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Formation of Quaternary Chiral Centers by N-Heterocyclic Carbene–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Trisubstituted Cyclic Enones

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: The copper-catalyzed conjugate addition of Grignard reagents to 3-substituted cyclic enones allows the formation of all-carbon chiral quaternary centers. We demonstrate in this article that N-heterocyclic carbenes act as efficient chiral ligands for this transformation. High enantioselectivities (up to 96% *ee*) could be obtained for a variety of substrates.

Keywords: asymmetry · conjugate addition · copper · Grignard reaction · N-heterocyclic carbenes

Introduction

The asymmetric copper-catalyzed conjugate addition (A.C.A.) is a reaction of choice for forming C–C bonds.[1] However, it remains a challenging reaction when applied to trisubstituted enones.[2–5] Some possibilities were already proposed, for example, organozinc nucleophiles associated with phosphoramidite ligands give excellent enantioselectivities on doubly activated Meldrum acid derivatives.[6–8] The zinc species were also associated with peptidic ligands on nitroolefin[9] or doubly activated cyclic enones[10] in high yields and enantiometric excesses (*ee*). However, the use of activated Michael acceptors is almost always needed to obtain good conversions, which is the fault of zinc nucleophiles that often react slowly, due to their low nucleophilicity. We proposed an alternative by using organoaluminum reagents with phosphorus-based ligands on nonactivated[11–14] cyclic enones. The main drawback of these approaches is the limitation in terms of easily available nucleophiles.

A new family of promising ligands called N-heterocyclic carbenes (NHCs),[15–21] which are believed to possess better electrodonating properties[22–24] and steric factors[23,25,26] than their phosphine counterparts, emerged and were tested in 1,4-addition reactions. Since the first publications in 2001 about the use of NHC–Cu complexes in the conjugate addition of organometallic nucleophiles on disubstituted enones, first by Woodward[27] in a racemic way, then by Alexakis[28a] and Mangeney[28b] in the chiral version, many papers were published about the subject.[29–34] The majority of these A.C.A. reactions were carried out by using organozinc nucleophiles on linear and cyclic enones with good *ee* values lying between 50 to 93%. Only Hoveyda reached 97% *ee* on the A.C.A. of silicon-based nucleophiles to cyclic disubstituted enones.

The use of trisubstituted enones to create quaternary chiral centers is more difficult due the steric hindrance of the β-position. As a result, only a few documents report on the subject. In 2006, Alexakis[35] and Hoveyda[36] published separately the first papers about the formation of quaternary chiral centers catalyzed by Cu–NHC complexes. Hoveyda used a large excess of organozinc nucleophiles with an Ag–NHC pre-catalyst. The use of a 1:1 mixture of Cu(OTf)·C_6H_6 and NHC allowed *ee* values of up to 93% to be obtained for the addition of Et_2Zn on 3-methylcyclohex-2-enone, and up to 97% to be obtained for the addition of

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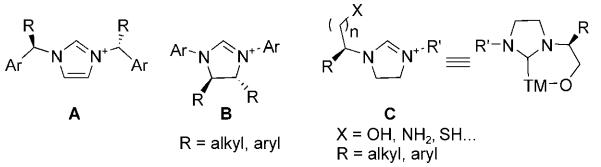
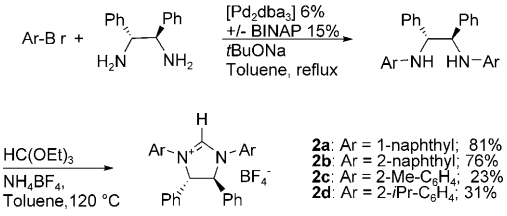
Ph_2Zn on the same substrate. The variation of the chelating group, from the phenol to sulfonyl allowed Hoveyda[37] to add zinc nucleophiles to activated five-membered trisubstituted cyclic enones. The difference of reactivity seems to come from the more strained metallacycle (seven-membered ring) and the lower basicity of the sulfonyl group relative to the phenol. To accelerate the reaction rate, Hoveyda also applied his methodology to the nucleophilic addition of organoaluminum reagents to five, six, and seven-membered cyclic enones.[38,39] The alkyl nucleophiles, namely methyl, ethyl, and isobutyl are commercially available. The aryl ones were synthesized by mixing the corresponding aryl lithium reagent with $AlEt_2Cl$. This methodology allowed *ee* values of up to 97% to be obtained for the addition of Et_3Al on methylcyclopentenone. After our group had carried out the first A.C.A. reactions with Grignard reagents and NHCs in high yields and *ee* values,[35] Tomioka proposed a C_2-symmetric NHC in 2008,[40] with the chiral back-induction of two phenyls on the methoxyphenol nitrogen substituent. With a 1:1.3 Cu/NHC ratio, he was able to obtain up to 80% *ee* for the addition of EtMgBr to the 3-methylcyclohex-2-enone. The purpose of the present paper is to find a simple methodology to functionalize trisubstituted cyclic enones by combining high reaction rates and *ee* values with a large scope of alkyl and aryl chains. We therefore propose to compare our C_2-symmetric and nonsymmetric NHCs to investigate the behavior of each family on trisubstituted cyclic enones.

NHCs may be separated into three families of ligands, depending on their chiral inducing ability. Herrmann's type C_2-symmetric NHC **A** bearing chiral substituents on the nitrogen atoms were the first to be synthesized.[41] The second C_2-symmetric family **B** possesses chiral bulky groups on the back of the ring, those inducing the chirality to the N- substituents and lowering their flexibility. Finally, the third family **C** is composed of NHCs bearing N-chiral substituents containing a strong chelating functionality, which binds to the TM (transition metal) and prevents any movement of the steric bulk around the reacting center.



***C_2*-Symmetric NHCs**: We started our investigations by synthesizing different C_2-symmetric NHCs through a Buchwald–Hartwig coupling of diphenylethanediamine (DPEDA)[42] and different bromo-aromatic reagents (Scheme 1). The obtained substituted diamines were then cyclized with triethylorthoformate to give the corresponding ImH^+. The fixed phenyl moieties on the back of the imidazolinylidene ring induced the stereoinformation on the nitrogen substituents, and by the way, to the reacting center.



Scheme 1. C_2-symmetric NHC synthesis. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; dba = (*E*,*E*)-dibenzylideneacetone.

With a panel of C_2-symmetric NHCs in hand, we tested them in the copper-catalyzed 1,4-addition on trisubstituted cyclic enones. We started our study by a screening of nucleophiles. The first observation we made was the total regioselectivity of the reactions in favor of the conjugate addition. As expected, the simplest NHC **1b**, with no chelating functionality or fixed stereoinducing groups, gave the worst results in terms of enantioselectivities and conversion. However, it allowed us to point out that organozinc nucleophiles were less reactive than the other ones, as there is no conversion after 16 h (Table 1, entry 1). Et_3Al and EtMgBr gave the best conversions but the enantioselectivities remained low (entries 2 and 3). For the ImH^+ **2a**, the rotation around the C–N axis was constrained, due to the stereoinduction from the back of the heterocycle. As a result, the stereoinformation was better transmitted to the reacting center and it was not surprising to see an increase of the *ee* values with those ligands (Scheme 2). As the chiral information is not fixed on the TM by a heteroatom chelation, the main advantage of that kind of C_2-symmetric NHC is some possible adaptability of the reactive volume, depending on the nucle-

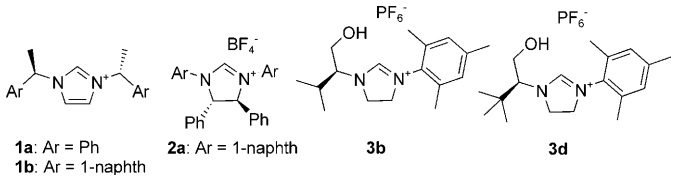
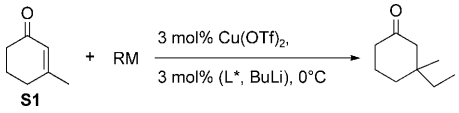
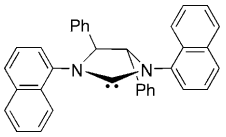


Table 1. Organometallics selection.



Entry	ImH^+	RM	*t* [h]	Prod.	Conv. [%][a]	*ee* [%], config.[b]
1	**1b**	Et_2Zn	16		1	–
2	**1b**	Et_3Al	16	**3**	85	9, (−) *S*
3	**1b**	EtMgBr	0.5	**2**	86	17, (+) *R*
4	**2a**	Et_3Al	16	**3**	94	54, (−) *S*
5	**2a**	EtMgBr	0.5	**3**	92	68, (−) *S*

[a] Determined by GCMS analysis after 16 h. [b] Determined by chiral GC analysis (Lipodex E).



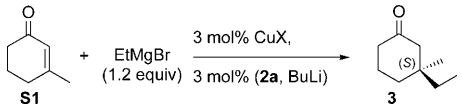
Scheme 2. C_2-symmetric NHC perspective view.

ophile size. This is not possible when the substituent is bound to the TM.

For both families, the aluminum species gave worse results in terms of enantioselectivity than their organomagnesium counterparts (Table 1, entries 2–3 and 4–5). Moreover, the Grignard reagents gave the shortest reaction times and we will see later that those nucleophiles were also basic enough to deprotonate the ImH^+, facilitating the procedure.

A screening of different copper sources, solvents, and temperatures was then carried out to find the best reaction conditions on the 1,4-addition of EtMgBr to 3,3-methylcyclohex-2-enone (Table 2).

Table 2. Copper salt and solvent screening.



Entry	CuX	Solvent	T [°C]	Conv. [%][a]	*ee* [%], config.[b]
1	$Cu(OTf)_2$	THF	0	>99	0
2	$Cu(OTf)_2$	M*t*BE	0	77	57, (−)
3	$Cu(OTf)_2$	CH_2Cl_2	0	80	40, (−)
4	$Cu(OTf)_2$	toluene	0	87	38, (−)
5	$Cu(OTf)_2$	dioxane	0	32	41, (−)
6	$Cu(OTf)_2$	Et_2O	RT	95	60, (−)
7	$Cu(OTf)_2$	Et_2O	0	92	68, (−)
8	$Cu(OTf)_2$	Et_2O	−40	85	37, (−)
9	CuBr	Et_2O	0	82	38, (−)
10	CuTC[c]	Et_2O	0	73	8, (−)
11	$[Cu(MeCN)_4]PF_6$	Et_2O	0	98	68, (−)
12	$[Cu(MeCN)_4]BF_4$	Et_2O	0	98	40, (−)

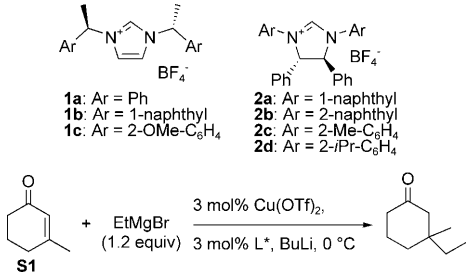
[a] Conversion determined by GCMS analysis after 30 min or 3 h. ($T<0$ °C). [b] Determined by chiral GC analysis (Lipodex E). [c] CuTC = copper thiophene carboxylate.

The most important parameter seemed to be the solvent. With the same copper source, the variation of solvent changed the enantioselectivity of the reaction dramatically. Indeed, as Et_2O gave the best *ee* (68%; Table 2, entry 7), the use of THF gave a racemate (entry 1). Methyl *tert*-butylether (M*t*BE), CH_2Cl_2, and toluene gave no improvement to our reaction (entries 2–4). Interestingly, dioxane in which the Schlenk equilibrium is shifted in favor of R_2Mg, since magnesium salt $MgBr_2$ precipitates in that solvent, still gave 41% *ee* with low conversion (entry 5). The best temperature for this reaction was 0 °C and $Cu(OTf)_2$ or $[Cu(MeCN)_4]PF_6$ (entries 1 and 12) appeared to be appropriate copper sources for the reaction.

By using the previously optimized reaction conditions, the addition of EtMgBr on 3-methylcyclohex-2-enone was tested with the different imidazolium salts (ImH^+) (Table 3).

For Hermann's type ImH^+, the best result was obtained by using ligand **1c** to give 42% *ee* (Table 3, entry 3) as **1a** gave only 9% *ee* (entry 1). With ligand **1b** containing a 2-ethylnaphthyl group, the *ee* drops to 17% (entry 2).

Table 3. C_2-symmetric NHC screening.



Entry	ImH^+	Prod.	Conv. [%][a]	*ee* [%], config.[b]
1	**1a**	**2**	81	9, (+) *R*
2	**1b**	**2**	86	17, (+) *R*
3	**1c**	**2**	75	42, (+) *R*
4	**2a**	**3**	92	68, (−) *S*
5[c]	**2a**	**3**	89	2, (−) *S*
6[d]	**2a**	**3**	94	73, (−) *S*
7[e]	**2a**	**3**	96	70, (−) *S*
8	**2b**	**3**	82	17, (−) *S*
9	**2c**	**3**	87	63, (−) *S*
10	**2d**	**3**	85	10, (−) *S*

[a] Conversion determined by GCMS analysis after 30 min or 3 h ($T<0$ °C). [b] Determined by chiral GC analysis (Lipodex E). [c] The substrate was added first, and then the Grignard reagent was added dropwise. [d] $Cu(OTf)_2$ (3 mol%), ImH^+ (4 mol%). [e] $Cu(OTf)_2$ (3 mol%), ImH^+ (6 mol%).

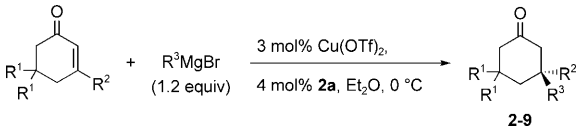
For ImH^+ salts **2a–d**, the results were more tricky: the enantioselectivity decreased in the following order: **2a** (68%) > **2c** (63%) ≫ **2b** (17%) > **2d** (10%) (Table 3, entries 4 and 8–10). The ligand **2d**, which gave up to 90% *ee* for the desymmetrization of trienes by Grubbs metathesis,[43] led to a disappointing result under our experimental conditions. The difference between **2a** and **2b** was certainly due to the remoteness of the naphthyl group from the reacting center going from 1-naphthyl to 2-naphthyl. When the environment surrounding the copper was less hindered the *ee* decreased dramatically.

The order of addition was also highly important. Indeed, if the Grignard reagent was added on the substrate, the *ee* dropped to 2% (Table 3, entry 5) when using ImH^+ **2a**. This observation could be explained if the active asymmetric species was an "ate-complex" or a higher-order cuprate, such as $[CuEt_2(NHC)]$. Indeed, when the Grignard reagent was added after the substrate, the Mg–Cu transmetallation time was shorter and only organocopper reagents were formed. When the Grignard reagent was added first, the transmetallation had time to occur twice to form the higher-order cuprate, which could be the asymmetric catalytic species that brings high *ee* values.

This contrasts with the copper-catalyzed asymmetric allylic substitution for which the Grignard reagent is added very slowly to the substrate to avoid the formation of cuprate species.[44,45] Finally, a Cu/NHC ratio of 1:1.3 gave the best *ee* values (Table 3, entry 6) and a 1:2 ratio decreased the *ee* values (entry 7).

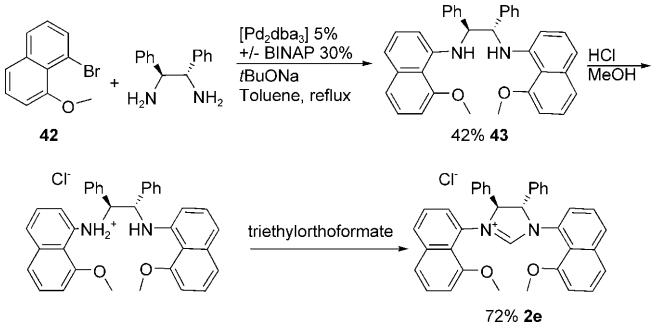
With our optimized conditions in hand, we applied our methodology to different alkyl organomagnesium reagents. It is interesting to observe the same facial selectivity of the nucleophilic approach. Indeed, the nucleophile always entered from the *Re* side of the cyclic enone when using ImH^+ **2a**, which was proven by the fact that the opposite major enantiomer was obtained when inverting the nucleophile and the substrate's substituent (Table 4, entries 1 and 6).

Table 4. Substrate variation.



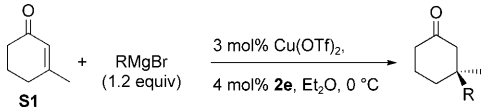
Entry	R^1	R^2	R^3	Prod.	Conv. [%][a]	*ee* [%], config.[b]
1	H	Me	Et	**3**	92	73, (−) *S*
2	H	Me	*n*Bu	**4**	99	73, (−) *S*
3	H	Me	but-3-en	**5**	81	73, (+) *R*
4	H	Me	*c*-pentyl	**6**	97	60, (−) *S*
5	H	Me	*i*Pr	**7**	99	39, (−) *S*
6	H	Et	Me	(*ent*)-**3**	99	21, (+) *R*
7	H	but-3-en	Et	**8**	88	50, (+) *S*
8	Me	Me	Et	**9**	93	71, (−) *S*

[a] Conversion determined by GCMS analysis after 30 min or 3 h ($T<0$ °C). [b] Determined by chiral GC analysis (Lipodex E).



Scheme 3. Synthesis of **2e**.

Table 5. Grignard variation with ligand **2e**.



Entry	R	Prod.	Conv. [%][a]	*ee* [%], config.[b]
1	Et	**3**	>99	67, (−) *S*
2	*n*Bu	**4**	>99	72, (−) *S*
3	*c*-pentyl	**6**	>99	56, (−) *S*
4	*i*Pr	**7**	>99	70, (−) *S*
5	*t*Bu	**10**	>99	0

[a] Conversion determined by GCMS analysis after 30 min or 3 h ($T<0$ °C). [b] Determined by chiral GC analysis (Lipodex E).

In accordance with Tomioka's work,[40] the variation of the counter-ion from BF_4^- to Cl^- has almost no effect on the *ee* of the conjugate addition. The linear nucleophiles, except methyl, which reacts with poor enantioselectivity, gave good results with *ee* values of around 73% (Table 4, entries 1–3). The addition of EtMgBr to the poorly reactive isophorone gave a promising 71% *ee* (entry 8). Unfortunately, when the Grignard reagent was α-branched, the *ee* decreased (entries 4–5).

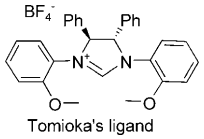
As the NHC naphthyl substituents were not coordinated to the copper, the steric bulk of the nucleophile may "push" those naphthyls away from the reacting center during the transmetallation step, and by doing so, leave the copper with weaker chiral induction as observed with the 2-naphthyl substituents. To prove this hypothesis, we used the C_2-symmetric NHC **2e**, containing the same structure as **2a**, but with two extra chelating methoxy groups (Scheme 3).

A copper salt and solvent screening showed that the best conditions for **2a** remained the best for **2e**. With those conditions in hand, we applied ImH^+ **2e** to a series of linear and branched Grignard reagents.

The linear nucleophiles gave the same results as with ImH^+ **2a**. In contrast, for the α-branched Grignard reagents, the results were totally different. With *c*-pentyl, the *ee* decreased slightly (60 to 56%; Table 5, entry 4), but with isopropyl, the *ee* increased dramatically from 39 to 70% (entry 6).

These results were in accordance with our previous hypothesis. Indeed, the presence of chelating substituents on the naphthyl group prevents the "opening" of the chiral pocket and the result was an increased *ee*. Moreover, the reaction pocket stayed big enough with ligand **2e** to allow the addition of a *tert*-butyl group on the 3-methylcyclohex-2-enone (**S1**) (Table 5, entry 5), but in a racemic way. The group of Tomioka[40] recently published a study in which they used a C_2-symmetric NHC substituted by two methoxyphenyls.

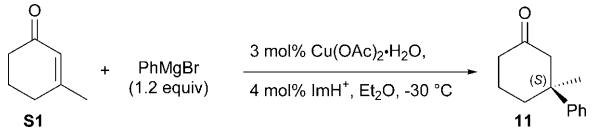
Their *ee* values were slightly better for the addition of isopropyl and ethyl organomagnesium nucleophile, but the presence of two naphthyls instead of two phenyls seems to bring a better regiocontrol. Indeed, in Et_2O we do not observe a 1,2-addition product with **2e**, unlike Tomioka's ligand, which gives around a 95:5 1,4/1,2 (1,4/1,2-addition) ratio.



With these encouraging results in hand, we wanted to extend the scope of our methodology by successfully adding aromatic nucleophiles on trisubstituted cyclic enones. As the two C_2-symmetric analogues react almost in the same way with linear Grignard reagents but differently with branched nucleophiles, we tested them in the addition of aromatic nucleophiles. Therefore, we started as usual by finding the best reaction conditions for the addition of PhMgBr to the 3-methylcyclohex-2-enone.

As for the alkyl Grignard reagents, the Herrmann's family gave the worst results (Table 6, entry 1). The ImH^+

Table 6. C_2-symmetric ligand screening for PhMgBr addition.



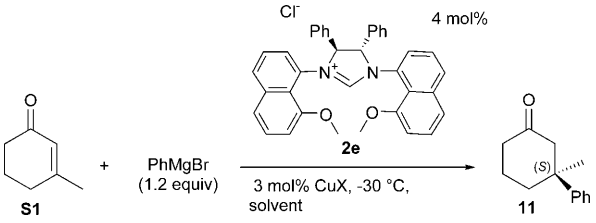
Entry	ImH^+	Add. t [min]	Ratio 1,2/1,4	Conv. [%][a]	ee [%][b]
1	**1b**	30	97:3	97	4, (+)
2	**2a**	30	72:28	99	88, (+)
3	**2b**	30	49:51	97	10, (+)
4	**2e**	30	16:84	99	48, (+)

[a] Conversion determined by GCMS analysis after 60 min. [b] Determined by chiral GC analysis (Hydrodex-B-3P).

2a gave very good *ee* values (88%), but the 1,4 regioselectivity was very low (entry 2). As for the addition of aliphatic Grignard reagents, ligand **2b** gave poor *ee* values, because of the remoteness of the naphthyl substituents from the reacting center. The main drawback of this reaction was the regioselectivity, largely in favor of the 1,2-addition. The use of ImH^+ **2e** allowed a better regiocontrol, although the *ee* was disappointingly low (48%; entry 4). Therefore, we made a short screening of different parameters to see if the *ee* could be increased.

Surprisingly, in this case, unlike the addition of an alkyl nucleophile, the best solvent was CH_2Cl_2 with high regioselectivity and *ee* values (Table 7, entry 6). The presence of the

Table 7. Reaction condition variation to increase regioselectivity.



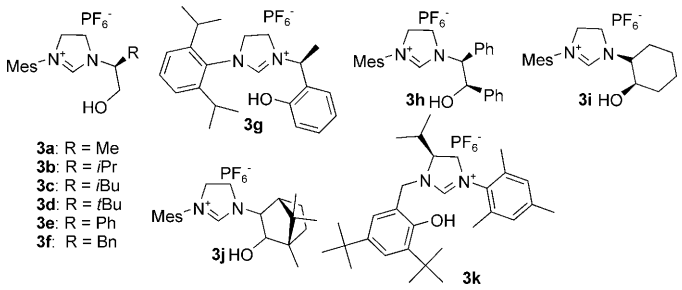
Entry	CuX	Solvent	Conv. [%][a]	Ratio 1,2/1,4	ee [%], config.[b]
1	$Cu(OAc)\cdot H_2O$	Et_2O	>99	16:84	48, (+)
2	$CuBr\cdot Me_2S$	Et_2O	>99	11:89	46, (+)
3	$[Cu(OTf)]_2\cdot C_6H_6$	Et_2O	>99	11:89	46, (+)
4	$[Cu(OTf)]_2\cdot C_6H_6$	toluene	>99	17:83	64, (+)
5	$Cu(OAc)\cdot H_2O$	toluene	>99	95:5	68, (+)
6	$CuBr\cdot Me_2S$	CH_2Cl_2	>99	13:87	70, (+)
7	$[Cu(OTf)]_2\cdot C_6H_6$	CH_2Cl_2	>99	28:72	72, (+)
8	$Cu(OAc)\cdot H_2O$	CH_2Cl_2	>99	20:80	70, (+)

[a] Conversion determined by GCMS analysis after 60 min. [b] Determined by chiral GC analysis (Lipodex E).

−OMe functionalities were also shown to be highly important, not for the enantioselectivity but for the regioselectivity of the reaction. In fact, almost all the reactions gave a much better 1,4/1,2 ratio with **2e** than with **2a**. The temperature parameter was also investigated, but −30°C remained the optimal temperature in terms of *ee* and regioselectivity. By lowering the temperature to −45°C or warming it to 0°C, the 1,2-addition was favored. Moreover, the phenyl copper complex seemed to become unstable at 0°C, because the reaction was messy and the complex became black after 10 min.

In conclusion, the C_2-symmetric NHCs were good ligands to catalyze regioselectively and enantioselectively the asymmetric conjugate addition of alkyl Grignard reagents, with *ee* values of up to 73% (Table 4). The presence of two methoxy chelating substituents on the NHC allowed the maintenance of the chiral information around the reactive center, and by doing so, enhanced the *ee* for the addition of α-branched nucleophiles (isopropyl, 39% *ee* with **2a** to 70% *ee* with **2e**). The addition of an aromatic organomagnesium nucleophile gave an impressive 88% *ee* with **2a**, but the regioselectivity dropped down. The use of the methoxy ImH^+ **2e** allowed the regioselectivity in favor of the 1,4-addition to increase by keeping a good *ee* value (70%).

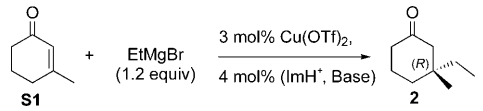
Alkoxy-substituted NHCs: As mentioned previously, the NHC containing a chelating group on the chiral substituent should induce better enantioselectivity, due to their fixed steric hindrance. We therefore followed a procedure developed by Mauduit[31] to synthesize a third family of NHCs containing an alkoxy group, whereas some were directly provided by Mauduit's group. The obtained ImH^+ compounds were then tested in the A.C.A. reaction. To begin the study with the bidentate ligands **3b**, a screening of solvents and temperatures was first carried out on the conjugate addition of EtMgBr to 3-methylcyclohex-2-enone.



The best results were obtained in Et_2O at 0°C (Table 8, entry 1). M*t*BE, which often showed better enantioselectivities than Et_2O[46] gave worse results in our case (entry 9). The temperature is also an important parameter. Indeed, in all solvents tested (except THF), the *ee* decreased with the temperature. In THF, the opposite was observed (entries 5 and 6); however, the *ee* was by far the worst of all the solvents tested.

Another advantage of using Grignard reagents, in addition to the ease of synthesizing a broad range of different alkyl or aryl magnesium nucleophiles, is the strong basicity of the compounds, which can deprotonate the ImH^+ in situ. Indeed, unlike aluminum and zinc nucleophiles, strong bases, such as *n*BuLi, were not required to activate the ImH^+. The absence of *n*BuLi had no influence on conversion and *ee* (Table 8, entries 3 and 4).

Table 8. Solvent and temperature screening.



S1 2

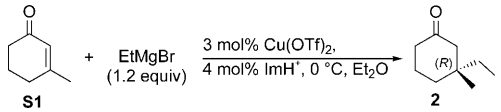
Entry	Solvent	ImH$^+$	Base	T [°C]	Conv. [%][a]	*ee* [%], config.[b]
1	Et_2O	**3b**	*n*BuLi	0	>99	69, (+)
2	Et_2O	**3b**	*n*BuLi	−30	85	67, (+)
3	Et_2O	**3d**	*n*BuLi	0	>99	80, (+)
4	Et_2O	**3d**	–	0	>99	80, (+)
5	THF	**3b**	*n*BuLi	0	92	26, (+)
6	THF	**3b**	*n*BuLi	−78	71	35, (+)
7	CH_2Cl_2	**3b**	DBU[c]	0	63	46, (+)
8	CH_2Cl_2	**3b**	DBU[c]	−30	66	44, (+)
9	M*t*BE	**3b**	*n*BuLi	0	47	49, (+)
10	M*t*BE	**3b**	*n*BuLi	−78	66	13, (+)

[a] Conversion determined by GCMS analysis after 30 min. [b] Determined by chiral GC (Lipodex E). [c] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

With these defined parameters in hand, we optimized the Cu/NHC ratio. The minimum ratio to obtain the highest *ee* (80%) was 1:1.3. Below that ratio, the *ee* decreased (70% *ee* for 1:1). Surprisingly, by increasing the ratio to 1:2, the *ee* stayed almost unchanged (78% *ee* for 1:2).

The results with different alkoxy NHCs showed clearly that the enantioselectivity of the reaction decreases with the steric hindrance on the nitrogen substituent. Indeed, the best *ee* values were obtained with *t*Bu ≈ *i*Bu > *i*Pr > Me > Bn ≫ Ph. As expected, the two ImH$^+$ compounds **3e** and **3f**, which contain an aromatic group, did not bring a strong chiral induction on the reacting center. In fact, as there is no π interaction between the aliphatic Grignard reagent and the phenyl moiety, only the steric hindrance influenced the reaction. By increasing the steric bulk around the reacting center, modifying the chiral or achiral substituent, the regioselectivity of the reaction decreased. Indeed, with exotic ligands **3g**, **3k**, and **3j**, the regioselectivity of the reaction decreased dramatically to almost 50:50 1,2/1,4 (Table 9, entries 7, 10, and 11). The active species seemed to become too hindered to favor the 1,4-addition. Compound **3d** gave the best enantioselectivity and led to almost total conversion (entry 4).

Table 9. Alkoxyde ImH$^+$ screening.



S1 2

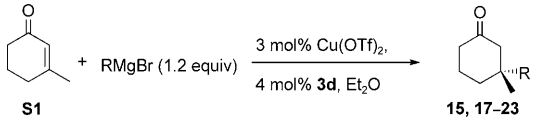
Entry	ImH$^+$	Ratio 1,2/1,4	Conv. [%][a]	*ee* [%][b]
1	**3a**	0:100	87	68, (+) *R*
2	**3b**	0:100	91	73, (+) *R*
3	**3c**	0:100	85	74, (+) *R*
4	**3d**	0:100	98	80, (+) *R*
5	**3e**	0:100	42	37, (+) *R*
6	**3f**	0:100	78	62, (+) *R*
7	**3g**	10:90	99	0
8	**3h**	0:100	99	13, (+) *R*
9	**3i**	0:100	99	0
10	**3j**	45:55	99	25, (+) *R*
11	**3k**	43:57	99	6, (−) *S*

[a] Conversion determined by GCMS analysis after 30 min. [b] Determined by chiral GC analysis (Lipodex E).

With our optimized conditions in hand, we extended the scope of the reaction with other Grignard reagents on 3-methylcyclohex-2-enone.

The bidentate ligand **3d** proved to efficiently catalyze the regio- and enantioselective A.C.A reactions of linear and branched Grignard reagents. Indeed, the addition of linear alkyl chains (ethyl, butyl, and butenyl) led to *ee* values of around 80 to 90% (Table 9, entry 4 and Table 10, entries 1 and 2). For α-branched nucleophiles (isopropyl, *c*-pentyl, and *c*-hexyl), the enantioselectivities stayed close to the range obtained for linear ones with 78 to 86% *ee* (Table 10, entries 5, 8, and 9). The β-branched nucleophiles gave contrasting results. Isobutyl gave the best result, with 96% *ee* (entry 3), but the trimethylsilyl-substituted nucleophile gave a poor 6% *ee* (entry 11). Knowing that this Grignard reagent was biphasic in Et_2O and the reaction gave almost only racemates in THF, we tried to make the same reaction with the Grignard reagent prepared in 2-methyltetrathydrofuran (Me-THF). Schmalz[47] and co-workers have reported that this solvent gave impressively high *ee* values in the 1,4-addition of Grignard reagents to cyclohexenone, whereas the THF gave racemates. Unfortunately, in our case, the obtained *ee* was smaller than 5% by using a Grignard reagent prepared in Me-THF and Et_2O as the reaction solvent and 0% when using only Me-THF.

Table 10. Variation of the Grignard reagent.



S1 15, 17–23

Entry	R	T [°C]	Substrate add. t [min]	Prod.	Conv. [%][a]	Yield [%][b]	*ee*, config.[c]
1	*n*Bu	0	60	**12**	100	–	78, *R*
2	Butenyl	−30	15	**13**	91	80	90, *S*
3	*i*Bu	−30	60	**14**	100	–	96, *S*
4	*i*Pr	0	10	**15**	70[d]	–	n.d.[e]
5	*i*Pr	−18	50	**15**	100	77	78, *R*
6	*c*-Pent	−15	10	**16**	86	–	84, *R*
7	*c*-Pent	−30	15	**16**	100	–	85, *R*
8	*c*-Pent	−30	60	**16**	100	80	86, *R*
9	*c*-Hex	−30	10	**17**	100	77	79, *R*
10	*t*Bu	−30	10	**10**	40	0	–
11	Me-TMS[f]	−30	5	**18**	99	–	0

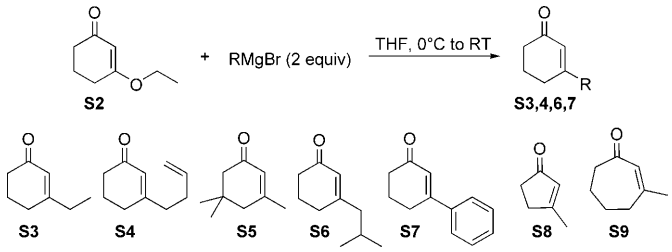
[a] Conversion determined by GCMS analysis after 15–30 min. [d] Isolated yield. [c] Determined by chiral GC analysis (Lipodex E). [d] Formation of many byproducts, observed per GCMS. [e] n.d. = not determined. [e] TMS = trimethylsilyl

Finally, in contrast to the C_2-symmetric NHC **2e**, for which a *tert*-butyl group could be added in a racemic way (Table 5, entry 8), the ImH$^+$ **3d** gave 40% conversion to only the 1,2-addition product and degradation products

after 2 h (Table 10, entry 10). The lack of reactivity of the *tert*-butyl organomagnesium nucleophile was certainly due to the tiny reactive pocket, which prevented the approach of such a bulky group. Indeed, in the racemic way, without NHC, the 1,4-addition product was obtained with more than 99% conversion, but with the NHC, many degradation products and 30% of the 1,2-addition product were obtained.

The reaction temperature was an important factor. In all cases, the chiral R_2Cu species seemed to be active between a range of temperatures. Above or below that temperature, we observed competition in regioselectivity and byproduct formation (Table 10, entries 4–5). Surprisingly, we could expect that when slowing down the reaction rate by decreasing the temperature (−15 to −30 °C), the *ee* should increase but no variation was observed (entries 6–7). As the 1,4- and 1,2-additions were competitive, it seemed that when the temperature was below −40 °C, the 1,4-addition rate decreased faster than the 1,2-addition, and the direct addition was consequently promoted.

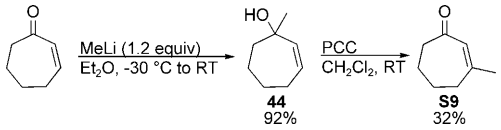
Now that the methodology was well established for the A.C.A. reaction with 3-methylcyclohex-2-enone, we wanted to extend the scope of our research to different aliphatic substrates. We started therefore by synthesizing different linear and branched trisubstituted cyclic enones (Scheme 4).



Scheme 4. Substrates synthesis.

The six-membered rings were synthesized by treating cyclohexanedione with iodine, to form the cyclic ketoenol ether **S2** in good yield on a 60 g scale.[48] This intermediate was then treated with the corresponding Grignard reagent to give the desired substrate in good yield.[11] In this way, we obtained the two substrates **S3**–**S4**, one β-branched **S6** and one aromatic substituted substrate **S7**. To test the activity of our complex on a desactivated cyclic enone, we used the commercially available isophorone **S5**.

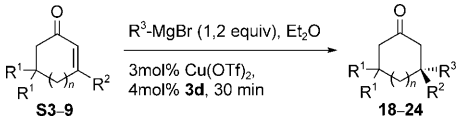
The seven-membered ring was synthesized by applying a procedure published by Dauben (Scheme 5).[49] Cycloheptenone was treated with methyl lithium, to give the corresponding tertiary allylic alcohol **44** in good yield. This last product was mixed with PCC to form the desired methyl cycloheptenone in poor yield.



Scheme 5. Seven-membered ring synthesis. PCC = pyridinium chlorochromate.

The substrates containing a linear substituent (**S3**–**S4**) gave good *ee* values of around 70% (Table 11, entries 1–2). This result was not surprising for the addition of MeMgBr. It is well known that methyl nucleophiles are poorly reactive and difficult to add with good stereocontrol. A motivating point was the good *ee* obtained with the less reactive isophorone **S5** (entry 3). By going to a bulkier isobutyl substituent, the enantio-discrimination worked better and the *ee* values rose up to 81% (entry 4). Another promising result was obtained with the addition of EtMgBr on the phenyl substituted substrate **S7** (72% *ee*; entry 5). A general trend, as for C_2-symmetric NHCs, is the observation of the same facial selectivity as obtained with the NHC **3d**. Indeed, we always obtained the opposite major enantiomer by inverting the nucleophile and the substituent on the substrate. In contrast to the C_2-symmetric **2a** ImH^+, the stereoselectivity for the ligand **3d** is on the *Si* face.

Table 11. Substrate variation.



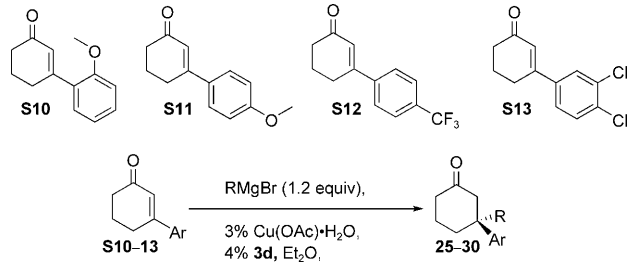
Entry	Substrate	R^3	T [°C]	Prod.	Conv. [%][a]	Yield [%][b]	*ee* [%], config.[c]
1	**S3**	Me	0	**3**	98	67	68, (−) *S*
2	**S4**	Et	0	**19**	99	84	69, (+) *R*
3	**S5**	Et	0	**20**	100	85	82, (+) *R*
4	**S6**	Et	0	**21**	98	69	81, (+) *R*
5	**S7**	Et	0	**22**	98	87	72, (+) *S*
6	**S8**	Et	0	**23**	98	90	38, (+) *R*
7	**S8**	Et	−10	**23**	98	90	46, (+) *R*
8	**S9**	Et	0	**24**	99	76	82, (+) *R*

[a] Conversion determined by GCMS analysis after 30 min. [b] Isolated yield. [c] Determined by chiral GC analysis (Lipodex E).

The experiments realized upon varying the ring size gave interesting results. In the case of **S8**, contrary to the six-membered ring, the temperature played an important role. Indeed, the *ee* rose up from 38% at 0 °C to 46% at −10 °C (Table 11, entries 6 and 7). On the other hand, the seven-membered substrate **S9** gave *ee* values comparable to those obtained with the six-membered rings (entry 8). It seems, therefore, that the five-membered ring is too flat to allow a good approach of the catalyst, which led to low enantiocontrol.

As the addition of EtMgBr on the phenylcyclohexenone **S7** gave a promising 72% *ee* (Table 11, entry 5), new aromatic substrates containing electro-attracting and withdrawing aryl groups were synthesized. We used the same methodology as described previously to observe the electronic effects on the conjugate addition reactions in the copper-cata-

Table 12. Aromatic substituted cyclohexenones.



Entry	R-	Ar-	Cu [mol%]	NHC [mol%]	Prod.	Conv. [%][a]	Yield [%]	Ratio 1,2/1,4	*ee* [%][b]
1	Et	**S10**	3	0	**25**	97	–	23:77	0
2[c]	Et	**S10**	5	7.5	**25**	99	–	98:2	n.d.[d]
3	Et	**S10**	10	13	**25**	40	–	99:1	n.d.[d]
4	Et	**S11**	3	4	**26**	84	72	52:48	78
5	Me	**S11**	5	7	**27**	90	–	55:45	15
6	Et	**S12**	3	4	**28**	99	72	33:67	80
7	Et	**S13**	3	4	**29**	99	86	20:80	80
8	Me	**S13**	5	7	**30**	99	51	51:49	23

[a] Conversion determined by GCMS analysis after 60 min. [b] Determined by chiral GC analysis (Hydrodex-B-3P). [c] Reaction carried out at −30 °C. [d] n.d. = not determined.

lyzed 1,4-addition with different alkyl magnesium nucleophiles (Table 12).

The obtained results were very interesting in terms of regioselectivity. Indeed, the racemic addition of EtMgBr on the *ortho*-substituted aromatic substrate **S10** gave a racemate with a 1,2/1,4 ratio of 23:77. However, by adding the chiral complex, the regioselectivity was inversed and the 1,2-addition product became favored (Table 12, entries 1–3). As the addition of more catalyst did not change the outcome of the reaction, we concluded that the *o*-OMe-substituted substrate **S10** is too stericaly hindered to allow the approach of the larger NHC–Cu complex, in contrast to the free copper complex.

The *p*-OMe electron-donating substrate **S11** gave 78% *ee* for the addition of EtMgBr, but MeMgBr gave a poor 15% *ee* (Table 12, entries 4 and 5). The regioselectivity around 50:50 in the two cases was mediocre. When going to electron-withdrawing substrates, the outcomes of the reaction change drastically. Indeed, the *p*-CF_3 substrate **S12** gave a very good 80% *ee* with a regioselectivity of 33:67 in favor of the 1,4-addition product (entry 6). The regioselectivity was even better when starting from the chloro-substituted adduct **S13** (20:80) while keeping a high enantiocontrol (entry 7).

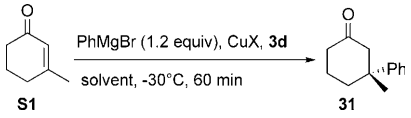
For these reactions, the regioselectivity depends on the electronic effects of the aromatic substituents. Indeed, by comparing **S11**, **S12**, and **S13**, one may observe that the electrodonating −OMe group (Table 12, entry 5), by decreasing the reactivity of the β-position, gave worse regioselectivity than the electron-withdrawing $-CF_3$ (entry 6) and −Cl substituents (entry 7). These groups activate the β-position of the cyclic substrate by decreasing its electronic density, and in doing so, increased the electrophilicity of that position. Therefore, the 1,4-addition was favored.

As described previously, the conjugate addition on trisubstitued enones is a tricky reaction. But with the promising results obtained with aliphatic Grignard reagents, we increased the challenge and tried to insert aromatic Grignard reagents. These reactions were not only difficult in term of enantioselectivity, but also in term of regioselectivity. There were only few papers concerning A.C.A. reactions describing the formation of quaternary carbon centers containing an aromatic substituent. Most of the time, the aromatic group was already on the substrate[13,50] or only phenyl and *p*-anisyl[35,36,40] were inserted. It was only recently, that our group proposed a viable method to insert a large panel of aromatic aluminum species.[51] Therefore, we tried to apply our methodology to the addition of aromatic organomagnesium reagents on aliphatic cyclohexenones.

To begin the study, we first made a screening of solvents and copper salts to find out the best conditions for the addition of the simplest aromatic, PhMgBr, on the 3-methylcyclohex-2-enone.

Relative to the methodology with alkyl Grignard reagents, Et_2O remained the best solvent for the reaction but Cu(acetate)$_2$·H_2O gave the best results in terms of regio- and enantioselectivity (Table 13, entry 2). Interestingly, as for

Table 13. Solvent and copper salt screening for aromatic addition.



Entry	Solv.	CuX	Add. *t* [min]	Conv. [%][a]	Ratio 1,2/1,4	*ee* [%][b]
1	Et_2O	Cu(acac)$_2$[c]	20	>99	5:95	65
2		Cu(acetate)·H_2O		99	12:88	70
3[d]		Cu(acetate)·H_2O		99	18:82	70
4	MtBE	Cu(OTf)$_2$		72	30:70	66
5		Cu(acac)$_2$[c]		98	22:78	50
6		Cu(acetate)·H_2O		98	99:1	n.d[e]
7	CH_2Cl_2	Cu(acac)$_2$[c]	20	98	16:84	58
8		Cu(acetate)·H_2O		88	30:70	44

[a] Conversion determined by GCMS analysis after 30 min. [b] Determined by chiral GC (Hydrodex-B-3P). [c] acac = acetylacetonate. [d] Carried out with Cl^- instead of PF_6^- as the counter-ion. [e] n.d. = not determined.

the C_2-symmetric NHC **2e**, the variation of the counter-ion had no effect on the enantioselectivity of the reaction (entries 2 and 3). In this case, contrary to the work of Loh,[46] M*t*BE gave worse results than Et_2O in both regio- and enantioselectivities (entries 1 vs. 5 and 2 vs. 6). CH_2Cl_2 gave a lower regioselectivity, and the *ee* values were about 20% lower than with their Et_2O counterparts (entries 7 and 8). In THF and tetrahydropyran (THP), which coordinates strongly to the magnesium, we tested seven copper salts, but we obtained almost no enantioselectivity for the reaction. Finally, with toluene as the solvent, which was expected to bring some π–π interactions with the Grignard reagent, the enantioselectivity was poor and moderate regioselectivity was observed at around 50:50 for the seven tested copper salts.

As for the alkyl Grignard reagents, the *ee* was not influenced by the addition time, but the regioselectivity was largely better when the addition was done slowly. By increasing the addition time of the substrate, the regioselectivity improved, going from 22:78 to 12:88. This would imply that the catalytic cycle of the aryl Cu–NHC complexes was slower than for the alkyl counterpart. Indeed, by using alkyl Cu–NHC complexes in the same range of addition time, only the 1,4-addition product was observed. For aryl Cu–NHC complexes, if the substrate was added too quickly, the catalytic cycle was too slow to absorb it completely, and a part of the substrate was, therefore, consumed by the free Grignard reagent in excess in the reaction, giving the 1,2-addition product. This hypothesis was supported by the addition of an increased amount of copper to 10 mol%. Indeed, the reaction with three times more catalyst gave an improvement in the regioselectivity going from around 37:63 to 22:78. In contrast, the *ee* decreased dramatically from 70 to 53% with formation of a brown aggregate. In fact, as the Cu–NHC complex was poorly soluble in Et_2O, the presence of a too high concentration of complex favors the aggregation of an insoluble NHC/Cu heap of unknown ratio. This could leave some free copper in solution, which by giving only a racemic product, lowers the total enantioselectivity of the reaction, but increases the regioselectivity.

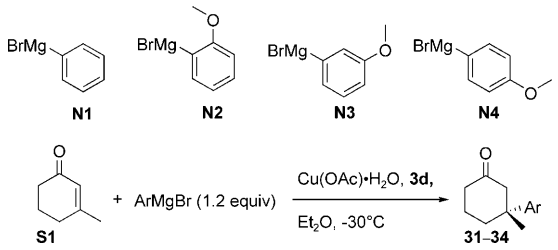
The Cu/NHC ratio was also important. There was a maxima at around 1:1.5. Below and above this ratio, the *ee* diminished. Surprisingly, the regioselectivity in favor of the conjugate addition was better when the formed complex contains more than one NHC. Indeed, with a 1:1 ratio, the regioselectivity was worse than for a 1:1.5 or 1:2 ratio. This effect could be explained by the electron-donating effect of the NHC. Although the steric hindrance increases in the presence of more NHC, which should disadvantage the conjugate addition, the electron density brought by the extra NHC on the reacting center, may accelerate the catalytic cycle, and by the way, favor the 1,4-addition.

These attempts have not brought the expected improvements, because the 1,2/1,4 ratio could not be enhanced. We could lower the Cu/NHC ratio to 1:1,3 by keeping a high *ee* and good regioselectivity, which means that the best ratio for alkyl additions was also the best for aryl ones.

New aromatic Grignard reagents **N1–N4** were freshly synthesized by adding dropwise an ethereal solution of aryl bromide onto magnesium turnings. We then used these aromatic Grignard regents on the two alkylcyclohexenones **S1** and **S3**.

The *o*-anisol derivative **N2** was the worst one. The reaction worked almost in a complete 1,2-addition way. No *ee* was obtained, even if the amount of copper was increased to 5 mol% (Table 14, entry 2). The steric bulk issued from the *ortho*-methoxy group certainly prevented the approach on the stericaly hindered β-position. The *m*-anisole **N3** gave an excellent 90% *ee*, but the regioselectivity was strongly in favor of the 1,2-addition product, even if 5 mol% of catalyst was added (entry 5). Surprisingly, under the same conditions, although the *p*-anisole **N4** should be less bulky than its *meta*- counterpart **N3**, it gave even worse enantio- and regioselectivity (entry 4). Perhaps, the electron-donating methoxy group in the *para*-position brings more electron density to the nucleophile, thus making it harder and more reactive. This means that the catalytic cycle becomes even less competitive against the free nucleophile, entering in a 1,2-addition way. The same electron-donating group in the *meta*-position brings no extra electronic density onto the carbon nucleophile and the steric bulk is barely bigger than its *para*-counterpart. Therefore, as the steric hindrance is almost the same for **N3** and **N4**, but **N4** is more nucleophilic, this could explain why there was more 1,2 product when using *para*-methoxy-substituted phenyl Grignard reagents then *meta*- ones.

Table 14. Aromatic Grignard reagent variation.

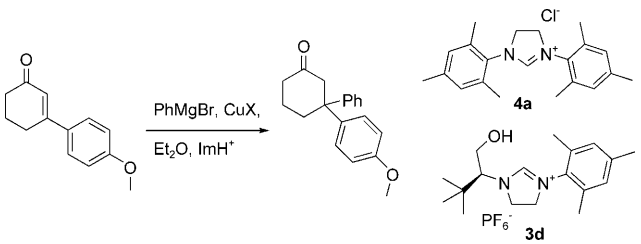


Entry	R-	Ar-	Cu [mol%]	NHC [mol%]	Prod.	Conv. [%][a]	Ratio 1,2/1,4	*ee* [%], config.[b]
1	Me	**N1**	3	4	**31**	99	12:88	70, (−)
2	Me	**N2**	3	4	**32**	>99	100:0	n.d.
3	Me	**N3**	5	7.5	**33**	67	70:30	90
4	Me	**N4**	5	6.5	**34**	>99	77:23	70

[a] Conversion determined by GCMS analysis after 60 min. [b] Determined by SFC.

To see the limitations of our methodology, we go one step further and try the formation of all-carbon quaternary centers containing two aromatic rings. Different copper sources, NHCs, and temperatures were applied. Also activations with TMSCl was attempted, but for now, only the 1,2-addition product was obtained (Scheme 6).

To conclude this chapter, the alkoxy-ImH$^+$ **3d** gave the best results in terms of conversions and enantiomeric excesses. This bidentate NHC family shows good to excellent aptitude in the enantioselective catalysis of the addition of alkyl (up to 96%) and aryl nucleophiles (up to 90%). The regioselectivity for the aryl addition is the drawback of our methodology, but it will certainly be improved in following research.



Scheme 6. Quaternary centers containing two aromatic rings.

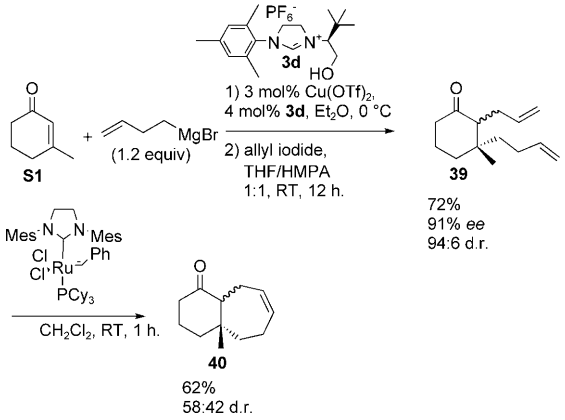
Applications in synthesis: With these different ImH^+ compounds in hand, we now possess the tools needed to catalyze the A.C.A. reactions of Grignard reagents to different aliphatic and aromatic trisubstituted cyclic enones. This process allows the isolation of valuable synthons with high yields and *ee* values. This is why we focused on developing synthetic applications to demonstrate the value of our methodology.

As the 1,4-addition reaction goes through a magnesium enolate step, it should be possible to trap it with an electrophile in a one-pot procedure, to open the door to easy α-functionalization. The problem lies in the fact that magnesium enolates, relative to lithium enolates,[52] are much less nucleophilic. They have generally to be trapped by an oxophilic electrophile, such as Ac_2O[53] or TMSOTf,[50] in a first step, and then be treated by MeLi·LiBr to form the lithium enolate, which becomes then highly reactive.[54]

We first tried to make the allylic trapping reaction in one pot, by adding allyl iodide after the conjugate addition. Unfortunately, the magnesium enolate was not reactive enough to attack it directly. Also by activating it with a Pd source and warming the reaction to 45 °C for 5 h, no conversion was obtained and only the protonated product was obtained. After some optimization, we observed that adding a combination of HMPA/THF 1:1, as the cosolvent, permits the α-allylation of the substrate with total retention of configuration and good diastereoselectivity (Table 15, entry 3). The same methodology was then used to α-alkylate the substrate, by using methyl iodide (entry 4). In this case, the diastereoselectivity of the reaction was not good, because of the too small steric inducting difference between the methyl and ethyl at the β-position for the small methyl iodide.

For the trapping of benzaldehyde (Table 15, entry 1) and bromine (entry 2), it was not necessary to add HMPA because of the high electrophilicity of the reactant. The reactions work well by keeping the high *ee* of the ethyl addition. For benzaldehyde, the alcohol obtained was oxidized to eliminate one asymmetric center, and by the way, make the analysis easier.

The opportunity to insert different functionalities as halide, alkyl, allyl, or benzylic alcohol allowed the enhancement of the synthetic possibilities of our methodology. To improve the value of the addition/allylic trapping sequence, we thought to go one step further and try to synthesize a bicyclic compound by using our methodology (Scheme 7). We



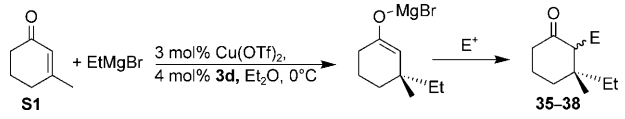
Scheme 7. Addition/trapping/ring-closing metathesis sequence. HMPA = hexamethylphosphoramide.

started, therefore, by adding a butenyl Grignard reagent onto the 3-methylcyclohex-2-enone and trapping the formed magnesium enolate with allyl iodide. The obtained dialkene substrate was then cyclized by metathesis with Grubbs II catalyst to form bicyclic six–seven membered rings with high *ee* values and moderate *cis*/*trans* diastereoselectivity.

Recently, a report by Williams described the synthesis of the 5,14-bis-*epi*-spirovibsanin A and other natural products of the vibsanin family.[55] The first step was the racemic conjugate addition of 2-methylpent-2-enyl Grignard reagent to 3-methylcyclohex-2-enone. As it was exactly the field we had investigated, we tried to reproduce the first step of this synthesis but with asymmetric induction.

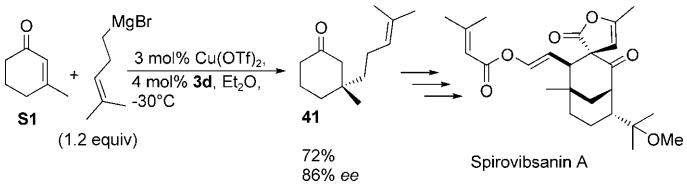
We applied our best conditions to complete the first step enantioselectively and were pleased to see that our methodology allowed to us reach 86 % *ee* for the first step of the vibsane synthesis (Scheme 8).

Table 15. Enolate trapping.



Entry	E^+	Reaction time	Prod.	Conv. [%][a]	Yield [%][b]	*ee* [%][c] 1st/ 2nd diastereomer	d.r.[d]
1	benzaldehyde[e]	30 min	**37**	100	75	77/68	41:59
2	Br_2	30 min	**38**	100	78	76/78	32:67
3[f]	allyl iodide	25 h	**35**	>99	81	76[g]	70:30
4[f]	MeI	12 h	**36**	99	79	76[g]	59:41

[a] Conversion determined by GCMS analysis after 30 min. [b] Isolated yield. [c] Determined by chiral GC analysis. [d] d.r. = diastereomeric ratio. [e] The obtained alcohol is oxidized to eliminate diastereoisomers. [f] HMPA/THF 1:1, 40 °C. [g] *ee* of the first step.



Scheme 8. Total synthesis of bis-*epi*-spirovibsanin A.

Conclusion

We have showed that the two different families of NHC ligands we tested are viable ligands for the A.C.A. reactions of Grignard reagents on cyclic trisubstituted enones.

The C_2-symmetric DPEDA-based family of NHC ligands allowed to good results to be obtained in terms of conversion and enantioselectivity. As these ligands had the possibility to adapt somewhat the size of the reactive pocket to the size of the nucleophile, they could catalyze the 1,4-addition of a bulky *tert*-butyl group on 3-methylcyclohex-2-enone with total 1,4 regioselectivity but with no enantioselectivity. Despite the fact that these kind of ligands were difficult to synthesize with good yield, they allowed the 1,4-addition of linear Grignard reagents to the 3-methylcyclohex-2-enone with high yields and good *ee* values lying between 70–80% with perfect regioselectivity. By switching to branched nucleophiles (*c*-pentyl and isopropyl), the *ee* values dropped to between 40 to 60%, but with perfect regioselectivity.

The alkoxy-substituted ligand family gave better results for the 1,4-addition of linear Grignard reagents (ethyl, butyl, and butenyl) to 3-methylcyclohex-2-enone with *ee* values between 80 and 90%. The use of branched nucleophiles (isobutyl, isopropyl, *c*-hexyl, and *c*-pentyl) also gave excellent results in term of enantioselectivities lying between 78 and 96% with perfect regioselectivities. We were pleased to see that our methodology was not substrate dependant. Indeed, the variation of the alkyl group on the cyclic substrate (ethyl, butenyl, isophorone, isobutyl, and phenyl) gave very good results keeping the *ee* values between 68 and 90%. By changing the ring size to a seven-membered ring, the *ee* values were comparable to the six-membered ring ones, but by decreasing the ring size to five carbon atoms, the *ee* values dropped to 40%. We also used aromatic substituted six-membered enones, which produced very good *ee* values of around 80%. Unfortunately in these cases, the regioselectivity of the reaction decreased dramatically. The presence of an electron-withdrawing aromatic group gave better regiocontrol than an electron-donating substituent, but the results were between 50:50 and 20:80 for the 1,2/1,4-addition. Finally, the addition of aromatic Grignard reagents on alkyl-substituted cyclic enones gave very good *ee* values of up to 90% for the addition of *m*-OMe phenyl Grignard with often poor 1,4 regioselectivity.

We finally developed synthetic applications, which involved trapping the formed magnesium enolates with MeI, benzaldehyde, bromine, and allyl iodide. These enolate trappings allowed the functionalization of the cyclic substrates at the α-position with many different functionalities. Our methodology was also successfully applied to the first step of the total synthesis of bis-*epi*-spirovibsanin A with 86% *ee* for the addition of 2-methylpent-2-enyl Grignard reagent to the 3-methylcyclohex-2-enone.

Experimental Section

General procedures: All reactions were conducted under an inert atmosphere. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were dried on alumina columns and degassed prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to residual $CHCl_3$. Evolution of the reactions was followed by a GCMS Hewlett Packard (EI mode) HP6890–5973. An asterisk on GCMS indicates the major peak. Optical rotations were measured at 20°C in a 1 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} °cm^{2}g^{-1} (concentration *c* given as g/100 mL). 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); retention times (t_R) are given in min. All Grignard reagents except ethyl and methyl magnesium bromide (Aldrich) were synthesized in Et_2O by addition of the corresponding bromide onto magnesium. Flash chromatography was performed by using silica gel 32–63 μm, 60 Å. The syntheses of starting substrates and imidazolium catalysts are described in the Supporting Information.

Typical procedure for 1,4-addition reactions: A flame-dried Schlenk tube was charged with copper salt (3.0 mol%) and the chiral ImH^+ salt (4.0 mol%). The system was flushed under N_2 and dry Et_2O (2.5 mL) was added. The mixture was cooled down to the desired reaction temperature in an ethanol cold bath. The Grignard reagent (1.2 equiv) in Et_2O was added dropwise to the solution for 5 min. A solution of the substituted cyclohexenone in Et_2O (8 mL) was then added dropwise to the solution at the desired low reaction temperature for 15 min and the solution was stirred for another 30 min. The reaction was hydrolyzed at the reaction temperature by addition of HCl 1 M (30 mL) (or MeOH if the reaction temperature lies under −20°C) and the aqueous layer was separated and extracted further with diethyl ether (3×10 mL). The combined organic layers were dried on $MgSO_4$, filtrated, and concentrated in vacuo to give an oily residue. This crude product was purified by flash chromatography on a silica column with pentane/Et_2O 10:1 to give the pure product.

(*R*)-3,3-Ethylmethylcyclohexanone (2):[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.26 (t, 2H, J=6.6 Hz), 2.16 (d, 1H, J=13.6 Hz), 2.08 (d, 1H, J=13.6 Hz), 1.88–1.81 (m, 2H), 1.64–1.48 (2m, 2H), 1.33 (q, 2H, J=7.3 Hz), 0.88 (s, 3H), 0.83 ppm (t, 3H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.8, 53.7, 41.4, 39.0, 35.7, 34.3, 24.7, 22.5, 8.1 ppm; $[\alpha]_D^{20}$=+4.74 (c=1.64 in $CHCl_3$); *ee*=80% *R* (the absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, 75–23–20–170—5, v=40 cm s^{-1}): t_{R1}=15.5 (*R*), t_{R2}=19.9 min (*S*)).

(*S*)-3,3-Ethylmethylcyclohexanone (3):[11] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound **2**; $[\alpha]_D^{20}$=−4.50 (c=1.70 in $CHCl_3$); *ee*=68% *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, isotherm 75°C, v=40 cm s^{-1}): t_{R1}=16.3 (*R*), t_{R2}=19.5 min (*S*)).

(*S*)-3,3-Butylmethylcyclohexanone (4):[56] ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.19 (t, 2H), 2.11 (q, 2H), 1.78 (quint., 2H), 1.55–1.41 (m, 2H), 1.18 (m, 6H), 0.83 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.2, 53.8, 41.3, 41.0, 38.5, 35.8, 25.5, 25.1, 23.4, 22.1, 14.0 ppm; $[\alpha]_D^{20}$=−12.3 (c=15.4 in $CHCl_3$); *ee*=72% *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, 80–0–1–170–5; v=30 cm s^{-1}): t_{R1}=25.7 (*R*), t_{R2}=27.4 min (*S*)).

(*R*)-3-(3-Butenyl)-3-methylcyclohexanone (5):[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.82–5.72 (m, 1H), 5.01 (d, 1H, J=16.9 Hz), 4.92 (d, 1H, J=10.1 Hz), 2.28–2.24 (t, 2H, J=6.8 Hz), 2.20–2.08 (q, 2H, J=13.6 Hz), 2.03–1.97 (m, 2H), 1.88–1.82 (m, 2H), 1.66–1.51 (m, 2H), 1.36–1.32 (t, 2H, J=8.6 Hz), 0.92 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 212.2, 138.9, 114.5, 53.8, 41.1, 41.0, 38.6, 35.9, 27.9, 25.0, 22.2 ppm; $[\alpha]_D^{20}=\delta$=+1.9 (c=1.9 in $CHCl_3$); *ee*=73% *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Hydrodex B-3P, isotherm 140°C): t_{R1}=10.6 (*S*), t_{R2}=10.9 min (*R*)).

(*S*)-3,3-*c*-Pentylmethylcyclohexanone (6): ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.23–2.17 (m, 3H), 2.06–2.02 (m, 1H), 1.85–1.69 (m, 3H), 1.61–1.50 (m, 8H), 1.17–1.13 (m, 2H), 0.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.7, 52.4, 49.6, 41.2, 40.6, 35.1, 26.4, 25.6, 22.1, 20.9 ppm;

ee = 56 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E, 120–1–20–170–5, $v = 40$ cm s^{-1}): $t_{R1} = 13.1$ (*R*), $t_{R2} = 14.3$ min (*S*)).

(*S*)-3,3-Isopropylmethylcyclohexanone (7):[10] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$–2.22 (m, 3H), 2.11 (m 1H), 1.98–1.77 (m, 2H), 1.64 (m, 2H), 1.51 (sept., 1H), 0.85–0.86 (d, 6H, $J = 1.7$ Hz), 0.80 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.9$, 52.0, 41.2, 36.4, 34.2, 22.1, 19.9, 17.1, 16.9 ppm; *ee* = 70 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E, 60–0–1–110–20–170–5, $v = 45$ cm s^{-1}): $t_{R1} = 21.4$ (*R*), $t_{R2} = 24.6$ min (*S*)).

(*S*)-3-Ethyl-3,5,5-trimethylcyclohexan-1-one (9):[57] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.19$–2.06 (m, 4H), 1.60 (d, 1H, $J = 14.2$ Hz), 1.49 (d, 1H, $J = 14.2$ Hz), 1.43–1.24 (m, 2H), 1.02 (m, 6H), 0.96 (s, 3H), 0.85–0.82 ppm (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 212.9, 54.5, 53.0, 48.8, 39.0, 37.3, 36.3, 32.5, 30.9, 27.0, 8.4 ppm; $[\alpha]_D^{20} = -1.89$ ($c = 1.70$ in $CHCl_3$); *ee* = 71 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Chirasil DEX-CB, 60–110–2–170–5, $v = 40$ cm s^{-1}): $t_{R1} = 133.7$ (*R*), $t_{R2} = 134.0$ min (*S*)).

3,3-*tert*-Butylmethylcyclohexenone (10):[58] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$–2.31 (m, 2H), 2.15–2.11 (m, 2H), 2.0–1.74 (m, 4H), 0.92 (s, 9H), 0.86 ppm (s, 3H); MS (EI): *m*/*z*: 168, 112, 97*, 83, 69, 55; *ee* = 0 % (enantiomeric excess was measured by chiral GC analysis (Hydrodex B6 *tert*-butyldimethylsilyl (TBDMS), 80–0–1–95–0–170–5, $v = 45$ cm s^{-1}): $t_{R1} = 10.3$, $t_{R2} = 10.7$ min).

(*S*)-3,3-Phenylmethylcyclohexanone (11):[59] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$–7.32 (m, 4H), 7.22–7.19 (m, 1H), 2.89 (d, 1H, $J = 14.2$), 2.45 (d, 1H, $J = 14.2$), 2.33–2.30 (t, 2H), 2.22–2.16 (m, 1H), 1.96–1.84 (m, 2H), 1.71–1.63 (m, 1H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.5$, 147.5, 128.6, 126.3, 125.6, 53.2, 42.9, 40.9, 38.0, 29.9, 22.1 ppm; *ee* = 70 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Hydrodex-B-3P, isotherm 140 °C, $v = 48$ cm s^{-1}): $t_{R1} = 23.1$ (*R*), $t_{R2} = 23.8$ min (*S*)).

(*R*)-3,3-Butylmethylcyclohexanone (12):[56] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound **4**; $[\alpha]_D^{20} = +4.74$ ($c = 1.64$ in $CHCl_3$); *ee* = 78 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, 80–0–1–170–5, $v = 40$ cm s^{-1}): $t_{R1} = 26.5$ (*R*), $t_{R2} = 27.2$ min (*S*)).

(*S*)-3-(3-Butenyl)-3-methylcyclohexanone (13):[11] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound (**5**); $[\alpha]_D^{20} = -2.45$ ($c = 1.71$ in $CHCl_3$), *ee* = 90 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Hydrodex B-3P, isotherm 135 °C): $t_{R1} = 6.5$ (*S*), $t_{R2} = 6.7$ min (*R*)).

(*S*)-3,3-Isobutylmethylcyclohexanone (14):[11] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.29$–2.26 (m, 2H), 2.20 (d, 1H, $J = 13.4$ Hz), 2.10 (d, 1H, $J = 13.4$ Hz), 1.92–1.83 (m, 2H), 1.74–1.64 (m, 2H), 1.60–1.56 (m, 1H), 1.26–1.17 (m, 2H), 0.95 (s, 3H), 0.93 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.7$, 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}; MS (EI): *m*/*z*: 153 (2), 125 (9), 112 (9), 111 (100), 110 (3), 107 (2), 98 (2), 97 (9), 95 (7), 93 (2), 85 (1), 84 (2), 83 (22), 82 (4), 81 (2), 79 (2), 77 (1), 71 (2), 70 (6), 69 (25), 68 (3), 67 (6), 65 (1), 58 (1), 57 (5), 56 (15), 55 (98), 54 (2), 53 (5); HRMS (ESI-MS): *m*/*z*: calcd for $C_{11}H_{20}ONa$: 191.1406364 $[M+Na]^+$; found: 191.1408390; $[\alpha]_D^{20} = +2.19$ ($c = 1.73$ in $CHCl_3$); *ee* = 96 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, isotherm 80 °C, $v = 60$ cm s^{-1}): $t_{R1} = 12.9$ (*S*), $t_{R2} = 15.8$ min (*R*)).

(*R*)-3,3-Isopropylmethylcyclohexanone (15):[10] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound **7**; $[\alpha]_D^{20} = +12.2$ ($c = 1.70$ in $CHCl_3$); *ee* = 77 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E 60–1–130, $v = 49$ cm s^{-1}): $t_{R1} = 24.3$ (*R*), $t_{R2} = 26.3$ min (*S*)).

(*R*)-3,3-*c*-Pentylmethylcyclohexanone (16): ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound (**6**); MS (EI): *m*/*z*: 180 (2), 122 (14), 112 (10), 111 (77), 110 (18), 97 (18), 83 (14), 82 (13), 69 (25), 67 (17), 55 (100); HRMS (EI-MS): *m*/*z*: calcd for $C_{12}H_{20}O$: 180.151415 $[M]^+$; found: 180.151440; $[\alpha]_D^{20} = +7.11$ ($c = 1.70$ in $CHCl_3$); *ee* = 86 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E, isotherm 125 °C, $v = 60$ cm s^{-1}): $t_{R1} = 6.9$ (*R*), $t_{R2} = 7.4$ min (*S*)).

(*R*)-3,3-*c*-Hexylmethylcyclohexanone (17): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$–2.12 (m, 3H), 2.02–1.99 (m, 1H), 1.85–1.78 (m, 1H), 1.77–1.62 (m, 5H), 1.60–1.56 (m, 2H), 1.52–1.46 (m, 1H), 1.17–1.00 (m, 4H), 0.93–0.83 (m, 2H), 0.75 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.8$, 51.9, 46.6, 41.1, 41.0, 34.1, 27.0, 27.0, 26.8, 26.6, 26.6, 21.9, 21.0 ppm; MS (EI): *m*/*z*: 194 (<1), 112 (12), 111 (90), 110 (17), 97 (39), 83 (20), 82 (17), 69 (17), 67 (14), 55 (100); HRMS (EI-MS): *m*/*z*: calcd for $C_{13}H_{22}O$: 194.167066 $[M]^+$; found: 194.166980; $[\alpha]_D^{20} = +4.55$ ($c = 1.70$ in $CHCl_3$); *ee* = 79 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E, isotherm 125 °C, $v = 60$ cm s^{-1}): $t_{R1} = 10.9$ (*R*), $t_{R2} = 11.2$ min (*S*)).

3,3-Methyl-[(trimethylsilyl)methyl]cyclohexanone (18): ^{1}H NMR (400 MHz, $CDCl_3$):$\delta = 2.22$–2.09 (m, 4H), 1.83–1.77 (m, 2H), 1.61–1.56 (m, 2H), 0.95 (s, 3H), 0.68 (s, 2H), 0.00 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 212.5, 57.3, 41.2, 39.6, 32.3, 29.1, 28.4, 22.8, 1.26; MS-EI: *m*/*z*: 197, 183, 170, 155, 130, 115, 75, 73*, 55; *ee* = 0 % (enantiomeric excess was measured by chiral GC analysis (Lipodex E, isotherm 100 °C, $v = 45$ cm s^{-1}): $t_{R1} = 7.0$, $t_{R2} = 7.3$ min).

(*R*)-3,3-Butenyl-ethylcyclohexanone (19): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.82$–5.72 (ddt, 1H, $J = 6.6$, 10.1, 13.1 Hz), 4.97 (m, 2H), 2.28–2.25 (m, 2H), 2.15 (s, 2H), 1.97–1.90 (m, 2H), 1.86–1.80 (m, 2H), 1.60–1.57 (m, 2H), 1.34–1.28 (m, 4H), 0.81–0.77 ppm (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.6$, 139.0, 114.6, 52.0, 41.3, 41.1, 36.1, 33.6, 29.5, 27.5, 21.8, 7.5 ppm; $[\alpha]_D^{20} = +7.6$ ($c = 1.70$ in $CHCl_3$); *ee* = 69 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC (Hydrodex-B-3P isotherm 135 °C, $v = 40$ cm s^{-1}): $t_{R1} = 13.1$ (*S*), $t_{R2} = 13.3$ min (*R*)).

(*R*)-3-Ethyl-3,5,5-trimethylcyclohexan-1-one (20):[57] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound (**9**); $[\alpha]_D^{20} = +8.52$ ($c = 1.70$ in $CHCl_3$); *ee* = 82 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Chirasil DEX-CB, 60–110–2–170–5, $v = 40$ cm s^{-1}): $t_{R1} = 133.8$ (*R*), $t_{R2} = 134.5$ min (*S*)).

(*R*)-3,3-Ethyl-isobutylcyclohexanone (21): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.26$ (t, 2H, $J = 6.8$ Hz), 2.18 (d, 1H, $J = 13.7$), 2.14 (d, 1H, $J = 13.7$), 1.91–1.75 (m, 2H), 1.70–1.63 (m, 1H), 1.60 (t, 2H, $J = 12.4$ Hz), 1.37 (d, 1H, $J = 7.6$ Hz), 1.34 (d, 1H, $J = 7.3$ Hz), 1.19–1.15 (m, 2H), 0.92–0.85 (m, 6H), 0.79 ppm (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.9$, 52.7, 46.0, 42.0, 41.3, 34.0, 29.8, 25.6, 25.6, 23.7, 21.9, 7.8 ppm; MS (EI): *m*/*z*: 182 (<1), 153 (32), 125 (66), 97 (69), 95 (11), 83 (22), 70 (10), 69 (28), 67 (11), 55 (100); HRMS (EI-MS): *m*/*z*: calcd for $C_{12}H_{22}O$: 182.167066 $[M]^+$; found: 182.167160; $[\alpha]_D^{20} = +4.43$ ($c = 1.70$ in $CHCl_3$); *ee* = 81 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, isotherm 87 °C, $v = 40$ cm s^{-1}): $t_{R1} = 25.8$ (*R*), $t_{R2} = 27.9$ min (*S*)).

(*S*)-3,3-Ethyl-phenylcyclohexanone (22): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$–7.29 (m, 2H), 7.27–7.24 (m, 2H), 7.21–7.17 (m, 1H), 2.94 (d, 1H, $J = 14.4$ Hz), 2.39 (d, 1H, $J = 14.4$ Hz), 2.31–2.27 (m, 2H), 2.20–1.95 (m, 2H), 1.87–1.53 (m, 4H), 0.62–0.58 ppm (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.8$, 146.0, 128.6, 126.7, 126.3, 50.8, 46.7, 41.3, 36.5, 35.9, 21.8, 8.2 ppm; IR (neat): $\nu\ddot{U} = > = 2993$, 2961, 2873, 1710, 1444, 1227 cm^{-1}; MS (EI): *m*/*z*: 202 (12), 174 (11), 173 (72), 145 (13), 131 (13), 117 (15), 115 (12), 103 (10), 91 (28), 69 (13), 55 (100); $[\alpha]_D^{20} = +58.3$ ($c = 1.70$ in $CHCl_3$); *ee* = 72 % *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Chirasil DEX-CB 135–0–1–160, $v = 40$ cm s^{-1}): $t_{R1} = 18.5$ (*S*), $t_{R2} = 19.0$ min (*R*)).

(*R*)-3,3-Ethylmethylcyclopentanone (23):[60] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$–2.26 (m, 2H), 2.07 (d, 1H, $J = 6.00$ Hz), 2.00 (d, 1H, $J = 6.00$ Hz), 1.83–1.70 (m, 2H), 1.43 (q, 2H, $J = 7.6$ Hz), 1.03 (s, 3H), 0.90 ppm (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 220.4$, 52.0, 39.9, 37.0, 34.9, 34.1, 24.7, 9.2 ppm; $[\alpha]_D^{20} = +22.59$ ($c = 1.70$ in $CHCl_3$); *ee* = 46 % *R* (absolute configuration was assigned in analogy with the literature;[11] enantio-

meric excess was measured by chiral GC analysis (Lipodex E isotherm 60 °C, $v = 40$ cm s^{-1}): $t_{R1} = 15.2$ (R), $t_{R2} = 18.0$ min (S)).

(R)-3,3-Ethylmethylcycloheptanone (24):[36] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.53$ (d, 1H, $J = 12.2$ Hz), 2.46–2.42 (m, 2H), 2.36 (d, 1H, $J = 12.2$ Hz), 1.83–1.51 (m, 6H), 1.41–1.23 (m, 2H), 0.91 (s, 3H), 0.87 ppm (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.4$, 54.4, 44.0, 42.1, 35.3, 34.9, 25.4, 24.7, 24.2, 8.0 ppm; IR (neat): $\tilde{\nu}$2966, 2932, 1736, 1797, 1457 cm^{-1}; MS (EI): m/z: 154 (2), 125 (23), 112 (10), 97 (40), 96 (50), 86 (47), 84 m (19), 84 (74), 83 (18), 81 (15), 70 (17), 69 (21), 56 (15), 55 (100), 49 (16), 47 (20); HRMS (ESI-MS): m/z: calcd for $C_{10}H_{19}O$: 155.1439; found: 155.1436 $[M+H]^+$; $[\alpha]_D^{20} = +10.33$ ($c = 1.41$ in $CHCl_3$); $ee = 82\%$ R (absolute configuration was assigned in analogy with the literature;[36] enantiomeric excess was measured by chiral GC (Lipodex E isotherm 60 °C, $v = 50$ cm s^{-1}): $t_{R1} = 24.3$ (R), $t_{R2} = 25.7$ min (S)).

(S)-3-Ethyl-3-(4-methoxyphenyl)cyclohexanone (26): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.17$–7.15 (m, 2H), 6.86–6.84 (2H, m), 3.79 (s, 3H), 2.88 (d, 2H, $J = 14.2$ Hz), 2.37 (d, 2H, $J = 14.3$ Hz), 2.30–2.26 (m, 2H), 2.16–1.91 (m, 2H), 1.86–1.78 (m, 2H), 1.76–1.52 (m, 2H), 0.59 ppm (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.9$, 157.8, 136.9, 127.7, 113.8, 55.3, 50.9, 46.1, 41.2, 36.5, 36.1, 21.7, 8.1 ppm; $[\alpha]_D^{20}\delta = +92.7$ ($c = 1.9$ in $CHCl_3$); $ee = 78\%$ S (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral SFC (S2-AS 5%-2–1–15%, $v = 2$ mL s^{-1}): $t_{R1} = 4.3$ (R), $t_{R2} = 4.7$ min (S)).

(S)-3-Methyl-3-(4-methoxyphenyl)cyclohexanone (27):[36] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$–7.22 (m, 2H), 6.87–84 (m, 2H), 3.79 (s, 3H), 2.85 (d, 1H, $J = 14.2$ Hz), 2.41 (d, 1H, $J = 14.2$ Hz), 2.20–2.11 (m, 2H), 1.92–1.82 (m, 2H), 1.71–1.61 (m, 2H), 1.30 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 126.8$, 116.2, 115.0, 113.9, 55.4, 53.4, 42.5, 40.9, 38.2, 30.2, 22.2 ppm; $[\alpha]_D^{20} = +63.6$ ($c = 1.3$ in $CHCl_3$); $ee = 15\%$ S (absolute configuration was assigned in analogy with the literature;[11,36] enantiomeric excess was measured by chiral SFC (S2-OD 2%-2–1–15% $v =$ 2 mL min^{-1}): $t_{R1} = 5.4$ (R), $t_{R2} = 6.0$ min (S)).

(S)-3-Ethyl-3-[4-(trifluoromethyl)phenyl]cyclohexanone (28): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$–7.56 (m, 2H), 7.39–7.36 (m, 2H), 2.91 (d, 1H, $J = 14.3$ Hz), 2.44 (d, 1H, $J = 14.4$ Hz), 2.34–2.28 (m, 2H), 2.22–2.16 (m, 1H), 2.06–1.97 (m, 1H), 1.92–1.73 (m, 1H), 1.72–1.64 (m, 2H), 1.62–1.47 (m, 1H), 0.60 ppm (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.9$, 149.3, 127.1, 125.6, 125.6, 125.5, 125.5, 50.5, 46.9, 41.1, 36.6, 35.9, 21.6, 8.0 ppm; $[\alpha]_D^{20} = +41.2$ ($c = 2.1$ in $CHCl_3$); $ee = 80\%$ S (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Chirasil-Dex-CB 100–0–1–170—10, $v = 40$ cm s^{-1}): $t_{R1} = 50.7$ (S), $t_{R2} = 53.2$ min (R)).

(S)-3-(3,4-Dichlorophenyl)-3-ethylcyclohexanone (29): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$–7.38 (m, 2H), 7.15–7.11 (m, 1H), 2.88 (d, 1H, $J = 14.2$ Hz), 2.47 (d, 1H, $J = 14.2$ Hz), 2.39–2.32 (m, 2H), 2.21–1.85 (m, 3H), 1.80–1.61 (m, 3H), 0.66 ppm (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.5$, 145.5, 132.8, 130.9, 130.5, 128.8, 126.3, 50.5, 46.6, 41.0, 36.1, 35.7, 21.6, 8.0 ppm; GCMS (80–1–20–270—6, $v =$ 45 cm s^{-1}): m/z: 11.68 (272, 270, 241, 173, 159, 149, 136, 128, 115, 89, 69, 55*); $ee = 80\%$ S (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral SFC (S2-AS, 2%-2–1–15%, $v = 2$ mL s^{-1}): $t_{R1} = 5.07$ (R), $t_{R2} = 5.46$ min (S)).

(S)-3-(3,4-Dichlorophenyl)-3-methylcyclohexanone (30): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.37 (m, 2H), 7.16–7.13 (m, 1H), 2.81 (d, 1H, $J = 14.1$ Hz), 2.45 (d, 1H, $J = 14.2$ Hz), 2.36–2.31 (m, 2H), 2.17–2.10 (m, 1H), 1.96–1.87 (m, 2H), 1.73–1.64 (m, 1H), 1.30 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.3$, 147.9, 130.6, 128.1, 125.4, 117.7, 115.4, 52.9, 42.9, 40.8, 37.8, 29.7, 22.1 ppm; $[\alpha]_D^{20} = +76.0$ ($c = 1.0$ in $CHCl_3$); $ee = 23\%$ S (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral SFC (S2-AS, 2%-2–1–15%, $v = 2$ mL s^{-1}): $t_{R1} = 7.0$ (R), $t_{R2} = 7.6$ min (S)).

(R)-3,3-Phenylmethylcyclohexanone (31):[59] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound **11**; $[\alpha]_D^{20}$: −26.3 ($c = 1.70$ in $CHCl_3$); $ee =$ 66% R (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Hydrodex-B-3P, isotherm 140 °C, $v = 38$ cm s^{-1}): $t_{R1} = 31.7$ (R), $t_{R2} = 32.7$ min (S)).

(R)-3,3-Ethyl-phenylcyclohexanone (32):[36] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound **22**; $[\alpha]_D^{20} = -22.2$ ($c = 1.69$ in $CHCl_3$); $ee = 34\%$ R (absolute configuration was assigned in analogy with the literature;[11,36] enantiomeric excess was measured by chiral GC analysis (Chirasil DEX-CB, 135–0–160–20–170–5; $v = 40$ cm s^{-1}): $t_{R1} = 18.2$ (S), $t_{R2} = 18.6$ min (R)).

(R)-3-(3-Methoxyphenyl)-3-methylcyclohexanone (33):[51] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.22 (m, 1H), 7.62–6.86 (m, 2H), 6.77–6.73 (dd, 1H, $J = 8.2$, 2.4 Hz), 3.80 (s, 3H), 2.86 (d, 1H, $J = 14.1$ Hz), 2.42 (d, 1H, $J = 14.2$ Hz), 2.31 (t, 2H, $J = 6.7$ Hz), 2.21–2.13 (m, 1H), 1.94–1.81 (m, 2H), 1.74–1.63 (m, 1H), 1.31 ppm (s, 3H); $[\alpha]_D^{20} = -55.3$ ($c = 0.8$ in $CHCl_3$); $ee = 90\%$ R (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral SFC (S5-AD, 5%-2–1–15%, $v = 2$ mL min^{-1}): $t_{R1} = 4.7$ (R), $t_{R2} = 7.1$ min (S)).

(R)-3-(4-Methoxyphenyl)-3-methylcyclohexanone (34):[36] ^{1}H NMR (400 MHz, $CDCl_3$): see data for compound (**27**); $[\alpha]_D^{20} = -42.5$ ($c = 1.5$ in $CHCl_3$): $ee = 70\%$ R (absolute configuration was assigned in analogy with the literature;[11,36] enantiomeric excess was measured by chiral SFC (S2-OD, 2%-2–1–15%, $v = 0$ 2 mL min^{-1}): $t_{R1} = 5.8$ (R), $t_{R2} = 6.3$ min (S)).

2-Allyl-3,3-ethylmethylcyclohexanone (35): Mixture of two diastereomers 70:30 (175 mg, 97%); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 213.2$, 212.9, 137.9, 137.7, 115.4, 115.3, 61.5, 58.3, 42.2, 41.7, 41.4, 40.9, 34.7, 34.4, 33.4, 28.8, 28.2, 27.0, 24.8, 22.9, 22.6, 20.9, 7.9, 7.4 ppm; $ee = 76\%$ R; (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis on the ethyl addition (Lipodex E, iso 75 °C, $v = 45$ cm s^{-1}): $t_{R1} = 11.0$ (R), $t_{R2} = 13.8$ min (S)); GCMS (80–1–20–270–6; $v = 45$ cm s^{-1}): m/z: 6.91 (major) (180, 151, 109, 96, 81, 67, 55*), 6.95 (180, 151, 109, 96, 81, 67, 55*); HRMS (EI-MS): m/z: calcd: 180.1512; found: 180.1514 (accuracy = −0.2).

3-Ethyl-2,3-dimethylcyclohexanone (36): Mixture of two diastereomers 59:41 (122 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.41$–2.32 (m, 2.8H), 2.31–2.22 (m, 2.1H), 1.97–1.69 (m, 5.5H), 1.52–1.45 (m, 1.6H), 1.43–1.35 (m, 2.1H), 1.31–1.21 (m, 1H), 1.19–1.15 (m, 1H), 0.98–0.96 (m, 4.1H), 0.93–0.92 (m, 2.9H), 0.90–0.86 (m, 3.1H), 0.79–0.75 (m, 2.2H), 0.73 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.7$, 214.4, 55.6, 52.1, 41.6, 41.1, 41.0, 40.7, 35.0, 34.4, 33.7, 25.5, 25.1, 22.5, 22.2, 20.0, 8.8, 8.3, 7.9, 7.4 ppm; $ee = 76\%$ R (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis on the ethyl addition (Lipodex E, iso 75 °C, $v =$ 45 cm s^{-1}): $t_{R1} = 11.5$ (R), $t_{R2} = 14.4$ min (S)).

2-Benzoyl-3,3-ethylmethylcyclohexanone (37): Mixture of two diastereomers 41:59 (132 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$–7.94 (m, 2H), 7.58–7.54 (m, 1H), 7.47–7.43 (m, 2H), 4.39 (m, 1H), 2.83–2.72 (m, 1H), 2.52–2.44 (m, 1H), 2.40–2.19 (m, 2H), 2.07–1.95 (m, 1H), 1.92–1.76 (m, 1H), 1.56–1.31 (m, 3H), 1.25 (s, 1H), 0.97 (s, 1H), 0.92 (s, 1H), 0.86 (t, 2H, $J = 7.3$ Hz), 0.70–0.67 ppm (t, 1H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.6$, 208.3, 197.0, 197.0, 138.7, 138.4, 133.4, 133.4, 128.8, 128.8, 128.7, 128.7, 69.1, 68.0, 43.5, 42.6, 39.3, 38.9, 32.4, 31.9, 31.9, 31.1, 23.6, 23.2, 22.3, 21.7, 7.9, 7.6 ppm; $ee = 77\%$ R (1st diastereomer), ee 68% R (2nd diastereomer) (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Chirasil Dex-CB, 110–0–1–170–5; $v = 40$ cm s^{-1}): 1st diastereomer: $t_{R1} = 50.7$ (R), $t_{R2} = 51.1$ (S); 2nd diastereomer: $t_{R1} = 53.2$, $t_{R2} = 53.6$ min).

2-Bromo-3,3-ethylmethylcyclohexanone (38): Mixture of two diastereomers 32:67 (171 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.23$ (s, 1H), 4.05 (s, 1H), 3.11–3.03 (m, 1H), 2.95–2.88 (m, 1H), 2.30–2.23 (m, 1.5H), 1.87–1.80 (m, 4H), 1.68–1.55 (m, 1.5H), 1.50–1.43 (m, 3.2H), 1.42–1.32 (m, 2.2H), 1.02 (s, 3H), 0.99 (s, 3H), 0.92–0.82 ppm (m, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.7$, 204.0, 65.5, 63.7, 42.3, 41.2, 37.1, 36.1, 31.9, 31.4, 31.2, 28.0, 22.9, 21.4, 21.3, 21.1, 8.0, 7.1 ppm; $ee = 76\%$ R (1st diastereomer), $ee = 78\%$ R (2nd diastereomer) (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (Lipodex E, 80–60–1–120–80–170–3, $v =$ 40 cm s^{-1}): 1st diastereomer: $t_{R1} = 68.8$ (R), $t_{R2} = 74.0$ (S); 2nd diastereomer: $t_{R1} = 88.0$, $t_{R2} = 88.9$ min).

2-Allyl-3-(but-3-enyl)-3-methylcyclohexanone (39): Mixture of two diastereomers 94:6 (148 mg, 72%); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.8$, 212.4, 138.8, 137.8, 137.5, 136.7, 136.5, 116.4, 116.3, 115.6, 115.4, 114.6,

114.5, 114.5, 61.7, 58.7, 53.9, 53.5, 49.6, 49.3, 43.8, 42.1, 41.6, 41.4, 40.9, 40.4, 37.2, 36.3, 35.5, 35.4, 34.8, 34.0, 33.8, 33.7, 28.9, 28.8, 28.3, 28.2, 28.0, 27.9, 27.7, 27.5, 25.5, 22.9, 22.8, 22.6, 21.1 ppm; GCMS (80–1–20–270–6, $v=45\ cm\,s^{-1}$): *m/z*: 7.9 (10%) (206, 191, 162, 151, 109, 95, 81*, 67, 55), 8.0 (76%) (206, 191, 162, 151, 109, 95, 81*, 67, 55), 8.1 (14%) (206, 191, 162, 151, 109, 95, 81*, 67, 55); *ee* = 91% *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis on the butenyl addition (Hydrodex B3P, iso 130 °C, $v=43\ cm\,s^{-1}$): $t_{R1}=8.7$ (*S*), $t_{R2}=9.0$ min (*R*)).

4a-Methyl-2,3,4,4a,5,6,9,9a-octahydro-1*H*-benzo[7]annulen-1-one (40): Two diastereomers 58:42 (62%); ^{1}H NMR (400 MHz, $CDCl_3$): 1st diastereomer: $\delta=5.81$–5.75 (m, 1H), 5.74–5.69 (m, 1H), 2.54–2.51 (m, 1H), 2.43–2.29 (m, 3H), 2.19–2.14 (m, 3H), 2.01–1.82 (m, 3H), 1.63–1.57 (m, 1H), 1.55–1.45 (m, 2H), 0.87 (s, 3H); 2nd diastereomer: 5.70–5.68 (m, 2H), 2.59–2.52 (m, 1H), 2.48–2.45 (m.1H), 2.36–2.20 (m, 3H), 2.07–2.00 (m, 1H), 1.97–1.92 (m, 2H), 1.87–1.74 (m, 3H), 1.52–1.48 (m, 1H), 1.45–1.39 (m, 1H), 1.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 1st diastereomers: $\delta=213.5$, 132.3, 130.4, 57.5, 43.0, 41.9, 41.3, 40.0, 23.6, 23.3, 22.9, 18.6; 2nd diastereomer: 214.4, 131.6, 129.0, 59.4, 40.1, 39.8, 39.1, 35.9, 27.4, 25.5, 23.3, 22.0 ppm; MS-EI: *m/z*: 178, 163, 150, 145, 135, 117, 107, 91, 79*, 67, 55.

3-Methyl-3-(4-methylpent-3-enyl)cyclohexanone (41):[55] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.08$ (t, 1H, $J=5.9$ Hz), 2.31–2.26 (m, 2H), 2.23–2.10 (m, 2H), 1.98–1.85 (m, 4H), 1.68 (s, 3H), 1.67–1.60 (m, 2H), 1.60 (s, 3H), 1.31–1.26 (m, 2H), 0.94 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) : 212.4, 131.7, 124.4, 53.8, 41.8, 41.2, 38.7, 36.0, 25.8, 25.0, 22.3, 22.2, 17.7 ppm; $[\alpha]_D^{20}=-6.8$ ($c=1.17$ in $CHCl_3$); *ee* = 86% *S* (absolute configuration was assigned in analogy with the literature;[11] enantiomeric excess was measured by chiral GC analysis (lipodex E, 80–0–1–120, $v=45\ cm\,s^{-1}$): $t_{R1}=28.1$ (*S*), $t_{R2}=29.5$ min (*R*)).

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