]	*ee*[b] [%]	Abs. conf.
1	CuTC	**L1**	Et_2O	82	62	*R*
2	CuTC	**L2**	Et_2O	84	62	*S*
3	CuTC	**L3**	Et_2O	46	88	*S*
4	CuTC	**L4**	Et_2O	77	94	*R*
5[c]	CuTC	**L4**	Et_2O	85	90	*R*
6[d]	CuTC	**L4**	Et_2O	>95	88	*R*
7	CuTC	**L4**	THF	15	94	*R*
8	CuTC	**L5**	Et_2O	91	93	*R*
9	CuTC	**L6**	Et_2O	89	78	*S*
10	CuTC	**L7**	Et_2O	>95	97	*R*
11	CuTC	**L8**	Et_2O	82	72	*R*
12	CuTC	**L9**	Et_2O	51	62	*S*
13	CuTC	**L10**	Et_2O	>95	74	*R*
14	CuTC	**L11**	Et_2O	>95	16	*S*
15	$[Cu(CH_3CN)_4]BF_4$	**L1**	THF	76	77	*R*
16	$[Cu(CH_3CN)_4]BF_4$	**L3**	THF	46	88	*S*
17	$[Cu(CH_3CN)_4]BF_4$	**L4**	THF	64	94	*R*
18	$[Cu(CH_3CN)_4]BF_4$	**L4**	Et_2O	7	66	*R*
19	$[Cu(CH_3CN)_4]BF_4$	**L7**	THF	<5	nd[e]	–
20	$[Cu(CH_3CN)_4]BF_4$	**L8**	THF	66	84	*R*
21	$[Cu(CH_3CN)_4]BF_4$	**L9**	THF	65	02	*S*

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Reaction performed at −25 °C. [d] Reaction performed at −15 °C. [e] Not determined.

To optimise reaction conditions for the copper-catalyzed A.C.A. of trimethylaluminium reagents, the addition of Me_3Al was done to 3-ethylcyclohex-2-enone (**2**; Table 2).

As expected, the absolute configuration of the adduct **28** is opposite to that given in Table 1, thus showing that the face selectivity remains the same whatever the organoaluminium species. As previously, biphenols **L4** and **L7** gave the best results in terms of conversion and enantioselectivity (Table 2, entries 3, 5 and 14). In general, the conversions were better in diethyl ether than in THF, even if the asymmetric induction was quite similar or slightly inferior. It should be noticed, here also, that there is a major matched/mismatched effect (Table 2, entries 15 vs 16 and 17 vs 18) in THF, and that the absolute configuration of the conjugate adduct is dictated by the amine moiety of the ligand in THF, and by its binaphthol part in Et_2O.

Table 2. Cu-catalyzed A.C.A. of Me_3Al to **2**.



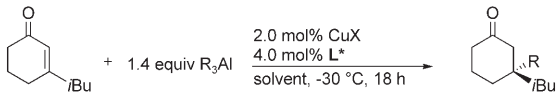
2 **28**

Entry	CuX	Ligand	Solvent	Conv.[a] [%]	*ee*[b] [%]	Abs. conf.
1	CuTC	**L1**	Et_2O	>95	80	*S*
2	CuTC	**L3**	Et_2O	>95	93	*R*
3	CuTC	**L4**	Et_2O	>95	94	*S*
4	CuTC	**L6**	Et_2O	>95	86	*R*
5	CuTC	**L7**	Et_2O	84	96	*S*
6	CuTC	**L8**	Et_2O	>95	92	*S*
7	CuTC	**L9**	Et_2O	>95	88	*R*
8	CuTC	**L10**	Et_2O	>95	74	*S*
9	CuTC	**L11**	Et_2O	>95	23	*R*
10	$[Cu(CH_3CN)_4]BF_4$	**L1**	THF	66	75	*S*
11	$[Cu(CH_3CN)_4]BF_4$	**L3**	THF	25	84	*R*
12	$[Cu(CH_3CN)_4]BF_4$	**L4**	THF	48	88	*S*
13	$[Cu(CH_3CN)_4]BF_4$	**L6**	THF	67	86	*R*
14	$[Cu(CH_3CN)_4]BF_4$	**L7**	THF	65	96	*S*
15	$[Cu(CH_3CN)_4]BF_4$	**L8**	THF	61	87	*S*
16	$[Cu(CH_3CN)_4]BF_4$	**L9**	THF	16	20	*S*
17	$[Cu(CH_3CN)_4]BF_4$	**L10**	THF	19	56	*S*
18	$[Cu(CH_3CN)_4]BF_4$	**L11**	THF	18	12	*S*

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC.

The experimental conditions were further optimized by copper-catalyzed A.C.A. of the two aluminium species to the bulkier substrate **3** to determine the limits of our system. As previously, biphenols **L4** and **L7** gave the best results in terms of conversion and enantioselectivity (Table 3, entries 3 and 5) for the copper-catalyzed A.C.A. of trimethylaluminium species. The conversions were worse than for the less hindered substrates (**1** and **2**) in diethyl ether and very low in THF. However, the level of asymmetric induction remained high. The addition of triethylaluminium species never succeeded even at higher temperature and with more equivalents of organometallic species. These attempts showed us that the steric hindrance was a non-negligible factor to generate chiral quaternary centers with good conversions. However, these problems could be solved by different experimental conditions (see later).

Table 3. Cu-catalyzed A.C.A. of R_3Al to **3**.



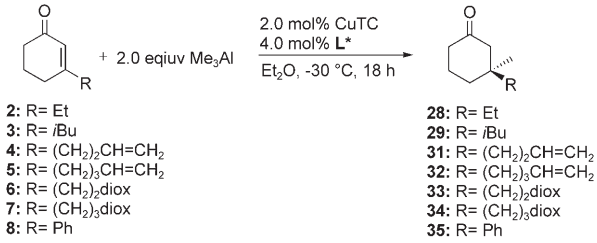
3

29: R= Me
30: R= Et

Entry	CuX	Ligand	Solvent	R_3Al	Conv.[a] [%]	*ee*[b] [%]	Abs. conf.
1	CuTC	**L1**	Et_2O	Me_3Al	70	73	*R*
2	CuTC	**L3**	Et_2O	Me_3Al	42	90	*S*
3	CuTC	**L4**	Et_2O	Me_3Al	35	92	*R*
4	CuTC	**L6**	Et_2O	Me_3Al	88	85	*S*
5	CuTC	**L7**	Et_2O	Me_3Al	42	93	*R*
6	CuTC	**L8**	Et_2O	Me_3Al	65	88	*R*
7	CuTC	**L9**	Et_2O	Me_3Al	36	83	*S*
8	CuTC	**L10**	Et_2O	Me_3Al	19	74	*R*
9	CuTC	**L11**	Et_2O	Me_3Al	15	12	*S*
10	CuTC	**L1**	Et_2O	Et_3Al	00	–[c]	–[c]

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Not determined.

Scope and limitations: The optimized conditions determined previously were used to screen various α,β-unsaturated ketones. First, the copper-catalyzed asymmetric conjugate addition of trimethylaluminium species to several 3-trisubstituted cyclohex-2-en-1-ones was studied because of the synthetic utility of the methyl group in organic chemistry (Scheme 2, Table 4). Moreover, two equivalents of the aluminium reagents were added in order to overcome the low reactivity of hindered substrates.



Scheme 2. Copper-catalyzed asymmetric conjugate addition of Me_3Al to various 3-substituted cyclohexenones.

Table 4. Cu-catalyzed asymmetric conjugate addition of Me_3Al to various 3-substituted enones.

Entry	Substrate	Ligand	Adduct	Conv.[a] [%] (yield [%])	*ee*[b] [%]	Abs. conf.
1	**2**	**L4**	28	>95 (78)	94	*S*
2	**2**	**L7**	28	84 (nd[c])	97	*S*
3	**3**	**L4**	29	35 (nd[c])	93	*R*
4	**3**	**L7**	29	42 (nd[c])	93	*R*
5	**4**	**L4**	31	>95 (nd[c])	91	*R*
6	**4**	**L7**	31	>95 (80)	95	*R*
7	**5**	**L4**	32	>95 (nd[c])	93	*S*
8	**5**	**L7**	32	>95 (76)	95	*S*
9[d]	**6**	**L4**	33	>95 (81)	95	*R*
10[d]	**7**	**L7**	34	>95 (62)	92	*S*
11	**8**	**L4**	35	00 (–)	nd[c]	

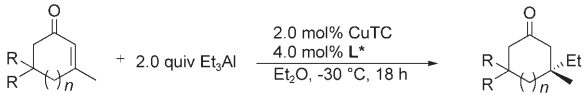
[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Not determined. [d] Reaction performed with 5.0 mol% of CuTC and 10.0 mol% of **L4**.

The addition of trimethylaluminium to 3-ethyl cyclohex-2-en-1-one (**2**) afforded excellent yields and enantioselectivities, which reached 97% *ee* with **L7** (Table 4, entry 2). Although the enantioselectivity remained high (93% *ee*; Table 4, entries 3 and 4), the A.C.A. to 3-isobutylcyclohex-2-en-1-one (**3**) proceeded with lower conversion owing to the increased steric demand. In this respect 3-phenylcyclohex-2-en-1-one (**8**) did not give any adduct (Table 4, entry 11), whereas substrates **4** and **5**, both of which contain a remote double bond, gave excellent yields and enantioselectivities (91 and 93% *ee*, respectively with **L4**; 95% with **L7**; Table 4, entries 5 to 8). Finally, an acetal functionality on **6**

and **7** was tolerated, again with high yields and asymmetric induction up to 95% *ee* (Table 4, entries 9 and 10).

Then, the copper-catalyzed asymmetric conjugate addition of triethylaluminium species to several cyclic 3-methyl α,β-unsaturated ketones was studied (Table 5).

Table 5. Cu-catalyzed asymmetric conjugate addition of Et_3Al to various 3-methyl-substituted enones.



12: *n*= 1, R= Me
17: *n*= 2, R= H
18: *n*= 0, R= H

36: *n*= 1, R= Me
37: *n*= 2, R= H
38: *n*= 0, R= H

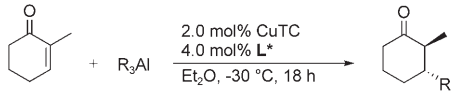
Entry	Substrate	Ligand	Adduct	Conv.[a] [%] (yield [%])	*ee*[b] [%]	Abs. conf.
1[c]	**12**	**L1**	**36**	00 (–)	–	–
2[d]	**17**	**L4**	**37**	>95 (56)	81	*R*
3[d]	**17**	**L7**	**37**	>95 (55)	86	*R*
4[d]	**17**	**L8**	**37**	>95 (58)	95	*R*
5[c]	**18**	**L1**	**38**	00 (–)	–	–

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Reaction performed with 1.4 equiv of Et_3Al. [d] Enone added before Et_3Al, see Section on improved experimental conditions.

As expected, isophorone **12** did not give any adduct because of its steric hindrance (Table 5, entry 1). On the other hand, the five-membered cyclic substrate **18** did not give any adduct either (Table 5, entry 5). The larger ring system **17** gave the desired adduct in good yield and excellent enantioselectivities up to 95% *ee* when the "reverse addition" procedure was applied (see Section on improved experimental conditions). In this case the binaphthol ligand **L8** (Table 5, entry 4) was more efficient than biphenol-based ones.

To increase the interest of our methodology, the 2-trisubstituted α,β unsaturated ketone **13** was submitted to the copper-catalyzed A.C.A. of triorganoaluminium species (Table 6). The reaction proceeded with complete conversion with good to high levels of asymmetric induction whatever the organoaluminium reagent used. This substrate was quite interesting since the copper-catalyzed asymmetric conjugate addition was never reported. The crude hydrolyzed product afforded a *trans*/*cis* ratio around 80:20 and was isomerized with DBU and isolated as a pure *trans* form to determine its absolute configuration by correlation with the literature.[17] The best results were obtained with the binaphthol ligand **L8** (93% *ee* for Et_3Al; Table 6, entry 9 and 90% *ee* for Me_3Al; Table 6, entry 6).

Table 6. Cu-catalyzed A.C.A. of R_3Al to 2-methylcyclohex-2-en-1-one (**13**).



13

39: R= Me
40: R= Et

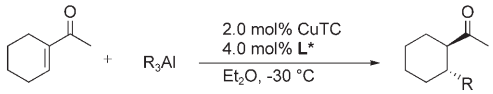
Entry	Ligand	R_3Al (equiv)	Adduct	Conv.[a] [%]	*ee*[b] [%]	Abs. conf.
1	**L1**	Me_3Al (2.0)	**39**	>95	88	(2*S*,3*R*)
2	**L3**	Me_3Al (2.0)	**39**	>95	86	(2*R*,3*S*)
3	**L4**	Me_3Al (2.0)	**39**	>95	80	(2*S*,3*R*)
4	**L6**	Me_3Al (2.0)	**39**	>95	87	(2*R*,3*S*)
5	**L7**	Me_3Al (2.0)	**39**	>95	76	(2*S*,3*R*)
6	**L8**	Me_3Al (2.0)	**39**	>95	90	(2*S*,3*R*)
7	**L1**	Et_3Al (1.4)	**40**	>95	84	(2*S*,3*R*)
8	**L4**	Et_3Al (1.4)	**40**	86	63	(2*S*,3*R*)
9	**L8**	Et_3Al (1.4)	**40**	>95 (50)[c]	93	(2*S*,3*R*)

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Isolated yield.

Lastly, some attempts were done with the exocyclic α,β-unsaturated ketone **14** to find out if a rigid substrate is necessary to obtain high levels of enantioselectivity (Table 7). It appeared that the major diastereomer obtained was the *cis* one, the kinetic product of protonation from the least hindered side of the enolate. However, the mixture of isomers could be equilibrated to a *trans*/*cis* ratio of 95:5, in presence of DBU at room temperature. The *trans* isomer could be isolated in a pure form to determine its absolute configuration by comparison of its optical rotation with previously reported data.[18] We assumed that the face selectivity remained the same whatever the added group (Me or Et) under an identical catalytic system.

Some attempts to generate selectively the kinetic *cis* isomer by quenching the aluminium enolate with ethyl salicylate, as described by Krause, did not increase the *cis*/*trans* ratio.[19] Substrate **14** is quite interesting since it did not give

Table 7. Cu-catalyzed A.C.A. of R_3Al to 1-cyclohexenylethan-2-one (**14**).



14

41: R= Me
42: R= Et

Entry	Ligand	R_3Al (equiv)	*t* [h]	Adduct	Conv.[a] [%]	*ee*[b] [%]	Abs. conf.
1	**L1**	Me_3Al (2.0)	18	**41**	>95 (72)[c]	81	(1*R*,2*R*)
2	**L4**	Me_3Al (2.0)	18	**41**	88 (51)[c]	84	(1*R*,2*R*)
3	**L6**	Me_3Al (2.0)	18	**41**	95	76	(1*S*,2*S*)
4	**L7**	Me_3Al (2.0)	18	**41**	77	86	(1*R*,2*R*)
5	**L8**	Me_3Al (2.0)	18	**41**	95	78	(1*R*,2*R*)
6	**L1**	Et_3Al (1.4)	48	**42**	92	59	(1*R*,2*R*)
7	**L4**	Et_3Al (1.4)	48	**42**	90	64	(1*R*,2*R*)
8	**L6**	Et_3Al (1.4)	48	**42**	73	18	(1*S*,2*S*)
9	**L7**	Et_3Al (1.4)	48	**42**	53	28	(1*R*,2*R*)
10	**L8**	Et_3Al (1.4)	48	**42**	49	nd[d]	–

[a] Conversion determined by GC-MS. [b] *ee* determined by chiral GC. [c] Isolated yield. [d] Not determined.

any conjugate adduct when zinc species were added[20] while the use of aluminium reagents was successful (Table 7). However, the reaction rate was low, especially when Et_3Al was added (Table 7, entries 8 to 10). The conjugate addition of trimethylaluminium species proceeded with high levels of enantioselectivity up to 86% in presence of **L7** (Table 2, entry 4). Surprisingly, the enantioselectivity decreased during the A.C.A. of triethylaluminium reagents to 28% *ee* with **L4** as chiral ligand. These results showed that the more flexible substrate **14** was tolerated in the copper-catalyzed asymmetric conjugate addition of triorganoaluminium species.

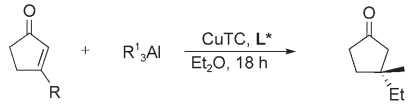
Improved experimental conditions: Although we have discovered a way to build chiral quaternary carbon centers that allows the straightforward construction of chiral building blocks for more elaborated natural products, some substrates did not give any conjugate adduct (**8**, **12**, and **18**) and it was necessary to find special reaction conditions to overcome this lack of reactivity.

The first modifications of previously described experimental conditions were performed for five-membered ring substrates (**18** and **19**). In fact, it has been reported by Chan that copper-catalyzed A.C.A. of triorganoaluminium reagents was possible to simple cyclopent-2-en-1-one[21] and we have shown that the Lewis acidity of the aluminium species overcame the steric hindrance of 3-substituted cyclohex-2-en-1-ones.[3] Compounds **18** and **19** were the substrates of choice to develop new experimental conditions since they did not have a too large steric bulk, which was the main limit of the previously described catalytic system. In a first step, we extensively changed the reaction temperature, the copper salt, the solvent and the catalyst loading for the copper-catalyzed A.C.A. of triethylaluminium compounds to 3-methylcyclopent-2-en-1-one (**18**) in presence of a phosphoramidite ligand **L1** without any success. To compare our results with those obtained by Chan[21] on cyclopent-2-enone, the exact same experimental conditions were used. It is noteworthy that the order of introduction of the reagents was opposite to ours. We first added the aluminium species and, then, the substrate at the desired temperature. Chan first introduced the substrate, at room temperature, and then, at the desired temperature, the organoaluminium species. To check the influence of the order of introduction of the reagents on conversion, the copper-catalyzed A.C.A. of R_3Al was carried out in the presence of phosphoramidite ligand **L1**.

Interestingly, the addition of organoaluminium species to the catalyst and the substrate ("reverse" addition) had a very important influence on the conversion of the reaction. Whereas the "normal" addition led to only 14% conversion (Table 8, entry 1), the "reverse" one led to a quasi-complete conversion with 54% of enantioselectivity with the simple biphenol-based phosphoramidite **L1**. Higher asymmetric induction could not be obtained with an increase of the catalyst loading (Table 8, entries 2 to 4). The enantioselectivity dropped when the reaction was performed at higher temperature (Table 8, entry 5). A similar effect was observed when Me_3Al was added, although less important than with Et_3Al (Table 8, entries 6 and 7). Thus, these experiments showed that the lack of reactivity of our substrates was probably due to the experimental procedure and not to a lack of efficiency of the phosphoramidite ligands. Moreover, we have demonstrated that the phosphoramidite ligands were stable in presence of Me_3Al in coordinating solvent (Et_2O or THF) whereas they were cleaved in presence of CH_2Cl_2 into an aminophosphine species.[22] Thus, this higher reactivity could be due to the formation of a more reactive Cu cluster using the "reverse" order of introduction of the reagents.

To find good "reverse" experimental conditions for the copper-catalyzed conjugate addition of organoaluminium species, we extensively looked for the best phosphoramidite ligand and, then, for the best copper salt. As for 3-substituted cyclohex-2-en-1-ones, the best results for triethylalumini-

Table 8. Cu-catalyzed A.C.A. to 3-substituted cyclopent-2-en-1-ones in presence of **L1**.



18: R= Me
19: R= Et

38

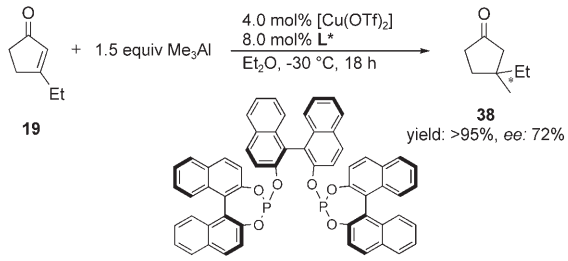
Entry	Substrate	Addition[a]	R^1Al (equiv)	T [°C]	CuX (mol%)	Ligand (mol%)	Conv.[b] [%]	*ee*[c] [%]	Abs. conf.
1	**18**	normal	Et_3Al (2.0)	−30	CuTC (2.0)	**L1** (4.0)	14	nd[d]	–
2	**18**	reverse	Et_3Al (2.0)	−30	CuTC (2.0)	**L1** (4.0)	95	54	*R*
3	**18**	reverse	Et_3Al (2.0)	−30	CuTC (2.0)	**L1** (8.0)	47	54	*R*
4	**18**	reverse	Et_3Al (2.0)	−30	CuTC (4.0)	**L1** (16.0)	95	53	*R*
5	**18**	reverse	Et_3Al (2.0)	−15	CuTC (2.0)	**L1** (8.0)	70	47	*R*
6	**18**	reverse	Et_3Al (2.0)	−30	CuTC (2.0)	**L7** (4.0)	>95	80	*R*
7	**18**	reverse	Et_3Al (2.0)	−30	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	*ent*-**L7** (8.0)	>95	93	*S*
8	**19**	normal	Me_3Al (2.0)	−30	CuTC (2.0)	**L1** (4.0)	09	nd[d]	–
9	**19**	reverse	Me_3Al (2.0)	−30	CuTC (2.0)	**L1** (4.0)	26	00	–
10	**19**	reverse	Me_3Al (2.0)	−30	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	*ent*-**L7** (8.0)	50	33	*R*

[a] Normal: first R_3Al, then enone; reverse: first enone, then R_3Al. [b] Conversion determined by GC-MS. [c] *ee* determined by chiral GC. [d] Not determined.

um and **18** were obtained with the biphenol-based ligand **L7** in terms of conversion (>95%) and enantioselectivity (93% *ee*) (Table 8, entry 7). The copper salts screening showed that the use of Kubas salt ($[Cu(CH_3CN)_4]BF_4$), or other inorganic salts did not give the conjugate adduct **38** in good conversions, in contrast to the excellent results obtained in terms of conversion and enantioselectivity for the copper-catalyzed A.C.A. of diethylzinc species to disubstituted enones.[23] The addition of trimethylaluminium to **19** was more problematic. Even the use of phosphoramidite ligand **L7** led to a dramatic decrease of the conversion and the asymmetric induction (50% conv., 33% *ee* (*S*)) (entry 10). However, these results could be improved to >95% conversion and 72% *ee* with a chiral diphosphite ligand as depicted in Scheme 3.[24] As expected, the absolute configuration of conjugate adduct **38** was opposite depending on the enone and the aluminium species added, thus showing that the face selectivity remained the same.

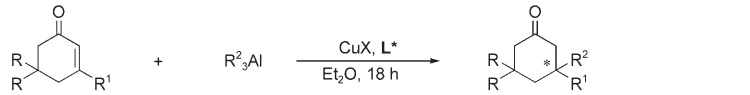
As the order of introduction of the reagents seemed to influence the formation of chiral conjugate adduct, a new series of experiments was done with **1**. As expected, the addition of triethylaluminium to a mixture containing the catalyst and the substrate had a positive effect since a small increase of the asymmetric induction was observed (up to 67% *ee* with **L1**) with a complete conversion. To complete our previous results we went back to the study of the Cu-catalyzed asymmetric conjugate addition of R_3Al to six-membered ring substrates that did not give any adduct or with low conversion (Table 9).

We first began with the most hindered substrate **12** that presents 1,3-diaxial interactions, during the nucleophilic approach, due to the *gem*-dimethyl groups (Table 9, entries 1 to 6). The order of introduction of the reagents had a strong influence since when the enone was added to the triethylaluminium species ("normal") no conjugate adduct was obtained, whereas when the triethylaluminium species was added to the substrate ("reverse") a conversion of 35% was obtained with an enantioselectivity of 82% with the simple biphenol based phosphoramidite **L1** (Table 9, entries 1 and 2). A slight improvement of the conversion was achieved at −10°C, but a drop of enantioselectivity was observed with standard conditions (Table 9, entry 3). Change of the copper salt to $[CuOTf]_2{\cdot}C_6H_6$ combined with a higher temperature considerably increased the conversion of the reaction to 61% with 75% *ee* (Table 9, entry 4). However, use of the more hindered and efficient, in terms of enantioselectivity, ligand *ent*-**L7** led to a slowdown of the reaction rate (Table 9, entry 5) which was overcome by adding 4.0 equivalents of the organometallic species and doubling the catalyst loading to give the desired chiral adduct **36** in 87% yield (97% *ee*; Table 9, entry 6). To check if these new experimental conditions developed for the highly hindered substrate **12** were more general than the previous ones, the copper-catalyzed A.C.A. of trimethylaluminium species was



Scheme 3. Synthesis of compound **38**.

Table 9. Cu-catalyzed A.C.A. of R_3Al to six-membered ring substrates.



3: R= H, R^1= *i*Bu
8: R= H, R^1= Ph
9: R= H, R^1= *p*-$CF_3C_6H_4$
10: R= H, R^1= *p*-$OMeC_6H_4$
11: R= H, R^1= *o*-$OMeC_6H_4$
12: R= Me, R^1= Me

29: R= H, R^1= *i*Bu, R^2= Me
35: R= H, R^1= Ph, R^2=Me
43: R= H, R^1= *p*-$CF_3C_6H_4$, R^2= Me
44: R= H, R^1= *p*-$OMeC_6H_4$, R^2= Me
45: R= H, R^1= *o*-$OMeC_6H_4$, R^2= Me
36: R= Me, R^1= Me, R''= Et

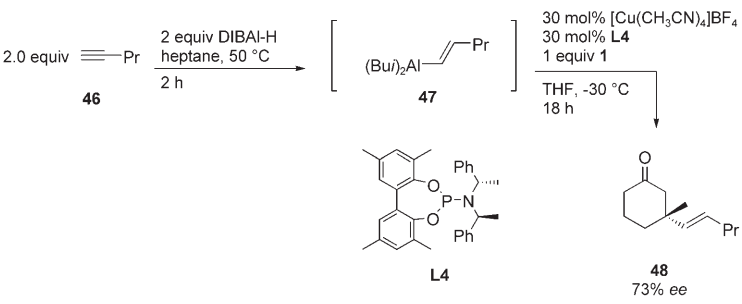
Entry	Substrate	Addition[a]	R^2Al (equiv)	CuX (mol%)	Ligand (mol%)	*T* [°C]	Adduct	Conv.[b] [%]	*ee*[c] [%]	Abs. conf.
1	**12**	normal	Et_3Al (1.4)	CuTC (2.0)	**L1** (4.0)	−30	**36**	00	–	–
2	**12**	reverse	Et_3Al (2.0)	CuTC (2.0)	**L1** (4.0)	−30	**36**	35 (48 h)	82[d]	*R*
3	**12**	reverse	Et_3Al (2.0)	CuTC (2.0)	**L1** (4.0)	−10	**36**	22	77	*R*
4	**12**	reverse	Et_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (1.0)	**L1** (4.0)	−10	**36**	61	75[d]	*R*
5	**12**	reverse	Et_3Al (4.0)	$[CuOTf]_2{\cdot}C_6H_6$ (1.0)	*ent*-**L7** (4.0)	−10	**36**	28	96[d]	*S*
6	**12**	reverse	Et_3Al (4.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	*ent*-**L7** (8.0)	−10	**36**	>95 (87)[e]	97[d]	*S*
7	**3**	reverse	Me_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	**L7** (8.0)	−10	**29**	>95 (85)[e]	98	*R*
8	**8**	reverse	Me_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	*ent*-**L7** (8.0)	−10	**35**	70 (50)[e]	72	*R*
9	**9**	reverse	Me_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	**L7** (8.0)	−10	**43**	93	66	*S*
10	**10**	reverse	Me_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	**L7** (8.0)	−10	**44**	20	60	*S*
11	**11**	reverse	Me_3Al (2.0)	$[CuOTf]_2{\cdot}C_6H_6$ (2.0)	**L7** (8.0)	−10	**45**	>95	*rac*	–

[a] normal: first R_3Al, then enone; reverse: first enone, then R_3Al. [b] Conversion determined by GC-MS. [c] *ee* determined by chiral GC. [d] Constant *ee* during the reaction time. [e] Isolated yield.

then performed to the 3-isobutylcyclohex-2-en-1-one (**3**), which gave low results in terms of conversion (Table 3, entries 3 and 4). The "reverse" addition of reagents led to similar results as those obtained by the "normal" way with CuTC and **L4**. However, the use of the conditions developed for isophorone **1** led to an impressive increase of the conversion to more than 95%. The chiral adduct was generated in 85% isolated yield with an enantioselectivity reaching 98% in presence of **L7** and 2.0 equivalents of trimethylaluminium (Table 9, entry 7). The 3-aromatic cyclohex-2-en-1-ones (**8**–**11**) were quite difficult substrates since the steric effects, and the electronic effects were combined. We have seen that the simple 3-phenylcyclohex-2-en-1-one (**8**) did not give any adduct using the standard conditions previously reported (Table 4, entry 11). We found that these new improved conditions (Table 9, entry 8) enlarged the scope of our methodology, since it is not possible to obtain such chiral quaternary adducts by another procedure than copper catalysis.[5] However, the conversion of the reaction was not complete in 18 h and the enantioselectivity was lower than for other non-aromatic substrates (70% conv., 50% isolated yield, 72% *ee*; Table 9, entry 8). To check the influence of electronic effects on the β-position of the enone, some experiments of copper-catalyzed asymmetric conjugate addition of trimethylaluminium reagents were done on several 3-aryl cyclohex-2-en-1-ones (Table 9, entries 8 to 11) under the best experimental conditions. As expected, the substrate bearing an EWG (CF_3; Table 9, entry 9) on the aromatic ring had a higher reactivity than that bearing an EDG (OMe; Table 9, entry 10) in the same *para* position. The substrate with no substituent on the aromatic ring **8** presented an intermediate reactivity (Table 9, entry 8). That could be easily explained since an EWG tends to decrease the electronic density of the β-position and made it more electrophilic and reactive. The opposite was observed when the aromatic ring bore an EDG. However, the substrate bearing an OMe in *ortho* position gave the adduct with complete conversion, but as a racemate (Table 9, entry 11). Probably, due to the high oxophilicity of aluminium, a chelating phenomenon took place overcoming the electronic effects.

To enlarge the scope of the procedure developed to generate chiral quaternary centers, we tried to add aluminium species to tetrasubstituted α,β-unsaturated ketones. Unfortunately, all attempts were unsuccessful with both, 2-methyl-3-ethylcyclohexen-1-one (**15**), and 3,4,7,8-tetrahydronaphthalene-1,5(2*H*,6*H*)-dione (**16**). The five-membered tetrasubstituted jasmone (**20**) did not give any adduct either.[26]

Tandem hydroalumination-Cu-catalyzed A.C.A.: One main attraction of organoaluminium reagents is the ease with which novel reagents can be attained by hydro- and carboalumination reactions.[25] Hydroalumination of pent-1-yne (**46**) was performed under Zweifel conditions, and quantitatively led to the vinylalane species **47** in complete conversion. It was then added to the enone **1** in presence of copper salt and chiral phosphoramidite ligand to lead the conjugate adduct **48** in complete conversion and 73% *ee* (Scheme 4).



Scheme 4. Tandem hydroalumination–Cu-catalyzed A.C.A.

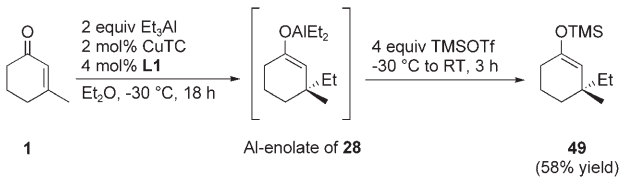
The use of "standard" conditions (CuTC, Et_2O) only led to the 1,2-addition–dehydration product. Increased catalyst loading up to 15.0 mol% or temperature did not give the conjugate adduct. Only, when 30.0 mol% of CuTC and 30.0 mol% of ligand were used, the formation of the conjugate adduct appeared, with 80% of asymmetric induction (*ent*-**L7**). However, there was not a complete selection in favor of the conjugate addition, and the 1,2-addition–dehydration product was observed in variable amounts. To discriminate against the 1,2-addition of vinylalane **47**, the experimental conditions were changed to the other set developed: $[Cu(CH_3CN)_4]BF_4$ and THF. Surprisingly, the 1,2-addition–dehydration product was never obtained even at room temperature. However, it was necessary to work with a high catalyst loading of 30.0 mol% to obtain good enantioselectivity (73% *ee*, **L4**). As expected, the more efficient but more hindered ligand **L7** did not give any conversion in this set of conditions. The (−)-stereoisomer was isolated which was assigned to the same facial selectivity as the other asymmetric conjugate additions as already observed for addition of vinalalane to disubstituted enone.[26] To the best of our knowledge only racemic addition of such vinylalane to trisubstituted enones have been reported before.[27]

Reactivity and use of aluminium enolates: The asymmetric conjugate addition is an essential method for the specific introduction of a hydrocarbon unit to the β-position of a carbonyl function. Furthermore, the eminent nucleophilicity of the metal enolate intermediate allows for reaction with various electrophiles, affording the α,β-vicinal structural modification of enones and providing a powerful tool for the synthesis of complex molecules. In contrast to zinc enolates, the reactivity of aluminium enolates is not well documented. Mole first reported, in 1974, the use of isolated aluminium enolates for an aldol reaction,[28] whereas Tsuda and Saegusa studied the alkylation and the silylation of aluminium enolates generated by hydroalumination of α,β-unsaturated carbonyl compounds.[16] Alkylation of the aluminium enolates generated from the MeCu-catalyzed reaction of α,β-unsaturated carbonyl compounds and DIBAl–H-HMPA with alkyl halides did not proceed easily. It has been found that conversion of the aluminium enolates into the "ate" complexes by addition of an equimolar amount of methyllithium in-

creases their nucleophilic reactivity toward alkyl halides to produce alkylated products in moderate to good yields.

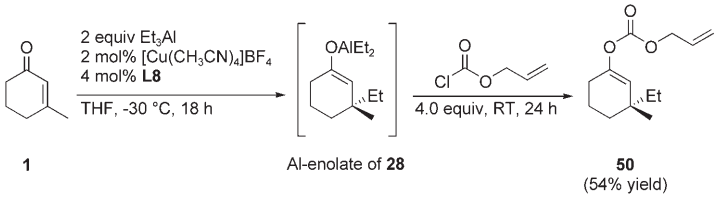
We first checked the stability of the aluminium enolate generated via the copper-catalyzed asymmetric conjugate addition of trimethylaluminium species to **4** and **5**, substrates bearing a remote double bond. Indeed, it could be envisaged that this intermediate species was not stable enough and reacted intramolecularly to undergo a carbometallation reaction and generated bicyclic systems, like zinc species which promoted an easy cyclization reaction of specific substrates.[29] However, the cyclization product was not obtained because of the high stability of the aluminium enolate probably due to the "strong" bond between the aluminium and the oxygen atoms. It was in accordance with previous results since the product of the undesired side trapping of the aluminium enolate to unreacted trisubstituted substrates was never observed. This high stability allowed the isolation of aluminium enolates by Mole.[30] Moreover, this very high stability prevented the reaction between various aluminium enolates, generated by copper-catalyzed asymmetric conjugate addition of triorganoaluminium reagents, and diethylcarbonate, or several allylating reagents under numerous experimental conditions. As the direct reaction with these aluminium enolates, generated by Cu-catalyzed A.C.A. of R_3Al, to form α,β-functionalized adducts was not feasible, we envisaged then to functionalize their oxygen atom in order to generate precursors of lithium enolates (silyl enol ether or enol acetate) or precursors of α-allylated adducts (enol acetates or allyl enol carbonate) via the Tsuji–Trost rearrangement.[31]

The silylation of aluminium enolates has been already reported by Tsuda[16] in good yields with a small excess of trimethylsilyl chloride. However, when we tried to silylate the aluminium enolate generated via the copper-catalyzed asymmetric conjugate addition of triorganoaluminium reagents to **1** with TMSOTf, the silyl enol ether could not be isolated in spite of its complete formation according to GC-MS. All attempts to the generation of the silyl enol ether **49** failed after purification. To confirm its formation, an optimization of the work-up and the purification was done to avoid the degradation of the compound and furnished it in 58% isolated yield (Scheme 5, see Experimental Section).We envisaged then to quench the aluminium enolate with other silylating reagents less sensitive to the slightly acidic conditions of the work-up and to the purification. Unfortunately, TBDMSCl and TBDPSCl did not give the silylated adducts, even after seven days at room temperature, probably because of their steric hindrance.



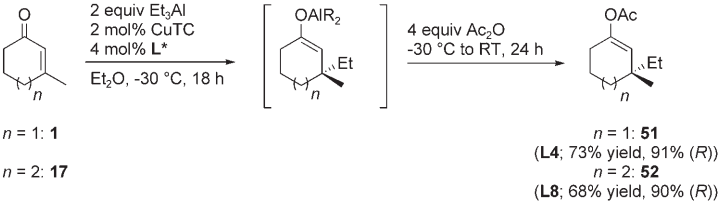
Scheme 5. Tandem Cu-catalyzed A.C.A. of Et_3Al–silylation reaction.

The formation of allyl enol carbonate was also envisaged and surprisingly, the CuTC–phosphoramidite ligand system, in diethyl ether, instead of CuBr, in THF, inhibited the reaction. In view of the importance of THF on conversion, in this tandem reaction, we used the other set of conditions previously developed (THF and $[Cu(CH_3CN)_4]BF_4$). Best results were obtained, since **50** was formed in good conversion (68%) in 24 h00 (Scheme 6). It could be possible to improve the conversion by an increase of the equivalents of allylchloroformate added.



Scheme 6. Tandem Cu-catalyzed A.C.A. of Et_3Al–allyl enol carbonate formation.

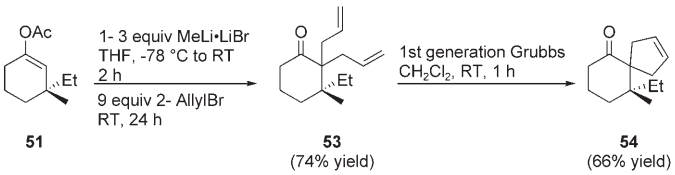
Finally, by analogy to disubstituted enones,[32] the *O*-acylation reaction was realized to generate enol acetates (Scheme 7), which are much more stable than silyl enol



Scheme 7. Tandem Cu-catalyzed A.C.A. of Et_3Al-*O*-acylation.

ethers and are precursors of lithium enolates[33–35] or monoallylated adducts via intermolecular Tsuji reaction.[31c] The tandem copper-catalyzed A.C.A-*O*-acylation worked well since whatever the ring-size, conversions were complete and good yields were obtained. The *C*-acylation was never observed. One-gram scale was tolerated since no loss of asymmetric induction was observed for the copper-catlyzed A.C.A. part of the reaction, and the enol acetate **51** was isolated in 73% yield.

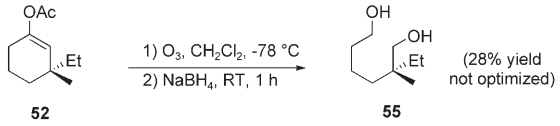
The lithium enolate could be quantitatively regenerated with no loss of enantioselectivity following the procedures described by House[33] and Posner.[34] The attempted α-allylation resulted in fact in the *gem*-bisallylated **53** product. With an excess of allyl bromide, **53** was generated in good yield and was cyclized via a ring closure metathesis to form the spirocyclic compound **54** in good yield (Scheme 8). The *gem*-bismethallylated intermediate could be similarly generated among various allylated adducts, and an improvement of the experimental conditions would be necessary.



51 53 (74% yield) 54 (66% yield)

Scheme 8. Bis-allylation-RCM reaction.

Finally, a reductive ozonolysis was done to generate a (1,6)-diol bearing a chiral quaternary carbon **55** (Scheme 9).



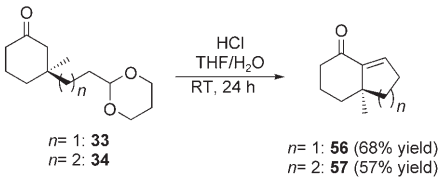
52 55

Scheme 9. Reductive ozonolysis.

To conclude on the reactivity of aluminium enolates, we saw that it was difficult to use them directly with electrophiles probably due to their high stability. However, the silylation, carbonation and *O*-acylation were feasible in good yields. These intermediates could eventually be used for later applications such as Tsuji reaction, ozonolysis, to generate more elaborated adducts.

To enlarge the scope of our methodology to generate chiral quaternary carbon centers, we explored the potential use of the chiral adducts formed. Novel routes to carbobicyclic compounds in enantiomerically pure form continue to offer a synthetic challenge since numerous products including terpenes and steroids show this structural feature. In the pursuit of novel catalytic asymmetric annulation strategies, we focused on the construction of enantiomerically pure carbobicyclic products. We envisaged to make an intramolecular aldolization–crotonization reaction with substrates bearing an acetal functionality, which could easily be deprotected in one-pot by acidic treatment (Scheme 10). This transformation gave bicyclic α,β-unsaturated compounds bearing a chiral quaternary center, and occurred without any loss of enantioselectivity. These fused bicyclic systems are important intermediates for asymmetric synthesis of sesquiterpenes derivatives.[36a]

This reaction worked well with six-membered ring compounds (**33** and **34**) and bicyclic adducts were obtained in good isolated yields. Compound **56** allowed us to determine

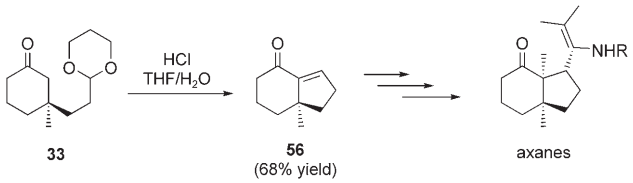


n= 1: **33**
n= 2: **34**

n= 1: **56** (68% yield)
n= 2: **57** (57% yield)

Scheme 10. Tandem aldolization–crotonization reaction.

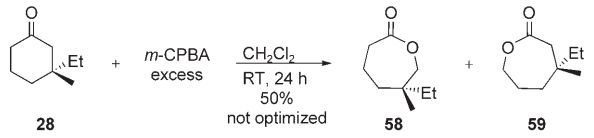
the absolute configuration of all new conjugate adducts bearing a chiral quaternary center by chemical correlation with this known compound. The negative optical rotation ($[\alpha] = -74.8$, $c = 1.53$, $CHCl_3$) corresponds to the *R* configuration of **56**, which is an intermediate in the synthesis of Axanes derivatives family isolated from the marine sponge *Axinella cannabia* (Scheme 11).[36b] It is assumed that all adducts listed in Tables 4, 5 and 9 follow the same trend.



33 56 (68% yield) axanes

Scheme 11. Synthetic approach to axanes.

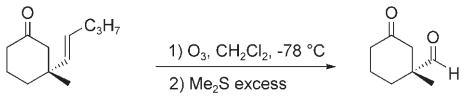
The Baeyer–Villiger reaction was a way to generate acyclic adducts since a simple basic treatment could lead to acyclic adducts bearing a chiral quaternary center. However, it was necessary that the carbon in β-position bearing quaternary center influenced the regioselectivity of such a reaction. Thus, the Baeyer–Villiger reaction was also performed with various peracids. A good selectivity of 85:15 was observed when the adduct **28** was treated with *m*-CPBA (Scheme 12) in favor of **58**. The oxygen insertion took place preferentially on the more hindered side. However, changing the oxidative reagent to CF_3CO_3H or CH_3CO_3H led to worse selectivity and a decrease of the reaction rate.



28 58 59

Scheme 12. Ring expansion by Baeyer–Villiger oxidation.

Finally, the adduct arising from the tandem hydroalumination–A.C.A. was submitted to oxidative ozonolysis to generate the aldehyde **60** (Scheme 13).



49 60

Scheme 13. Ozonolysis reaction.

The 1,4-ketoaldehyde **60** is described in the literature and allowed us to compare its optical rotation[37] and to confirm that the face selectivity remained the same whatever the organoaluminium species for a given catalytic system. Such a derivative bearing an aldehyde in the α-position to the

chiral quaternary center, as **60**, could be used for further functionalizations such as Horner–Wadsworth–Emmons reaction, 1,2-addition, cross metathesis, to generate more elaborated molecules. Thus, the scope of our methodology was greatly enlarged.

Conclusion

To summarize, we took advantage of the Lewis acidity of triorganoaluminium species to overcome the steric hindrance of β-trisubstituted Michael acceptors, and to generate chiral quaternary centers via copper-catalyzed asymmetric conjugate addition. The biphenol-based ligands **L4** and **L7** afforded the best results whatever the set of conditions used, whereas the binaphthol **L8** gave good results in some cases. Several "simple" substrates gave excellent conversions (yields) and enantioselectivities in similar experimental conditions as to those used for disubstituted substrates, whereas some Michael acceptors (five-membered ring system, highly hindered substrates) needed the carefully optimized conditions to give excellent results. The conditions developed were applied to other trisubstituted substrates (α-substitution or exocyclic ketone) without any loss of asymmetric induction. The first example of tandem hydroalumination–A.C.A. catalyzed by copper was developed with an enantioselectivity reaching 73%. Finally, aluminium enolates, generated by copper-catalyzed-A.C.A., could be used to form protected enols (silylation, carbonation, *O*-acylation). These stable intermediate compounds could react to generate more elaborated products. Similarly, conjugate adducts bearing chiral quaternary center could be elaborated into the more valuable intermediates in organic synthesis.

Experimental Section

General methods: All reactions were carried out under argon atmosphere with oven-dried glassware. Solvents were dried by filtration over alumina previously activated at 350 °C during 12 h under nitrogen before use. All solvents were degassed by nitrogen bubbling before use to all experiments. Triethylamine was distilled over CaH_2 prior to use. PC**L3** was degassed and distilled prior to use. Trimethylaluminium 2.0 M in heptane (Aldrich or Fluka), triethylaluminium 1.0 M in hexane (Aldrich or Fluka), methyllithium 1.6 M in diethyl ether (Acros), methyllithium·lithium bromide 1.5 M in Et_2O (Fluka) were used without any further purification. Copperthiophene carboxylate (FrontierScientific), $[Cu(OTf)_2]$ (Aldrich), and $[CuOTf]_2{\cdot}C_6H_6$ (Aldrich) were purchased and used without any further purification. Evolution of reaction was followed by GC-MS Hewlett Packard (EI mode) HP6890-5973 or by TLC (visualisation by UV and anisaldehyde, $KMnO_4$ or PMA staining). Flash chromatography was performed using silica gel 32–63 μm, 60 Å. ^1H (300, 400 or 500 MHz) and ^{13}C (75, 100 or 125 MHz) NMR spectra were recorded in $CDCl_3$ on Bruker AMX-300, −400 or −500 spectrometers. Chemical shift (δ) are given in ppm relative to residual deuterated solvent. Coupling constants are reported in Hz. Enantiomeric excesses were determined by chiral-GC (capillary column, 10 psi H_2), temperature programs are described as follows: initial temperature [°C]–initial time [min]–temperature gradient [°C min^{-1}]–final temperature [°C], or by chiral Supercritical Fluid Chromatography (SFC), with appropriated program using a gradient of methanol. Retention times (t_R) are given in minutes. Mass spectra were obtained by EI (70 eV) and High Resolution Mass Spectra (HRMS) by Electrospray Ionisation (ESI) or by Electronic Impact (EI). Optical rotations were measured at 20 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration c given as g 100 mL^{-1}).

Typical procedure for ligand (L1 to L11) synthesis: A solution of amine (22.2 mmol) in THF (10 mL) was added to a stirred mixture of Et_3N (111.1 mmol, 15.5 mL) and PC**L3** (22.2 mmol, 1.9 mL) at 0 °C, and the reaction mixture was stirred for 3 h at room temperature. Biphenol or binaphthol (22.2 mmol) in a solution of THF (5 mL) was slowly added to the reaction mixture at 0 °C and then the suspension was stirred at RT overnight. The suspension was diluted in toluene (8 mL) and filtered on neutral alumina, the solution was concentrated and purified by flash chromatography through neutral alumina using dry toluene as eluent, to give the pure ligand as a white solid or a colorless oil.

Ligand L1:[38] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.49$–7.45 (m, 2H, Ar), 7.38–7.10 (m, 16H, Ar), 4.60 (q, $J = 7.0$ Hz, 1H, CH), 4.58 (q, $J = 7.0$ Hz, 1H, CH), 1.73 ppm (d, $J = 7.0$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.0$, 151.9, 151.1, 151.0, 143.0, 131.2, 130.0, 129.8, 129.1, 129.0, 128.9, 128.2, 127.9, 127.7, 126.6, 125.3, 124.0, 122.5, 122.0, 52.7, 52.6, 22.2 ppm; ^{31}P (162 MHz, $CDCl_3$): $\delta = 147.0$ ppm; $[\alpha]_D^{20} = -236$ ($c = 3.0$ in toluene).

Ligand L3:[38] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.54 (m, 2H, Ar), 7.42–7.36 (m, 2H, Ar), 7.32–7.19 (m, 4H, Ar), 7.07–7.00 (m, 10H, Ar), 4.28 (t, $J = 10.3$ Hz, 1H, CH), 4.27 (t, $J = 10.3$ Hz, 1H, CH), 2.32–2.24 (m, 2H, CH_2), 2.17–2.10 (m, 2H, CH_2), 0.83 ppm (t, $J = 7.3$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.9$, 151.8, 150.9, 141.0, 131.4, 129.9, 129.7, 129.1, 129.0, 128.3, 127.5, 126.2, 124.6, 123.7, 122.5, 121.7, 59.8, 59.7, 29.6, 28.3, 11.6 ppm; ^{31}P (162 MHz, $CDCl_3$): $\delta = 144.4$ ppm; $[\alpha]_D^{20} = +231$ ($c = 3.5$ in toluene).

Ligand L4:[38] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–6.98 (m, 14H, Ar), 4.78–4.58 (m, 2H, CH), 2.47 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.71 ppm (d, $J = 7.0$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.0$, 147.9, 147.1, 143.5, 137.5, 133.3, 132.6, 131.0, 130.9, 130.2, 129.3, 129.0, 128.2, 128.1, 127.9, 127.8, 127.6, 126.5, 125.3, 109.6, 52.5, 20.8, 17.3, 16.3 ppm; ^{31}P (162 MHz, $CDCl_3$): $\delta = 144.4$ ppm; $[\alpha]_D^{20} = -221$ ($c = 2.2$ in toluene).

Ligand L5:[3] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$–7.03 (m, 14H, Ar), 4.32 (s, 2H, CH), 2.49 (s, 3H, CH_3), 2.36 (s, 6H, CH_3), 2.28 (m, 2H, CH_2), 2.07 (s, 2H, CH_2), 1.99 (s, 3H, CH_3), 0.78 ppm (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.9$, 147.3, 133.2, 132.7, 131.2, 131.1, 130.9, 130.4, 130.3, 129.3, 128.7, 128.2, 127.6, 126.4, 60.2, 23.2, 20.9, 20.8, 17.2, 16.4, 11.9 ppm; ^{31}P (162 MHz, $CDCl_3$): $\delta = 144.4$ ppm; $[\alpha]_D^{20} = -215$ ($c = 1.06$ in $CHCl_3$).

Ligand L6:[39] ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$–7.17 (m, 22H, Ar), 4.82–4.78 (m, 2H, CH), 1.90 ppm (d, $J = 7.0$ Hz, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 151.9$, 151.8, 151.0, 140.4, 132.9, 132.4, 131.2, 130.0, 129.8, 129.2, 129.0, 128.2, 127.9, 127.3, 127.0, 126.1, 125.7, 125.6, 125.3, 124.7, 124.1, 122.5, 122.1, 52.8, 52.7, 22.1 ppm; ^{31}P NMR (203 MHz; $CDCl_3$): $\delta = 146.3$ ppm; $[\alpha]_D^{20} = +405$ ($c = 1.12$ in $CHCl_3$).

Ligand L7:[39] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 6.8$ Hz, 2H, Ar), 7.52–7.02 (m, 16H, Ar), 4.89 (m, 2H, Ar), 2.55 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.85 ppm (d, $J = 4.0$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.5$, 141.2, 133.8, 133.3, 133.1, 132.7, 131.4, 130.6, 130.5, 129.7, 128.6, 128.2, 127.7, 127.6, 127.2, 126.6, 126.0, 125.8, 53.1, 53.0, 21.2, 17.8, 16.9 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 142.0$ ppm; $[\alpha]_D^{20} = -435$ ($c = 1.0$ in $CHCl_3$).

Ligand L8:[40] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$–8.98 (m, 4H, Ar), 7.74–7.17 (m, 18H, Ar), 4.63 (q, $J = 7.2$ Hz, 2H, CH), 1.75 ppm (d, J = 7.2 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.5$–122.4, 52.3, 51.1, 21.8 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 146.1$ ppm; $[\alpha]_D^{20} = -456$ ($c = 0.79$ in $CHCl_3$).

Ligand L9:[40] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$–7.78 (m, 4H, Ar), 7.65–7.24 (m, 18H, Ar), 4.47 (q, $J = 7.2$ Hz, 2H, CH), 1.75 ppm (d, $J = 7.2$ Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.5$–122.5, 54.5, 54.3, 23.1, 21.8 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 151.3$ ppm; $[\alpha]_D^{20} = +11$ ($c = 0.79$ in $CHCl_3$).

Ligand L10:[41] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–5.03 (m, 20H, Ar), 5.07 (dq, ^1J = 7.1, ^2J = 1.0 Hz, 2H, CH), 3.52 (s, 6H, -OCH_3), 1.61 ppm (d, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 150.7, 150.16, 133.0, 132.3, 131.4, 130.5, 129.5, 128.4, 128.2, 127.5, 127.4, 127.3, 127.2, 126.0, 125.8, 124.7, 124.4, 124.4, 124.3, 122.8, 122.5, 121.8, 119.4, 109.3, 65.9, 54.6, 48.3, 48.2, 22.2, 15.3 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 152.15 ppm; $[\alpha]_D^{20} = -272.2$ (c = 1.0 in $CHCl_3$).

Ligand L11:[41] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–6.52 (m, 20H, Ar), 4.99 (dq, ^1J = 7.1, ^2J = 1.2 Hz, 2H, CH), 3.58 (s, 6H, OCH_3), 1.55 ppm (d, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 149.9, 132.8, 132.5, 131.4, 130.3, 129.2, 128.3, 128.0, 127.7, 127.6, 127.4, 127.3, 125.9, 125.6, 124.7, 124.5, 124.2, 122.7, 121.5, 119.6, 109.2, 54.6, 50.3, 50.2, 22.6, 22.5 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 155.25 ppm; $[\alpha]_D$ = +144.3 (c = 1.1 in $CHCl_3$).

Typical procedure for 3-substituted enones synthesis: A flame-dried flask was charged with Grignard reagent (2.0 equiv) and cooled to 0 °C. The ethoxycyclohex-2-en-1-one or methoxycyclopent-2-enone (50 mmol) in THF (40 mL) was added dropwise. Once the addition was complete the reaction mixture was left at room temperature until complete disappearance of the starting material. The reaction was hydrolyzed by addition of aqueous sulfuric acid (5% w/w). Et_2O (50 mL) was added and the aqueous phase was separated and extracted further with Et_2O (3×20 mL). The combined organic fractions were washed with $NaHCO_3$, brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo. The oily residue was purified by Kugelrohr distillation under reduced pressure.

3-Ethylcyclohex-2-en-1-one (2):[42] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.89 (t, J = 1.4 Hz, 1H, CH), 2.37 (t, J = 3.3 Hz, 2H, CH_2), 2.29 (t, J = 5.7 Hz, 2H, CH_2), 2.25 (qd, ^1J = 7.4, ^2J = 0.6 Hz, 2H, CH_2), 2.0 (quint, J = 7.0 Hz, 2H, CH_2), 1.1 ppm (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.0, 167.8, 124.6, 37.4, 30.8, 29.7, 22.7, 11.2 ppm.

3-Isobutylcyclohex-2-en-1-one (3):[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (s, 1H, CH), 2.35 (t, J = 6.7 Hz, 2H, CH_2), 2.25 (t, J = 5.9 Hz, 2H, CH_2), 2.07 (d, J = 7.3 Hz, 2H, CH_2), 1.97 (quint, J = 6.4 Hz, 2H, CH2), 1.87 (m, 1H, CH), 0.9 ppm (d, J = 6.6 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 165.7, 126.9, 47.7, 37.3, 29.7, 26.4, 22.8, 22.5 ppm.

3-(3-Butenyl)cyclohex-2-en-1-one (4):[44] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80 (s, 1H, CH), 5.75–5.67 (m, 1H, CH), 4.98 (dd, ^1J = 17.1, ^2J = 1.5 Hz, 1H, =CH), 4.92 (dd, ^1J = 9.4, ^2J = 1.6 Hz, 1H, =CH), 2.29–2.19 (m, 8H), 1.94–1.89 ppm (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.9, 165.6, 137.1, 126.1, 115.7, 37.5, 37.4, 31.1, 29.9, 22.8 ppm.

3-(4-Pentenyl)cyclohex-2-en-1-one (5):[45] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (s, 1H, CH), 5.78–5.68 (m, 1H, CH), 4.99–4.91 (m, 2H, $=CH_2$), 2.31–1.90 (m, 10H), 1.59–1.51 ppm (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 166.5, 138.0, 125.9, 115.5, 37.5, 37.5, 33.4, 29.9, 26.2, 22.9 ppm.

3-[2-(1,3-Dioxan-2-yl)ethyl]cyclohex-2-en-1-one (6):[45] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (s, 1H, CH), 4.39 (t, J = 5.0 Hz, 1H, CH), 3.93 (dd, ^1J = 10.6, ^2J = 5.0 Hz 2H, CH_2), 3.60 (td, ^1J = 12.4, ^2J = 2.3 Hz, 2H, CH_2), 2.21–2.14 (m, 6H), 1.86–1.80 (m, 2H, CH_2), 1.65–1.60 (m, 2H, CH_2), 1.20 ppm (dt, ^1J = 13.4, ^2J = 1.2 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 165.8, 125.4, 101.0, 66.7, 37.2, 32.1, 32.0, 29.6, 25.6, 22.6 ppm.

3-Phenylcyclohex-2-en-1-one (8):[11a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.38 (m, 5H, Ph), 6.41 (t, J = 1.4 Hz, 1H, CH), 2.77 (td, ^1J = 6.1, ^2J = 1.3 Hz, 2H, CH_2), 2.48 (t, J = 6.7 Hz, 2H, CH_2), 2.15 ppm (quint, J = 6.4 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 159.8, 138.8, 130.0, 128.8, 126.1, 125.4, 37.2, 28.1, 22.8 ppm.

3-(4-(Trifluoromethyl)phenyl)cyclohex-2-en-1-one (9):[46] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 4H, Ar), 6.44 (s, 1H, CH), 2.80–2.77 (t, J = 5.8 Hz, 2H, CH_2), 2.53 (t, J = 6.8 Hz, 2H, CH_2), 2.20 ppm (quint, J = 6.3 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 158.2, 127.1, 126.6, 125.9, 125.7, 37.3, 28.3, 22.9 ppm.

3-(4-Methoxyphenyl)cyclohex-2-en-1-one (10):[46] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.0 Hz, 2H, CH Ar), 6.94 (d, J = 8.0 Hz, 2H, CH Ar), 6.41 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 2.78–2.74 (m, 2H, CH_2), 2.47 (t, J = 6.3 Hz, 2H, CH_2), 2.15 ppm (quint, J = 6.3 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 161.4, 159.3, 130.9, 127.8, 123.81, 114.3, 55.5, 37.3, 28.0, 22 ppm.

3-(2-Methoxyphenyl)cyclohex-2-en-1-one (11):[47] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3 (ddd, ^1J = 9.4, ^2J = 7.6, ^3J = 1.8 Hz, 1H, CH Ar), 7.20 (dd, ^1J = 9.3, ^2J = 1.8 Hz, 1H, CH Ar), 6.98 (td, ^1J = 7.6, ^2J = 1.0 Hz, 1H, CH Ar), 6.93 (d, J = 8.4 Hz, 1H, CH Ar), 6.21 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 2.75 (t, J = 5.8 Hz, 2H, CH_2), 2.49 (t, J = 6.3 Hz, 2H, CH_2), 2.11 ppm (q, J = 5.8 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 161.7, 156.6, 130.3, 128.7, 128.2, 120.7, 111.1, 55.4, 37.5, 30.0, 23.3 ppm.

3-Ethyl-2-methylcyclohex-2-en-1-one (15):[48] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38–2.31 (m, 4H, CH_2), 2.24 (q, J = 7.6 Hz, 2H, CH_2), 1.91 (quint, J = 6.3 Hz, 2H, CH_2), 1.75 (s, 3H, CH_3), 1.05 ppm (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 160.4, 130.2, 37.6, 30.2, 28.2, 22.5, 11.6, 10.2 ppm; IR (neat): $\tilde{\nu}$ = 2965, 2935, 2868, 2825, 1664, 1628 cm^{-1}; EI-MSHR: m/z: calcd for $C_9H_{14}O$: 138.1045, found 138.1045 $[M]^+$.

3-Ethylcyclopent-2-en-1-one (19):[49] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (s, 1H, CH), 2.57 (q, J = 7.1 Hz, 2H, CH_2), 2.44–2.37 (m, 4H), 1.17 ppm (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.1, 184.5, 128.6, 35.3, 31.3, 26.6, 11.4 ppm; IR (neat): $\tilde{\nu}$ = 2966, 1710, 1617, 1180 cm^{-1}; EI-MSHR: m/z: calcd for $C_7H_{10}O$: 110.0732, found 110.0731 $[M]^+$.

4-Chlorobutan-1-al (24): Pyridinium chlorochromate (30.10 g, 139.6 mmol, 2.0 equiv) in dry CH_2Cl_2 (200 mL) was suspended in a 250 mL round-bottomed flask equipped with a condenser. 4-chlorobutanol (1.0 equiv) in dry dichloromethane (20 mL) was added in one portion to the magnetically stirred solution. After 2 h, Et_2O (200 mL) was added and the supernacant decanted from the black residue. The insoluble gum was washed with Et_2O (3×50 mL) whereupon it became granular solid. The organic layers were filtered through a short pad of florisil, and the solvents were removed in vacuum in order to give a dark green oil. Distillation under reduced pressure (50 °C, 13 mm Hg) furnished the desired product in 49% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1H, CHO), 3.57 (t, J = 6.3 Hz, 2H, CH_2), 2.65 (dt, ^1J = 7.0, ^2J = 1.0 Hz, 2H, CH_2), 2.07 ppm (quint, J = 6.6 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 220.9, 44.0, 40.8, 24.7 ppm.

2-(3-Chloropropyl)-1,3-dioxane 25: 4-Chlorobutan-1-al (4.02 g, 37.7 mmol) and 1,3-propanediol (6.0 mL, 83.02 mmol) in dry toluene (50 mL) were placed in a round-bottomed flask equipped with a Dean-Stark under nitrogen. The reaction mixture was refluxed in presence of catalytic amount of p-TsOH·H_2O (200 mg) for 3 h. The reaction was quenched at room temperature by the addition of aqueous saturated solution of $NaHCO_3$. The organic layer was washed with water, dried over K_2CO_3 and solvent was removed in vacuo to give the desired protected aldehyde in quantitative yield. The crude mixture was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (t, J = 5.0 Hz, 1H, CH), 4.10 (dd, ^1J = 10.6, ^2J = 5.0 Hz, 2H, CH_2), 3.76 (td, ^1J = 12.4, ^2J = 2.3 Hz, 2H, CH_2), 2.13–2.01 (m, 1H, CH), 1.93–1.86 (m, 2H, CH_2), 1.77–1.72 (m, 2H, CH_2), 1.34 ppm (dd, ^1J = 13.4, ^2J = 1.3 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.4, 66.9, 44.9, 32.4, 27.1, 25.6 ppm.

3-(3-(1,3-Dioxan-2-yl)propyl)cyclohex-2-en-1-one (7):[50] Lithium (540 mg, 77.81 mmol) was suspended in dry Et_2O (10 mL) in presence of a catalytic amount of naphthalene. Dibromoethane and TMSCl (0.1 mL) were added at 0 °C in order to activate the lithium. 2-(3-chloropropyl)-1,3-dioxane (4.29 g, 26.08 mmol) in solution in dry Et_2O (20 mL) was added dropwise at 0 °C. A white precipitate was formed. At the end of the addition, the mixture was allowed to warm up to room temperature. At this stage an aliquot of the reaction showed no formation of the lithiated species. 3-Ethoxycyclohexenone (3.71 g, 26.5 mmol) in solution in dry THF (40 mL) was slowly added to the mixture at room temperature, and the reaction was stirred for 18 h. The reaction was quenched by the addition of water and Et_2O. The aqueous layer was extracted with Et_2O (3×), and the combined organic layers were washed with brine, dried over K_2CO_3, and concentrated in vacuo. The crude mixture was purified by flash chromatography (R_f = 0.27, pentane/Et_2O 1:2) in order to furnish the not totally clean product as a yellow oil (1.49 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (s, 1H, CH), 4.48 (t, J = 4.0 Hz, 2H, CH_2), 4.04 (dd, ^1J =

4.8, ^2J=11.6 Hz, 2H, CH_2), 3.71 (t, J=11.9 Hz, 2H, CH_2), 2.30 (t, J=6.6 Hz, 2H, CH_2), 2.24 (t, J=5.8 Hz, 2H, CH_2), 2.18 (t, J=6.6 Hz, 2H, CH_2), 2.07–1.98 (m, 1H, CH), 1.93 (quint, J=6.3 Hz, 2H, CH_2), 1.56–1.53 (m, 4H), 1.33–1.30 ppm (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 199.7, 166.0, 125.6, 101.6, 66.7, 37.6, 37.2, 34.4, 29.4, 25.6, 22.5, 21.1 ppm; IR (neat): $\tilde{\nu}$=2955, 2847, 1669, 1144 cm^{-1}; EI-MSHR: m/z: calcd for $C_{13}H_{20}O_3$: 224.1412, found 224.1407 $[M]^+$.

3,4,7,8-Tetrahydronaphthalene-1,5(2*H*,6*H*)-dione (16):[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.37 (t, J=6.3 Hz, 8H, CH_2), 1.88 ppm (quint, J=6.3 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.0, 145.4, 37.8, 21.9, 21.3 ppm.4

1-Methylcyclohept-2-en-1-ol (27): An ethereal solution of methyllithium (25.0 mL, 40.0 mmol) was added dropwise to a stirred solution of cycloheptenone (3.58 g, 32.49 mmol) in dry Et_2O (40 mL) at −30 °C. The resulting solution was allowed to warm to room temperature, stirred for 3 h, and quenched by the dropwise addition of water (20 mL). The phases were separated and the aqueous layer extracted with Et_2O (2× 20 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the alcohol (3.71 g, 90%) as a pale yellow oil. The crude mixture was used without any further purification. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 139.6, 129.6, 74.1, 40.9, 28.9, 27.6, 27.4, 24.4 ppm.

3-Methylcyclohept-2-en-1-one (17): A solution of 1-methylcyclohept-2-enol (3.71 g, 29.40 mmol) in dichloromethane (30 mL) was added in one portion to a magnetically stirred slurry of PCC (13.44 g, 62.3 mmol) in dry CH_2Cl_2 (90 mL), at room temperature. The resulting dark-red black mixture was allowed to stir for 2 h at room temperature and was diluted with Et_2O (120 mL). The ethereal solution was decanted from the black resinous polymer, which was washed with Et_2O (3×60 mL). The organic layers were washed successively with 5% aqueous sodium hydroxide (2× 300 mL), 5% aqueous HCl (300 mL), and saturated aqueous $NaHCO_3$ (2×150 mL). The solvent was removed at reduced pressure and the residue was purified by flash chromatography (R_f=0.33, pentane/Et_2O 3:1) to afford the desired product as a colorless oil (755 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.89 (s, 1H, CH), 2.54 (t, J=7.1 Hz, 2H, CH_2), 2.39 (t, J=5.1 Hz, 2H, CH_2), 1.93 (s, 3H, CH_3), 1.81–1.72 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.6, 158.3, 42.4, 34.4, 27.5, 25.0, 21.4 ppm; IR (neat): $\tilde{\nu}$=2934, 2866, 1652, 1440, 1376, 1268 cm^{-1}; EI-MSHR: m/z: calcd for $C_8H_{12}O$: 124.0888, found 124.0890 $[M]^+$.

Typical procedure for "normal" Cu-catalyzed asymmetric conjugate addition to trisubstituted enones: A flame-dried Schlenk tube was charged with copper salt (2.0 mol%) and the chiral ligand (4.0 mol%). Solvent (2.5 mL) was added and the mixture was stirred at room temperature for 30 min before being cooled to −30 °C. The trialkylaluminium (2.0 equiv for Me_3Al, 1.0 mL of a 2 M solution in heptane, or 1.4 equiv for Et_3Al, 1.6 mL of a 0.9 M in hexane) was introduced dropwise at such a rate that the temperature did not rise above −30 °C, and the reaction mixture was stirred at −30 °C for further 5 min. Then the Michael acceptor (1.0 equiv, 1.0 mmol) in Et_2O or THF (0.5 mL) was added dropwise. Once the addition completed the reaction mixture was left at −30 °C overnight. The reaction was hydrolyzed by the addition of MeOH at −30 °C, followed by aqueous saturated NH_4Cl solution or 2 N HCl (3 mL) at room temperature. Et_2O (10 mL) was added and the aqueous layer was separated and extracted further with Et_2O (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography (pentane/Et_2O) to yield the 1,4-adduct.

Typical procedure for "reverse" Cu-catalyzed asymmetric conjugate addition to trisubstituted enones: A flame-dried Schlenk tube was charged with copper salt (2.0 mol%) and the chiral ligand (4.0 mol%). Solvent (2.5 mL) was added and the mixture was stirred at room temperature for 30 min. Then the Michael acceptor (1.0 equiv, 1.0 mmol) in Et_2O or THF (0.5 mL) was added dropwise at room temperature and the reaction mixture was stirred for further 5 min before being cooled to −30 °C. Then, the trialkylaluminium (2.0 equiv for Me_3Al, 1.0 mL of a 2 M solution in heptane, or 1.4 equiv for Et_3Al, 1.6 mL of a 0.9 M in hexane) was introduced dropwise over 2 min. Once the addition was complete the reaction mixture was left at −30 °C overnight. The reaction was hydrolyzed by the addition of MeOH at −30 °C, followed by aqueous saturated NH_4Cl solution or 2 N HCl (3 mL) at room temperature. Et_2O (10 mL) was added and the aqueous layer was separated and extracted further with Et_2O (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography (pentane/Et_2O) to yield the 1,4-adduct.

3-Ethyl-3-methylcyclohexan-1-one (28):[4] ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.26 (t, J=6.6 Hz, 2H, CH_2), 2.16 (d of AB, J=13.6 Hz, 1H, CH_2), 2.08 (d of AB, J=13.6 Hz, 1H, CH_2), 1.88–1.81 (m, 2H, CH_2), 1.64–1.48 (2m, 2H, CH_2), 1.33 (q, J=7.3 Hz, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.83 ppm (t, J=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.5, 53.3, 41.0, 38.6, 35.3, 34.0, 24.4, 22.0, 7.7 ppm; $[\alpha]_D^{20}$=+5.45 (c= 1.64 in $CHCl_3$, 92% *ee R*. Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 60 °C, t_{R1}=32.8 min (*R*), t_{R2}=43.3 min (*S*)).

3-Isobutyl-3-methylcyclohexan-1-one (29):[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.29–2.23 (m, 2H, CH_2), 2.19 (d of AB, J=13.4 Hz, 1H, CH_2), 2.09 (d of AB, J=13.4 Hz, 1H, CH_2), 1.93–1.51 (3m, 5H), 1.19 (t, J=5.0 Hz, 2H, CH_2), 0.93 (s, 3H, CH_3), 0.91 ppm (dd, ^1J=6.6, ^2J=1.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.7, 54.6, 51.2, 41.3, 39.7, 36.8, 25.8, 25.7, 25.6, 24.2, 22.5 ppm; IR (neat): $\tilde{\nu}$=2956, 1716, 1467 cm^{-1}; ESI-MSHR: m/z: calcd for $C_{11}H_{20}ONa$: 191.1406364, found 191.1408390 $[M+Na]^+$; $[\alpha]_D^{20}$=−5.25 (c=1.73 in $CHCl_3$, 93% *ee R*. Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 80 °C, t_{R1}=13.0 min (*S*), t_{R2}= 15.6 min (*R*)).

3-(But-3-enyl)-3-methylcyclohexan-1-one (31):[3,44] ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.83–5.75 (m, 1H, CH), 5.00 (dd, ^1J=17.0, ^2J=1.7 Hz, 1H, CH), 4.93 (dd, ^1J=10.3, ^2J=1.3 Hz, 1H, CH), 2.32–2.24 (m, 2H, CH_2), 2.20 (d of AB, J=13.4 Hz, 1H, CH_2), 2.12 (d of AB, J=13.4 Hz, 1H, CH_2), 2.05–1.98 (m, 2H, CH_2), 1.90–1.83 (m, 2H, CH_2), 1.66–1.53 (m, 2H, CH_2), 1.39–1.34 (m, 2H, CH_2), 0.93 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=212.5, 139.1, 114.7, 54.0, 41.3, 41.2, 38.9, 36.2, 28.2, 25.2, 22.4 ppm; $[\alpha]_D^{20}$=+0.90 (c=1.71 in $CHCl_3$, 93% *ee R*. Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 130 °C, t_{R1}=6.4 min (*S*), t_{R2}=6.7 min (*R*)).

3-(Pent-4-enyl)-3-methylcyclohexan-1-one (32):[3,51] ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.82–5.72 (m, 1H, CH), 5.00–4.91 (m, 2H, =CH_2), 2.25 (t, J= 6.8 Hz, 2H, CH_2), 2.18 (d of AB, J=13.4 Hz, 1H, CH_2), 2.09 (d of AB, J=13.4 Hz, 1H, CH_2), 2.03–1.98 (m, 2H, CH_2), 1.87–1.81 (m, 2H, CH_2), 1.65–1.49 (2m, 2H, CH_2), 1.36–1.23 (m, 4H), 0.90 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.6, 138.9, 115.0, 54.1, 41.3, 38.9, 36.1, 34.6, 25.4, 23.0, 22.4 ppm; $[\alpha]_D^{20}$=−1.67 (c=1.70 in $CHCl_3$, 93% *ee S*. Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 130 °C, t_{R1}=10.1 min (*R*), t_{R2}=10.5 min (*S*)).

3-(2-(1,3-Dioxan-2-yl)ethyl)-3-methylcyclohexan-1-one (33):[3,36] ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.46 (t, J=5.0 Hz, 1H, CH), 4.08 (dd, ^1J=10.6, ^2J=4.9 Hz, 2H, CH_2), 3.73 (tt, ^1J=12.3, ^2J=2.4 Hz, 2H, CH_2), 2.29–2.22 (m, 2H, CH_2), 2.17–2.00 (m, 3H, CH_2 and CH), 1.89–1.78 (m, 2H, CH_2), 1.63–1.49 (m, 4H, CH_2), 1.38–1.30 (m, 3H, CH_2 and CH), 0.89 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=212.4, 102.9, 67.2, 54.1, 41.3, 38.4, 35.9, 35.8, 29.7, 26.1, 25.1, 22.4 ppm; $[\alpha]_D^{20}$=+0.08 (c=1.25 in $CHCl_3$, 94% *ee R*. Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 130 °C, t_{R1}=36.7 min (*S*), t_{R2}=37.4 min (*R*)).

3-(3-(1,3-Dioxan-2-yl)propyl)-3-methylcyclohexan-1-one (34):[50] ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.48 (t, J=5.4 Hz, 1H, CH), 4.06 (ddd, ^1J=6.0, ^2J=4.7, ^3J=0.9 Hz, 2H, CH_2), 3.72 (dt, ^1J=2.6 Hz, 2H, CH_2), 2.24 (t, J= 6.7 Hz, 2H, CH_2), 2.15 (d of AB, J=13.7 Hz, 1H, CH), 2.07 (d of AB, J=13.3 Hz, 1H, CH_2), 2.07–1.99 (m, 1H, CH), 1.85–1.70 (m, 2H, CH_2), 1.64–1.58 (m, 1H, CH), 1.54–1.48 (m, 3H, CH_2 an CH), 1.36–1.29 (m, 3H, CH_2 and CH), 1.26–1.17 (m, 2H, CH_2), 0.88 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=212.2, 102.0, 66.8, 53.7, 41.4, 40.9, 38.5, 35.7, 35.5, 25.7, 24.9, 22.0, 17.8 ppm; IR (neat): $\tilde{\nu}$=2955, 2849, 2848, 1709, 1144 cm^{-1}; EI-MSHR: m/z: calcd for $C_{14}H_{23}O_3$: 239.1647, found 239.1647

$[M-H]^-$; $[\alpha]_D^{20}=-1.84$ ($c=1.86$ in $CDCl_3$, 97% *ee S.* Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, 130–100–1–170, $t_{R1}=141.1$ min (*R*), $t_{R2}=141.8$ min (*S*)).

3-Methyl-3-phenylcyclohexan-1-one (35):[7,9] ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.33$ (d, $J=4.4$ Hz, 4H, CH Ar), 7.22 (sext, $J=4.4$ Hz, 1H, CH Ar), 2.89 (d of AB, $J=14.2$ Hz, 1H, CH_2), 2.45 (d of AB, $J=14.2$ Hz, 1H, CH_2), 2.32 (t, $J=6.8$ Hz, 2H, CH_2), 2.23–2.18 (m, 1H), 1.96–1.85 (2m, 2H, CH_2), 1.72–1.64 (m, 1H), 1.34 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=211.4$, 147.4, 128.5, 126.2, 125.5, 53.1, 42.8, 40.8, 37.9, 29.7, 22.0 ppm; $[\alpha]_D^{20}=-48.8$ ($c=1.15$ in $CHCl_3$, 72% *ee R.* Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Hydrodex-B-3P, isotherm 140 °C, $t_{R1}=31.7$ min (*R*), $t_{R2}=32.6$ min (*S*)).

3-Ethyl-3,5,5-trimethylcyclohexan-1-one (36):[9] ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.19$–2.07 (m, 4H, CH_2), 1.59 (d of AB, $J=14.1$ Hz, 1H, CH_2), 1.48 (d of AB, $J=14.1$ Hz, 1H, CH_2), 1.41–1.25 (2m, 2H, CH_2), 1.04 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.84 ppm (t, $J=7.6$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.7$, 54.3, 52.7, 48.6, 38.8, 37.0, 36.0, 32.3, 30.6, 26.8, 8.2 ppm; IR (neat): $\tilde{\nu}=2961$, 1713 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{11}H_{20}O$: 168.1514, found 168.1515 $[M]^+$; $[\alpha]_D^{20}=-9.5$ ($c=3.1$ in $CHCl_3$, 97% *ee S.* Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (chirasil DEX-CB, 60–110–2–170, $t_{R1}=134.9$ min (*R*), $t_{R2}=135.5$ min (*S*)).

3-Ethyl-3-methylcycloheptan-1-one (37):[7,9] ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.52$ (d of AB, $J=12.1$ Hz, 1H, CH_2), 2.43–2.39 (m, 1H), 2.36 (d of AB, $J=12.1$ Hz, 1H, CH_2), 1.79–1.49 (m, 6H), 1.36–1.24 (m, 2H, CH_2), 0.87 (s, 3H, CH_3), 0.85 ppm (t, $J=7.6$ Hz 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=214.4$, 54.4, 43.9, 42.1, 35.2, 34.8, 25.3, 24.6, 24.2, 7.9 ppm; IR (neat): $\tilde{\nu}=2966$, 2932, 1736, 1797, 1457 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{10}H_{19}O$: 155.1435, found 155.1439 $[M+H]^+$; $[\alpha]_D^{20}=+12.57$ ($c=1.41$ in $CHCl_3$, 93% *ee R.* Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (Lipodex E, 60–0–1–170, $t_{R1}=24.5$ min (*R*), $t_{R2}=25.7$ min (*S*)).

3-Ethyl-3-methylcyclopentan-1-one (38):[9] ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.34$–2.20 (m, 2H, CH_2), 2.06 (d of AB, $J=5.9$ Hz, 1H, CH_2), 2.00 (d of AB, $J=5.9$ Hz, 1H, CH_2), 1.83–1.69 (m, 2H, CH_2), 1.43 (q, $J=7.6$ Hz, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.89 ppm (t, $J=7.6$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=220.2$, 51.8, 39.7, 36.8, 34.7, 33.9, 24.4, 9.0 ppm; EI-MSHR: *m/z*: calcd for $C_8H_{14}O$: 126.1045, found 126.10420 $[M]^+$; IR (neat): $\tilde{\nu}=2960$, 1743, 1456 cm^{-1}. $[\alpha]_D^{20}=+55.0$ ($c=1.41$ in $CHCl_3$, 93% *ee R.* Absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral GC (lipodex E, isotherm 70 °C, $t_{R1}=9.1$ min (*R*), $t_{R2}=10.2$ min (*S*)).

2,3-Dimethylcyclohexan-1-one (39): ^1H NMR (500 MHz, $CDCl_3$) mixture of diastereomers: $\delta=2.61$–2.00 (4m, 4H, CH), 1.90–1.43 (3m, 4H, CH_2), 1.06 (d, $J=6.2$ Hz, 3H, CH_3 *trans*), 1.02 (d, $J=6.6$ Hz, 3H, CH_3 *trans*), 0.98 (d, $J=6.8$ Hz, 3H, CH_3 *cis*), 1.02 ppm (d, $J=7.1$ Hz, 3H, CH_3 *cis*); ^{13}C NMR (125 MHz, $CDCl_3$) mixture of diastereomers: $\delta=213.3$, 51.8, 49.3, 41.5, 41.1, 40.6, 37.3, 34.2, 31.1, 26.1, 23.3, 20.7, 14.5, 11.8, 11.7 ppm; IR (neat): $\tilde{\nu}=2932$, 1709, 1456, 908 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_8H_{14}O$: 126.1045, found 126.1044 $[M]^+$; $[\alpha]_D^{20}=-19.5$ ($c=1.39$ in $CHCl_3$, 94% *ee* (2*S*,3*R*), *trans/cis* 77:23). Enantiomeric excess was measured by chiral GC (Lipodex E, isotherm 70 °C, *trans* adduct: $t_{R1}=9.7$ min (2*S*,3*R*), $t_{R2}=10.5$ min (2*R*,3*S*); *cis* adduct $t_{R1}=12.5$ min, $t_{R2}=13.2$ min).

3-Ethyl-2-methylcyclohexan-1-one (40):[3,52] ^1H NMR (500 MHz, $CDCl_3$) mixture of diastereomers: $\delta=2.37$ (m, 1H, CH), 2.26 (m, 1H, CH), 2.16 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.62 (m, 2H, CH_2), 1.36 (m, 3H), 1.02 (d, $J=6.7$ Hz, 3H, CH_3), 0.90 ppm (t, $J=7.4$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *trans* diastereomer: $\delta=213.8$, 49.5, 46.7, 41.5, 29.7, 26.2, 25.9, 11.8, 10.2 ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *cis* diastereomer: $\delta=214.8$, 48.8, 43.9, 39.7, 26.5, 23.9, 21.9, 11.6, 11.3. $[\alpha]_D^{20}=-12.7$ ($c=1.29$ in $CHCl_3$, 82% *ee* (2*S*,3*R*)). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 70 °C, $t_{R1}=31.9$ min (2*S*,3*R*), $t_{R2}=33.8$ min (2*R*,3*S*)).

***trans*-1-(2-Methylcyclohexyl)ethan-2-one (41)**:[53,54] ^1H NMR (500 MHz, $CDCl_3$): $\delta=2.11$ (s, 3H, CH_3), 2.05 (td, $^1J=3.0$, $^2J=11.0$ Hz, 1H, CH), 1.80–1.56 (m, 5H), 1.30–1.17 (m, 3H), 0.98–0.90 (m, 1H), 0.81 ppm (d, $J=6.5$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=213.5$, 59.5, 34.7, 34.1, 29.8, 29.3, 26.2, 26.0, 20.9 ppm; IR (neat): $\tilde{\nu}=2926$, 2855, 1709 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_9H_{16}O$: 140.1201, found 140.1198 $[M]^+$; $[\alpha]_D^{20}=-9.4$ ($c=1.29$ in EtOH, 84% *ee* (1*R*,2*R*), *trans/cis* 94:06); enantiomeric excess was measured by chiral GC (chirasil DEX CB, 60–0–1–170, *trans* adduct: $t_{R1}=33.0$ min (1*S*,2*S*), $t_{R2}=34.1$ min (1*R*,2*R*) ; *cis* adduct: $t_{R1}=37.1$ min (1*S*,2*R*), $t_{R2}=38.0$ min (1*R*,2*S*)); absolute configuration of *trans* adduct was assigned in analogy with references.

***trans*-1-(2-Ethylcyclohexyl)ethan-2-one (42)**:[18] ^1H NMR (500 MHz, $CDCl_3$): $\delta=2.15$ (td, $^1J=3.0$, $^2J=11.0$ Hz, 1H, CH), 1.85–1.82 (m, 1H, CH), 1.78–1.69 (m, 3H), 1.53–1.45 (m, 1H), 1.31–1.18 (m, 5H), 1.05–0.99 (m, 1H), 0.81 ppm (t, $J=7.5$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=213.6$, 57.8, 40.2, 30.4, 30.0, 29.2, 27.6, 26.1, 26.0, 11.2 ppm; IR (neat): $\tilde{\nu}=2931$, 1708, 891 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{10}H_{18}O$: 154.1358, found 154.1358 $[M]^+$; $[\alpha]_D^{20}=-18.5$ ($c=1.17$ in $CHCl_3$, 75% *ee* (1*R*,2*R*), *trans/cis* 92:08); enantiomeric excess was measured by chiral GC (chirasil DEX CB, 60–0–1–110–20–170–5, *trans* adduct: $t_{R1}=41.6$ min (1*S*,2*S*), $t_{R2}=42.3$ min (1*R*,2*R*); *cis* adduct: $t_{R1}=43.8$ min (1*R*,2*S*), $t_{R2}=44.8$ min (1*S*,2*R*)).

3-Methyl-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (43): ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.58$ (d, $J=8.5$ Hz, 2H, CH Ar), 7.44 (d, $J=8.5$ Hz, 2H, CH Ar), 2.89 (d of AB, $J=14.2$ Hz, 1H, CH_2), 2.48 (d of AB, $J=14.5$ Hz, 1H, CH_2), 2.28–2.30 (m, 2H, CH_2), 2.27–2.13 (m, 1H), 1.99–1.87 (m, 2H, CH_2), 1.68–1.60 (m, 1H), 1.34 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=210.7$, 151.4, 128.5 (q, $^1J_{C,F}=31.9$ Hz), 126.1, 125.5 (q, $^2J_{C,F}=3.4$ Hz), 52.8, 43.1, 40.7, 37.8, 29.8, 21.9 ppm; IR (neat): $\tilde{\nu}=2951$, 1710, 1330, 1168, 1122, 909 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{14}H_{15}OF_3$: 256.1075, found 256.1075 $[M]^+$; $[\alpha]_D^{20}=+30.3$ ($c=1.4$ in $CDCl_3$, 66% *ee S*; absolute configuration was assigned in analogy with **43**). Enantiomeric excess was measured by chiral SFC (AD-2%-2–1–15% MeOH, 200 bar, 2 mL min^{-1}, 30 °C, $t_{R1}=3.8$ min (*R*), $t_{R2}=4.4$ min (*S*)).

3-(4-Methoxyphenyl)-3-methylcyclohexan-1-one (44):[7] ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.24$ (d, $J=15.6$ Hz, 2H, CH Ar), 6.86 (d, $J=15.5$ Hz, 2H, CH Ar), 3.79 (s, 3H, OCH_3), 2.86 (d of AB, $J=14.2$ Hz, 1H, CH_2), 2.43 (d of AB, $J=13.6$ Hz, 1H, CH_2), 2.31 (t, $J=7.3$ Hz, 2H, CH_2), 2.19–2.13 (m, 2H, CH_2), 1.70–1.62 (m, 1H), 1.30 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=211.9$, 157.8, 139.4, 126.6, 113.8, 55.2, 53.3, 42.3, 40.8, 38.0, 30.1, 22.0 ppm; $[\alpha]_D^{20}$ not determined; enantiomeric excess was measured by chiral SFC (OD H-2%-2–1–15% MeOH, 200 bar, 2 mL min^{-1}, 30 °C, $t_{R1}=5.9$ min (*R*), $t_{R2}=6.4$ min (*S*)).

3-(2-Methoxyphenyl)-3-methylcyclohexan-1-one (45): ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.24$–7.21 (m, 2H, CH Ar), 6.93–6.89 (m, 2H, CH Ar), 3.84 (s, 3H, OCH_3), 3.00 (d of AB, $J=14.5$ Hz, 1H, CH_2), 2.61–2.56 (m, 1H), 2.46 (d of AB, $J=14.2$ Hz, 1H, CH_2), 2.31 (t, $J=6.6$ Hz, 2H, CH_2), 1.89–1.81 (m, 2H, CH_2), 1.70–1.62 (m, 1H), 1.41 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=212.4$, 157.8, 134.8, 127.7, 127.4, 120.6, 111.8, 54.9, 53.4, 42.8, 40.9, 35.0, 26.3, 22.1 ppm; IR (neat): $\tilde{\nu}=2951$, 1711, 1242, 632 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{14}H_{18}O_2$: 218.1307, found 218.1306; $[\alpha]_D^{20}$ not determined; enantiomeric excess was measured by chiral SFC (OD H-1%-2–1–15% MeOH, 200 bar, 2 mL min^{-1}, 30 °C, $t_{R1}=9.9$ min (*R*), $t_{R2}=10.4$ min (*S*)).

(*E*)-3-Methyl-3-(pent-1-enyl)cyclohexan-1-one (48): 1N diisobutylaluminium hydride (2.0 mL, 2.0 mmol) in *n*-heptane (2.0 mL) was added to 1-pentyne (0.3 mL, 3.0 mmol) while maintaining the temperature below 40 °C. When the initial exothermic reaction has subsided, the reaction mixture was heated for 2 h at 50 °C. The vinylalane formed was used in solution in heptane. A flame-dried Schlenk tube was charged with $[Cu(CH_3CN)_4]BF_4$ (100.5 mg, 30 mol%) and the chiral ligand **L4** (152.2 mg, 30.0 mol%). Dry THF (2.5 mL) was added and the mixture was stirred at room temperature for 30 min. Then, the 3-methylcyclohexen-1-one (110.2 mg, 1.0 mmol) in THF (0.5 mL) was added dropwise at room temperature and the reaction mixture was stirred for further 5 min before being cooled to −30 °C. Then, the freshly prepared vinylalane in solution in heptane was introduced dropwise over 2 min. Once the addition was complete the reaction mixture was left at −30 °C overnight. The reaction was hydrolyzed by the addition of MeOH at −30 °C, followed by 2N HCl

(3 mL) at room temperature. Et_2O (10 mL) was added and the aqueous layer was separated and extracted further with Et_2O (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography (R_f=0.33, pentane/Et_2O 9:1) give the 1,4-adduct (122.5 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.37–5.24 (m, 2H, CH), 2.40 (dd of AB, ^1J=13.9, ^2J=1.3 Hz, 1H, CH_2), 2.30–2.17 (m, 2H, CH_2), 2.13 (d of AB, J=14.1 Hz, 1H, CH_2), 1.93 (q, J=7.3 Hz, 2H, CH_2), 1.81 (quint, J=5.8 Hz, 2H, CH_2), 1.70–1.64 (m, 1H), 1.61–1.54 (m, 1H), 1.33 (sext, J=7.3 Hz, 2H, CH_2), 1.02 (d, J= 1.9 Hz, 3H, CH_3), 0.83 ppm (td, ^1J=7.1, ^2J=1.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.5, 137.6, 128.4, 52.3, 40.8, 40.7, 37.0, 34.7, 28.1, 22.5, 22.1, 13.5 ppm; IR (neat): $\tilde{\nu}$=2957, 2930, 3871, 1713, 1455 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{12}H_{20}O$: 180.1514, found 180.1514 $[M]^+$; $[\alpha]_D^{20}$= −30.7 (c=1.1 in $CHCl_3$, 73% *ee R*. Absolute configuration was assigned in analogy with **60**). Enantiomeric excess was measured by chiral GC (hydrodex B-6-TBDM, 60–0–1–170–5, t_{R1}=53.7 min (*R*), t_{R2}=55.4 min (*S*)).

(*R*)-(3-Ethyl-3-methylcyclohex-1-enyloxy)trimethylsilane (49): A flame-dried Schlenk tube was charged with CuTC (3.9 mg, 2.0 mol%) and **L1** (4.0 mol%). Dry Et_2O (2.5 mL) was added and the mixture was stirred at room temperature for 30 min. 3-Methylcyclohex-2-en-1-one (110 mg, 1.0 equiv, 1.0 mmol) in Et_2O (0.5 mL) was then added dropwise at room temperature and the reaction mixture was stirred for further 5 min before being cooled to −30°C. Then, the triethylaluminium (2.0 equiv, 2.2 mL of a 0.9 M in hexane) was introduced dropwise over 2 min. Once the addition was complete the reaction mixture was left at −30°C overnight. The complete disappearance of the starting material was controlled by GC-MS, and the enantiomeric excess was measured by chiral GC (same method as 3-ethyl-3-methylcyclohexan-1-one **28**). The aluminium enolate was quenched, at −30°C, by the addition of 4 equiv TMSOTf (0.78 mL) previously dried over 0.5 mL of Et_3Al. The reaction mixture was allowed to warm to room temperature for 3 h. Then, the reaction was cooled to 0°C before been poured in Et_3N (2.0 mL) at 0°C. A saturated aqueous solution of $NaHCO_3$ (5.0 mL) was quickly dropwise added, and the aqueous layer was extracted with Et_2O (3×). The combined organic fractions were quickly dried over K_2CO_3, filtered and concentrated in vacuo. The oily residue was purified by filtration over a mixture of dry $NaHCO_3$ (2.0 g) and silica gel (8.0 g, R_f=0.3, pentane) to give the pure product as a colorless oil (123 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.65 (s, 1H, CH), 1.96–1.93 (m, 2H, CH_2), 1.70–1.64 (m, 2H, CH_2), 1.42–1.36 (m, 2H, CH_2), 1.42–1.36 (m, 1H), 1.32–1.25 (m, 3H), 0.93 (s, 3H, CH_3), 0.83 (t, J=7.3 Hz, 3H, CH_3), 0.18 ppm (s, 9H, Si-$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.2, 114.6, 35.6, 36.4, 34.1, 29.9, 27.5, 19.7, 8.5, 0.3 ppm; IR (neat): $\tilde{\nu}$=2961, 1664, 1363, 1252, 1200 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{12}H_{24}OSi$: 212.1596; found 212.1597 $[M]^+$; $[\alpha]_D^{20}$=−10.6 (c=1.12 in EtOH, 67% *ee R*).

(*R*)-Allyl-3-ethyl-3-methylcyclohex-1-enyl carbonate (50): A flame-dried Schlenk tube was charged with $[Cu(CH_3CN)_4]BF_4$ (2.0 mol%) and the chiral ligand **L8** (4.0 mol%). Dry THF (2.5 mL) was added and the mixture was stirred at room temperature for 30 min. 3-Methylcyclohex-2-en-1-one (1.0 equiv, 1.0 mmol) in THF (0.5 mL) was added dropwise at room temperature and the reaction mixture was stirred for further 5 min before being cooled to −30°C. Triethylaluminium (2.0 equiv, 2.2 mL of a 0.9 M in hexane) was then introduced dropwise over 2 min. Once the addition completed the reaction mixture was left at −30°C overnight. The complete disappearance of the starting material was controlled by GC-MS, and the enantiomeric excess was measured by chiral GC (same method as 3-ethyl-3-methylcyclohexan-1one **28**). The aluminium enolate was quenched, at −30°C, by the addition of 4 equiv allyl chloroformate (0.4 mL), and 2.0 mL of THF. The reaction mixture was allowed to warm to room temperature for 48 h. The reaction was hydrolyzed by addition of MeOH followed by 2 N HCl (3 mL) at room temperature. Et_2O (10 mL) was added and the aqueous layer was separated and extracted further with Et_2O (3×3 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography (R_f=0.62, pentane/Et_2O 95:5) to give a colorless oil (121 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.00–5.90 (m, 1H, CH), 5.38 (dd, ^1J=15.6, ^2J=1.5 Hz, 1H, CH), 5.28 (d, J= 10.4 Hz, 1H, CH), 5.25 (s, 1H, CH), 4.63 (dd, ^1J=5.6, ^2J=1.3 Hz, 2H, CH_2), 2.22–2.08 (m, 2H, CH_2), 1.78–1.73 (m, 2H, CH_2), 1.50–1.31 (2m, 4H, CH_2), 0.98 (s, 3H, CH_3), 0.84 ppm (t, J=7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.3, 147.6, 131.5, 123.0, 119.0, 68.6, 35.0, 34.9, 33.6, 26.6, 26.5, 19.4, 8.4 ppm; IR (neat): $\tilde{\nu}$=2961, 1756, 1249, 891 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{13}H_{20}O_3$: 224.1412, found 224.1412 $[M]^+$; $[\alpha]_D^{20}$=−6.9 (c=1.08 in $CHCl_3$, 67% *ee R*); enantiomeric excess was measured by chiral GC (Hydrodex-B6-TBDM, 60–0–1–170–5, t_{R1}=70.3 (*R*), t_{R2}=50.1 (*S*)).

Typical procedure for the Cu-catalyzed asymmetric conjugate addition of trialkylalanes–enol acetates formation:[32] The ligand (0.04 mmol) was added to a solution of CuTC (0.02 mmol) in dry Et_2O (2.5 mL) at room temperature under argon. The solution was stirred at room temperature for 30 min and the enone (1.0 mmol) in dry Et_2O (0.5 mL) was then added dropwise. The mixture was then cooled to −30°C and the trialkylalane was added dropwise so that the temperature did not rise over −30°C. The reaction mixture was stirred at −30°C until complete consumption of the starting material. Ac_2O (0.4 mL, 4.2 mmol) was added dropwise at −30°C and the reaction mixture was allowed to warm up to room temperature until complete conversion. The mixture was quenched by adding NH_4Cl_{sat}/HCl and Et_2O. The aqueous layer was extracted with Et_2O (3×), and the organic layers were washed with a saturated solution of $NaHCO_3$ and water before dried over $MgSO_4$ and filtered off. The solvents were removed in vacuo to afford the crude mixture, which was purified by flash chromatography (pentane/Et_2O). Enantiomeric excesses were determined on an aliquot before the addition of the acetic anhydride by chiral GC.

(*R*)-3-Ethyl-3-methylcyclohex-1-enyl acetate (51): ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.12 (s, 1H, CH), 2.17–2.03 (m, 5H), 1.76–1.70 (m, 2H, CH_2), 1.50–1.43 (m, 1H), 1.38–1.31 (m, 3H), 0.98 (s, 3H, CH_3), 0.84 ppm (t, J= 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.3, 147.4, 122.9, 35.0, 34.8, 33.6, 26.9, 26.6, 21.1, 19.4, 8.3 ppm; IR (neat): $\tilde{\nu}$=2963, 2938, 1755, 1688, 1214 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1309 $[M]^+$; $[\alpha]_D^{20}$ = −11.4 (c=2.09 in $CHCl_3$, 67% *ee R*).

(*R*)-3-Ethyl-3-methylcyclohept-1-enyl acetate (52): ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.17 (s, 1H, CH), 2.39–2.28 (m, 2H, CH_2), 2.11 (s, 3H, $COCH_3$), 1.79–1.65 (m, 5H), 1.50–1.35 (m, 3H), 1.04 (s, 3H, CH_3), 0.89 ppm (t, J=7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 169.7, 150.0, 127.1, 37.3, 36.1, 35.0, 32.0, 26.9, 25.9, 24.2, 21.0, 8.4 ppm; IR (neat): $\tilde{\nu}$=2962, 2923, 1748, 1679, 1457, 1366, 1224, 1202 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1462 $[M]^+$; $[\alpha]_D^{20}$= +6.12 (c=1.24 in $CHCl_3$, 90% *ee R*).

(*R*)-2,2-Diallyl-3-ethyl-3-methylcyclohexan-1-one (53): The enol acetate **51** (383.0 mg, 2.10 mmol) in THF (1.0 mL) was added dropwise to a 1.5 M in Et_2O solution of MeLi·LiBr (4.0 mL, 6 mmol) in dry THF (5.0 mL) at room temperature. The mixture was stirred for 2 h before being quenched at room temperature by the addition of ally bromide (1.5 mL, 17.2 mmol). The reaction was exothermic and stirred at room temperature overnight before the addition of Et_2O and water. The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (R_f=0.48, pentane/Et_2O 95:5) to give the title product (342 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.74–5.60 (m, 2H, 2CH), 5.07 (s, 2H, =CH_2), 5.03 (d, J=10.1 Hz, 2H, =CH_2), 2.39–2.10 (m, 6H), 1.76–1.64 (m, 3H), 1.56–1.48 (m, 1H), 1.27 (q, J=7.6 Hz, 2H, CH_2), 0.86 (s, 3H, CH_3), 0.83 ppm (t, J=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.2, 133.9, 133.5, 118.1, 118.0, 50.6, 50.4, 39.3, 39.2, 38.7, 34.0, 31.4, 31.3, 24.4, 7.7 ppm; IR (neat): $\tilde{\nu}$=2964, 1705, 910 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{15}H_{24}O$: 220.1827, found 220.1826 $[M]^+$; $[\alpha]_D^{20}$=+6.1 (c=1.25 in $CHCl_3$, 90% *ee R*).

***spiro*[4.5]-((*R*)-10-Ethyl-10-methyl)-dec-2-en-6-one (54)**: A solution of (*R*)-2,2-diallyl-3-ethyl-3-methylcyclohexanone (**53**) (322.2 mg, 1.46 mmol) in Et_2O (2.0 mL) was introduced to a solution of Grubb's first generation catalyst (64.0 mg, 0.08 mmol) in dry CH_2Cl_2 (8.0 mL). The mixture was stirred at room temperature until the complete disappearance of the starting material (1 h). The reaction was quenched with aqueous 1 M HCl. The aqueous fraction was extracted with Et_2O (3×) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The

crude residue was purified by flash chromatography (R_f=0.34, pentane/Et_2O 95:5) to give the title product (185.2 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.59–5.56 (m, 1H, CH), 5.54–5.51 (m, 1H, CH), 2.95 (dquint, ^1J=16.7, ^2J=2.2 Hz, 1H, CH_2), 2.78 (dquint, ^1J=16.7, ^2J=2.6 Hz, 1H, CH_2), 2.30 (d of AB, J=13.3 Hz, 1H, CH_2), 2.25 (d, J=16.7 Hz, 1H, CH_2), 2.19 (dd of AB, ^1J=13.6, ^2J=1.3 Hz, 1H, CH_2), 2.14 (d, J=16.7 Hz, 1H, CH_2), 1.85–1.76 (m, 2H, CH_2), 1.70–1.65 (m, 1H), 1.56–1.50 (m, 1H), 1.31 (q, J=7.6 Hz, 2H, CH_2), 0.90 (s, 3H, CH_3), 0.85 ppm (t, J=7.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 213.2, 128.2, 127.4, 54.8, 50.8, 41.8, 41.5, 38.7, 35.7, 33.9, 32.7, 24.3, 7.8 ppm; IR (neat): $\tilde{\nu}$=2926, 1708, 1366, 1217, 632 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_{13}H_{20}O$: 192.1514, found 192.1513 $[M]^+$; $[\alpha]_D^{20}$=−8.2 (c=1.09 in $CDCl_3$, 92% *ee R*).

(*R*)-2-Ethyl-2-methylhexane-1,6-diol (55): A solution of enol acetate **51** (368.3 mg, 2.02 mmol) in CH_2Cl_2/MeOH 3:1 (60 mL) was treated with O_3 at −78°C. After complete consumption of the substrate, excess O_3 was removed by O_2 and N_2 bubbling, and the mixture was treated with $NaBH_4$ (904 mg, 23.9 mmol). After stirring at −78°C for 30 min, the mixture was warmed up to room temperature. The reaction mixture was diluted with Et_2O and sequentially washed with aqueous saturated citric acid solution and saturated NaCl solution. The organic layer was concentrated in vacuo and the residue was purified by flash chromatography (R_f=0.26, Et_2O) to give the diol as a colorless oil (90.6 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.63 (t, J=6.3 Hz, 2H, CH_2), 3.34 (d of AB, J=10.7 Hz, 1H, CH_2), 3.30 (d of AB, J=11.0 Hz, 1H, CH_2), 2.85 (brs, 2H, OH), 1.53 (quint, J=6.6 Hz, 2H, CH_2), 1.32–1.21 (m, 6H), 0.80 (t, J=7.6 Hz, 3H, CH_3), 0.79 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=68.9, 62.4, 37.3, 35.3, 33.2, 28.8, 21.3, 19.4, 7.8 ppm; IR (neat): $\tilde{\nu}$=3368, 2938 cm^{-1}; EI-MSHR: *m/z*: calcd for $C_8H_{17}O$: 129.1279, found 129.1275 $[M-CH_3O]^+$; $[\alpha]_D^{20}$=−0.6 (c=2.9 in $CHCl_3$, 92% *ee R*).

(*R*)-7a-Methyl-1,2,5,6,7,7a-hexahydroinden-4-one (56):[36] According to literature, the 1,4-adduct **33** (565.8 mg, 2.5 mmol) was dissolved in a 6N HCl solution in THF (10 mL) at room temperature. After being stirred at room temperature for 18 h, the mixture was neutralized at 0°C with a sodium bicarbonate saturated solution, diluted with Et_2O, washed with water (3×), and one of brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (pentane/Et_2O) to afford pale yellow oil (255.2 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.43 (t, J=3.0 Hz, 1H, CH), 2.54–2.18 (3m, 5H), 2.03–1.79 (m, 6H), 1.57 (td, ^1J=13.9, ^2J=4.8 Hz, 1H), 1.07 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=200.8, 149.7, 136.4, 47.7, 42.5, 40.0, 38.5, 30.1, 24.2, 21.5 ppm; $[\alpha]_D^{20}$=−74.6 (c=1.53 in $CHCl_3$, 90% *ee R*; absolute configuration was attributed in comparison with literature data). Enantiomeric excess was measured by chiral GC (Hydrodex B-3P, isotherm 130°C, t_{R1}=5.6 min (*S*), t_{R2}=5.8 min (*R*)).

(*S*)-4a-Methyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (57):[50] The 1,4-adduct **34** (312.6 mg, 1.3 mmol) was dissolved with concentrated HCl (1.0 mL) and THF (15 mL) at room temperature. After being stirred at room temperature for 18 h, the mixture was neutralized at 0°C with a sodium bicarbonate saturated solution, diluted with Et_2O, washed with water (3×), brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (R_f=0.63, pentane/Et_2O 2:1) to afford the desired product (121.7 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.36 (t, J=3.5 Hz, 1H, CH), 2.49 (ddt, ^1J=17.1, ^2J=5.4, ^3J=2.9 Hz, 1H), 2.26–2.19 (m, 1H), 2.15–2.09 (m, 2H), 1.99–1.89 (m, 1H), 1.85–1.79 (m, 1H), 1.65–1.61 (m, 3H), 1.58–1.51 (m, 2H), 1.37 (td, ^1J=12.6, ^2J=5.1 Hz, 1H), 0.99 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=202.8, 144.4, 133.1, 40.2, 38.7, 37.6, 35.4, 25.7, 25.3, 19.1, 17.6 ppm; $[\alpha]_D^{20}$=−92.5 (c = 1.7 in $CHCl_3$, 92% *ee S*); enantiomeric excess was measured by chiral GC (Hydrodex B-3P, 130–20–20–170–5, t_{R1}=17.6 min (*R*), t_{R2}=18.7 min (*S*)).

(*R*)-6-Ethyl-6-methyloxepan-2-one (58): Ketone **28** (141.4 mg, 1.01 mmol) was introduced to a solution of *m*-CPBA (367.6 mg, 1.60 mmol) in dry CH_2Cl_2 (2 mL) at room temperature. The mixture was stirred at room temperature for 24 h and the resulting white precipitate was filtered off. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic fractions were washed with a saturated aqueous solution of $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (R_f=0.24, pentane/Et_2O 2:1) to afford the mixture of the two isomers (78 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.94 (d of AB, J=13.1 Hz, 1H, CH_2), 3.90 (d of AB, J=12.6 Hz, 1H, CH_2), 2.59 (t, J=3.3 Hz, 2H, CH_2), 1.77–1.71 (m, 2H, CH_2), 1.49–1.25 (m, 4H), 0.88 (s, 3H, CH_3), 0.83 ppm (t, J=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.8, 75.5, 40.1, 39.8, 36.3, 34.1, 18.9, 7.4 ppm; IR (neat): $\tilde{\nu}$ = 2965, 1735 cm^{-1}; ESI-MSHR: *m/z*: calcd for $C_9H_{17}O_2$: 157.1223, found 157.1219 $[M+H]^+$.

(*R*)-1-Methyl-3-oxocyclohexanecarbaldehyde (60):[37] A solution of 3-methyl-3-(pent-1-enyl)cyclohexan-1-one (**49**) (38.5 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) was treated with O_3 at −78°C. After complete consumption of the substrate, excess O_3 was removed by O_2 and N_2 bubbling, and the mixture was treated with an excess of Me_2S (0.1 mL). The mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with Et_2O and water. The aqueous layer was extracted 4 times and combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (R_f=0.12, pentane/Et_2O 3:2) to give the keto-aldehyde as a colorless oil (11 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.45 (s, 1H, CHO), 2.63 (d of AB, J=14.5 Hz, 1H, CH_2), 2.38–2.27 (m, 2H, CH_2), 2.13 (d of AB, J=14.5 Hz, 1H, CH_2), 2.02–1.90 (m, 2H, CH_2), 1.88–1.79 (m, 1H), 1.70–1.65 (m, 1H), 1.17 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ=208.9, 203.1, 50.1, 46.7, 40.5, 30.7, 21.6, 20.6 ppm; $[\alpha]_D^{20}$= +11.1 (c = 1.09 in $CDCl_3$, 73% *ee R*).

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