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Formation of Quaternary Stereogenic Centers by NHC–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Polyconjugated Cyclic Enones

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Abstract: The copper-catalyzed conjugate addition of various Grignard reagents to polyconjugated enones (dienone and enynone derivatives) is reported. The catalyst system, composed of copper triflate and an NHC ligand, led to the unusual selective formation of the 1,4-addition products. This reaction allows for the creation of all-carbon chiral quaternary centers with enantiomeric excesses up to 99%. The remaining unsaturation on the 1,4 adducts give access to valuable synthetic transformations.

Keywords: asymmetric synthesis · conjugate additions · copper · Grignard reagents · N-heterocyclic carbenes

Introduction

The conjugate addition reaction has become a very powerful tool for C–C bond formation. The asymmetric version of this reaction has been extensively studied over the past few decades, highlighting Cu and Rh as the catalysts of choice for this transformation.[1] With regard to copper catalysis, one of the most important breakthroughs came through the introduction of phosphorus ligands as very efficient chiral inductors.[2] Following this discovery, many groups have contributed to the further development of this reaction. The ubiquity of all-carbon quaternary stereogenic centers in Nature has inspired researchers to investigate the appropriate conditions that would lead to this motif.[3] These were successfully realized by the addition of diorganozinc reagents to very activated substrates, such as Meldrum acid derivatives,[4–6] nitroolefins[7] and doubly activated cyclic enones.[8] An improvement was achieved by the introduction of trialkylaluminum reagents to nonactivated trisubstituted cyclic enones.[9–12]

Indeed, the Lewis acidic character of this organometallic species led smoothly to the formation of quaternary centers with high enantiocontrol by using SimplePhos and phosphoramidite ligands. Strategies to introduce the aryl[13,36] and vinyl[14] moiety were also successfully developed through the use of triorganoaluminum reagents, increasing the variety of quaternary stereogenic centers that could be formed.

On the other hand, a very important contribution to the asymmetric conjugate addition (A.C.A.) is the reaction developed by Woodward and Fraser[15] through the use of a new class of ligand, the N-heterocyclic carbene (NHC), that shows strong electron-donating and steric proprieties. Since the first chiral example by the groups of Alexakis and Mangeney[16] by using diethyl zinc on cyclohexenone with NHC ligands, many reports have been published.[1] NHCs have also been shown to be valuable ligands for the creation of quaternary centers. Hoveyda et al. described the use of very efficient Cu–NHC complexes for the addition of diorganozinc reagents to not only methylcyclohexenone,[17] but also to the more challenging methylcyclopentenone.[18] However, zinc and aluminum did not allow for the introduction of many alkyl moieties. To circumvent this problem, our group focused on the use of Grignard reagents as highly versatile nucleophiles to create quaternary stereogenic centers. In 2006, through a collaboration with the Mauduit group, we revealed the highly enantioselective conjugate addition of Grignard reagents to trisubstituted cyclohexenone by using the NHC **L6** (see Figure 1).[19] Thanks to the contribution of many researchers in the field of A.C.A. reactions catalyzed by copper, new catalytic systems and also new Michael acceptors have emerged. Our expertise in the enantioselective conjugate addition prompted us to investigate polyconjugated Michael acceptors. These substrates correspond to an ex-

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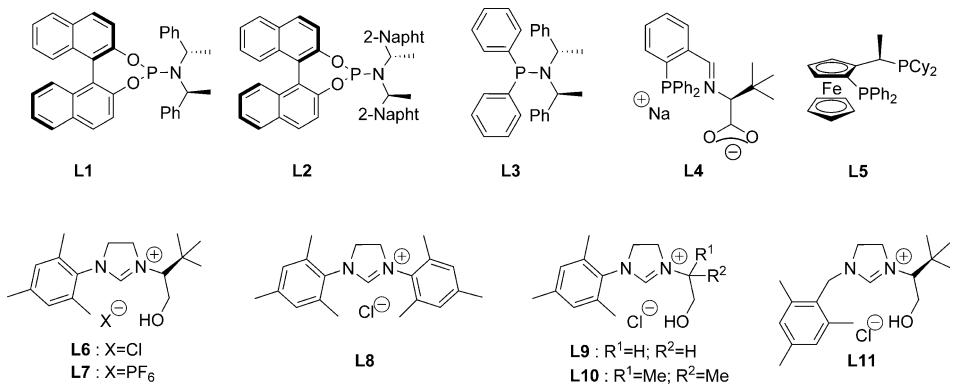
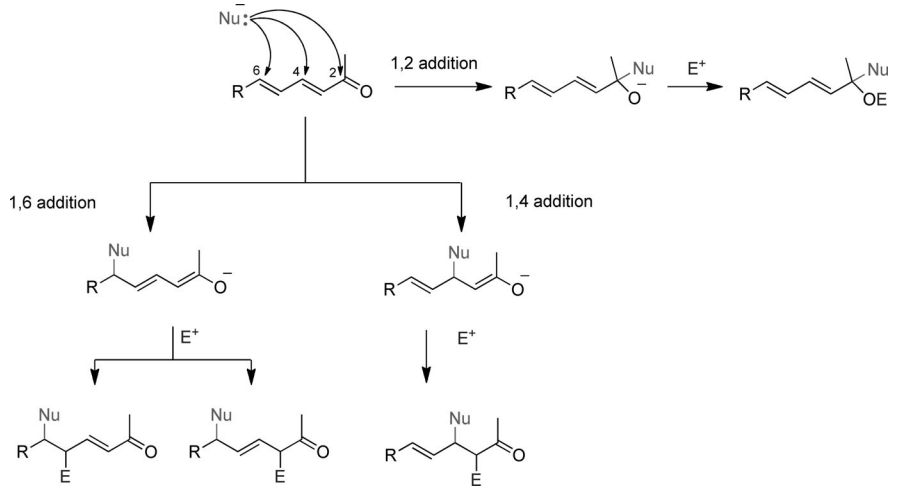


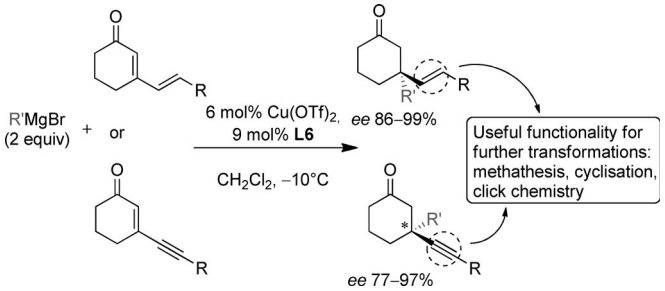
Figure 1. Selected ligands used in this study (2-Napht = 2-naphthyl).

tension of the conjugated system of typical Michael acceptors with double or triple bonds. These types of substrate posed a challenge in terms of regioselectivity due to the presence of various electrophilic sites that, upon nucleophilic attack, could lead to several regioisomers (Scheme 1).



Scheme 1. Regioselectivity with extended Michael acceptors (Nu = nucleophile, E = electrophile).

The Naef group were the pioneers in this field, describing the first conjugate addition of cuprates to dienoates, with exclusively 1,6 addition.[20] Furthermore, the conjugate addition to extended Michael acceptors has mainly been reported by the Krause group[21] in the beginning of the 1990s. They reported that copper reagents react preferentially in a 1,6 manner with α,β,δ,γ-unsaturated Michael acceptors. On the other hand, Yamamoto et al.[22] have shown that fine tuning of the copper reagent allows regioselective 1,4 or 1,6 addition. The last ten years have seen the development of an asymmetric version of this reaction.[23] Fillion et al. were the first to report the copper-catalyzed 1,6 addition of diorganozinc reagents to the Meldrum acid.[24] Subsequently, Feringa et al. disclosed the highly enantioselective and regioselective addition of Grignard reagents to dienoates.[25] Excellent 1,6 selectivity and high stereocontrol were reported thanks to ferrocene-based phosphine ligands and $CuBr{\cdot}Me_2S$ as the catalyst combination. An identical level of regioselectivity was also reported by Mauduit et al. and our group for the addition of diorganozinc reagents to cyclic dienones.[26] The Cu–diphenylphosphinoazomethinylate salt (DIPPAM) complex catalyzed the formation of the 1,6 adduct with very high enantioselectivity of up to 99% (Scheme 2). The general trend observed for copper catalysis led to a 1,6 addition. However, as demonstrated by Yamamoto et al., refinement of the copper reagents allows for the 1,4 addition.[22] Recently, we reported the copper-catalyzed A.C.A. of trialkylaluminum reagents to extended nitro-Michael acceptors, affording only the 1,4 adduct, with excellent stereocontrol.[27] Finally, two recent contributions from our laboratory have disclosed the addition of Grignard reagents to α,β,γ,δ-unsaturated cyclic enones (dienones and enynones), resulting in 1,4 selectivity.[28] This reaction has led to the formation of all-carbon stereogenic centers with very high enantioselectivity of up to 99%. Herein, we report a full account of this work, with several new dienone and enynone derivatives, and new synthetic applications of the reaction are also disclosed (Scheme 2).

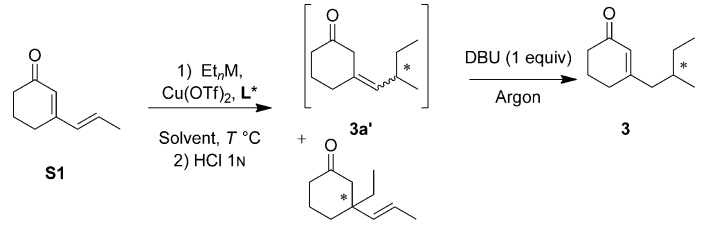


Scheme 2. Summary of this study (Tf = triflyl).

Results and Discussion

Dienones: Cyclohexenone derivatives have been extensively studied in the field of A.C.A. However, their polyconjugated analogues, the dienones, have received less attention. Hayashi et al. were the first to use this substrate type to develop the 1,6 conjugate addition of aryl zinc reagents to 3-alkenyl cyclohexen-2-ones, such as **S1**, by using Rh/2,2-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) catalysis with enantioselectivities up to 98% *ee*.[29] Our investigation into this substrate, by using copper catalysis, commenced with an initial study of the different organometallic reagents, such as Et_2Zn, Et_3Al, and EtMgBr, under different reaction conditions (Table 1).

Table 1. Optimization of the reaction with dienone **S1**.



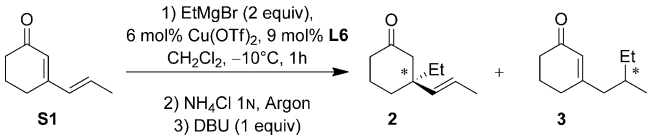
	RM ([equiv])	L*	Solvent	*T* [°C]	**2**/**3**[a]	Conv. [%][a]	Yield [%]	*ee* (**2**/**3**) [%][b]
1[c]	Et_2Zn (1.2)	**L2**	Et_2O	−30	0:100	100	66	–/89
2[d]	Et_2Zn (1.2)	**L4**	MeTHF	RT	0:100	100	75	–/97
3[c]	Et_3Al (1.2)	**L1**	Et_2O	−30	0:100	100	53	–/68
4[c]	EtMgBr (1.2)	**L1**	Et_2O	−30	0:100	100	n.d.	–/0
5[d]	EtMgBr (2)	**L5**	CH_2Cl_2	−10	0:100	100	n.d.	–/36
6	EtMgBr (1.2)	**L6**	Et_2O	0	78:22	100	n.d.	95.5/20
7[e]	EtMgBr (1.2)	**L6**	CH_2Cl_2	0	>99:1	28	n.d.	95/n.d.
8[e]	EtMgBr (2)	**L6**	CH_2Cl_2	0	>99:1	100	n.d.	95/n.d.
9[e]	EtMgBr (2)	**L6**	CH_2Cl_2	−10	>99:1	100	62	97/–
10[e]	reverse addition	**L6**	CH_2Cl_2	−10	51:49	100	n.d.	88/0

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] Reaction performed with Cu(OTf)$_2$/**L***=2:4 mol%. [d] Reaction performed with Cu(OTf)$_2$/**L***=5:10 mol%. [e] Reaction performed with Cu(OTf)$_2$/**L***=6:9 mol%. n.d.=not determined.

We first examined the copper-catalyzed A.C.A. of diethylzinc to **S1**. With respect to the general trend observed with copper reagents, we noted that only the 1,6 adduct was formed as the deconjugated isomer **3a′**. To prevent the formation of oxidative byproducts,[30] hydrochloric acid, which had previously been degassed with argon, was used to quench the reaction. The isomerization of **3a′** by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1 equiv) under argon led to totally reconjugated adduct **3**. By using phosphoramidite ligand **L2** we obtained good enantioselectivity (89%; Table 1, entry 1). Recently, Mauduit et al. and our group have discovered that diphenylphosphinoazomethinylate salts (DIPPAMs; **L4**) afford excellent enantioselectivity (97% *ee*) in MeTHF at room temperature (Table 1, entry 2).[26] Next, the evaluation of triethylaluminum reagents was performed; the best result was obtained by using ligand **L1**, affording a 68% *ee* (Table 1, entry 3). We also decided to test the Grignard reagents, with our first attempt using ligand **L1**, which led to the unique formation of the 1,6 adduct, but no enantioselectivity was detected (Table 1, entry 4). The ferrocene-based phosphine ligand **L5** was also tried and 1,6 selectivity was obtained with moderate enantiocontol (36% *ee*; Table 1, entry 5). NHC ligand **L6**, recently discovered to be a very efficient ligand in the A.C.A. of Grignard reagents to trisubstituted cyclic enones,[19] was also tested (Table 1, entry 6). Surprisingly, the 1,4 adduct was found to be the major regioisomer, corresponding to conjugate addition at the most hindered position. We were delighted to see that this transformation generates all-carbon quaternary centers with high enantioselectivity (95.5% *ee*). After optimization of the reaction conditions, the use of dichloromethane as the solvent allowed for almost perfect regioselectivity in favor of the 1,4 adduct with the same level of enantioselectivity. However, a decrease in reactivity was observed (Table 1, entry 7). We circumvented this problem by using two equivalents of the Grignard reagent (Table 1, entry 8). Furthermore, if the reaction temperature was decreased to −10°C, the reaction afforded a higher enantioselectivity of 97% *ee* (Table 1, entry 9). Altering the order of addition appeared to be detrimental to this reaction since the addition of the Grignard reagent to a mixture of the catalytic system and the substrate afforded a mixture of the regioisomers and a decrease in the enantioselectivity for the 1,4 adduct (Table 1, entry 10).

Next, a screening of different NHC ligands was carried out to determine whether this nontypical regioselectivity was specific to this family of ligands (Table 2). First, the achiral NHC **L8** was tested under the optimized reaction conditions (Table 2, entry 2). Only the formation of the 1,6 adduct was detected, highlighting the importance of the hydroxyl appendage on NHC **L6** for the 1,4 selectivity (Table 2, entry 1). Furthermore, **L9** and **L10** were employed to examine the effect of the substituent tethered at the β-position to the hydroxy group. Surprisingly, both ligands produced only the formation of the 1,6 isomer (Table 2, entries 3 and 4). These observations argue that the regioselectivity issue is highly dependent on chelation between the deprotonated alcohol and the transition metal during catalysis. Moreover, we presume that the selectivity issue is highly dependent on the byte angle formed between the carbene center, the transition metal and the hydroxyl group. Next, we studied NHC **L11** with the same features as **L6** on the hydroxyl arm, but with a homo mesityl moiety instead of a mesityl moiety on the other arm (Table 2, entry 5). Again, this structural change influenced the regioselectivity, forming the 1,4 adduct as the minor isomer. Finally, we observed an unexpected change in regioselectivity when **L7**, a homologue of **L6** with PF_6^- as the counteranion instead of Cl^-, was used. Whereas **L6** dis-

Table 2. Screening of the NHC ligand.



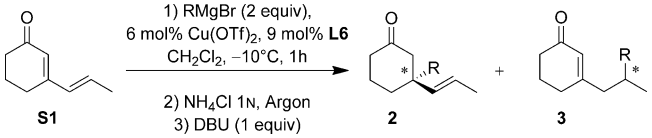
	L*	2/3[a]	Conv. [%][a]	*ee* (2/3) [%][b]
1	**L6**	>99:1	100	97/–
2	**L8**	0:100	100	–/–
3	**L9**	0:100	100	–/–
4	**L10**	0:100	100	–/–
5	**L11**	16:84	100	78/0
6	**L7**	32:68	100	95.5/0

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase.

played high regioselectivity in favor of the 1,4 adduct, **L7** furnished mainly the 1,6 adduct (Table 2, entry 6).

With these optimized conditions in hand we turned our attention to the scope of the reaction with respect to the Grignard reagent (Table 3). Firstly, the addition of linear or-

Table 3. Enantioselective 1,4 conjugate addition of several Grignard reagents to dienone **S1**.

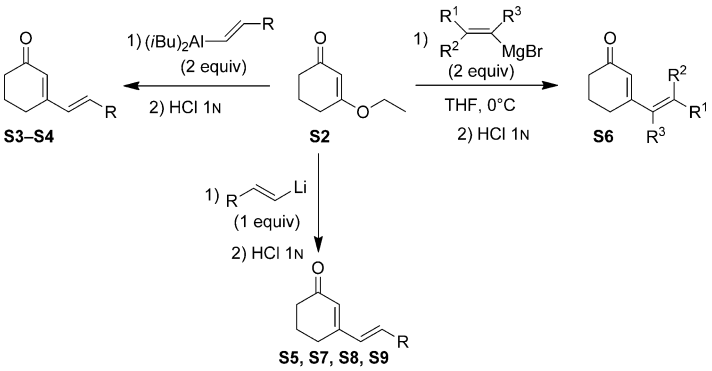


	R	Prod.	2/3[a]	Conv. [%][a]	Yield [%]	*ee* 2 [%][b]
1	Et	**2a**	>99:1	100	62	97
2	Bu	**2b**	96:4	100	67	97
3	But-3-enyl	**2c**	95:5	100	65	99
4	Me	**2d**	0:100	100	n.d.	–
5	*i*Bu	**2e**	56:44	100	39	99
6	*i*Pr	**2f**	65:35	100	25	95
7[c,d]	*i*Pr	**2f**	>99:1	100	53	94
8[c,d]	*i*Bu	**2e**	>99:1	100	58	89
9[c,d]	Cy	**2g**	>99:1	100	62	86
10	Ph	**2h**	n.d.	93	–	n.d.

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] Et_2O in the Grignard reagent was replaced with CH_2Cl_2. [d] The solution was twice as diluted as under the standard reaction conditions, and substrate addition times were 30 min instead of 15 min.

ganomagnesium reagents, such as ethyl, butyl, and but-3-enyl Grignard reagents, provided the 1,4 adducts in a high level of regioselectivity (greater than 95%) and excellent enantioselectivities of up to 99% (Table 3, entries 1–3). However, the addition of the methyl Grignard reagent resulted in a total shift in regioselectivity towards exclusive formation of the 1,6 adduct (Table 3, entry 4). This result can be attributed to the particular behavior of this Grignard reagent in conjugate addition reactions. Many modifications of the conditions have been tried in attempts to circumvent this selectivity problem. Unfortunately, the general trend towards a 1,6 addition,[21] as well as the preference for the least substituted position,[1a] appeared to be difficult to overcome. Selectivity problems were also observed with *i*BuMgBr and the secondary Grignard reagents, for which the established conditions provided a mixture of regioisomers (Table 3, entries 5 and 6).[28a] However, after optimization of the reaction conditions, we discovered that the presence of Et_2O was detrimental to the regiocontrol of these reactions. Indeed, by replacing Et_2O within the Grignard reagent with CH_2Cl_2, the 1,4 adducts were obtained as the major isomers (Table 3, entries 7, 8, and 9). The phenyl Grignard reagent was also tested, giving an inseparable mixture of compounds, and involving the formation of side products from the 1,2 addition and subsequent dehydration of the tertiary alcohol, among others (Table 1, entry 10).

Subsequently, various dienones were tested to extend the scope of this reaction. We started by synthesizing different dienone derivatives (Scheme 3, Figure 2). The six-membered



Scheme 3. Synthesis of substrates.

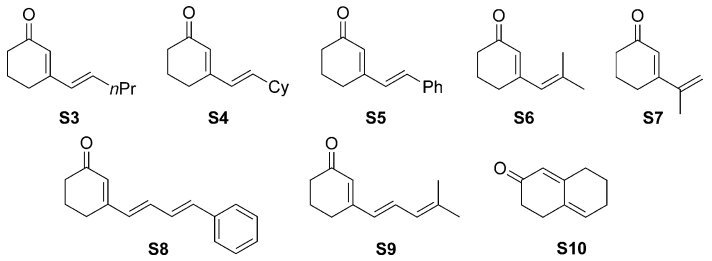
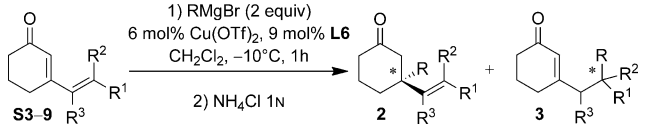


Figure 2. Substrate scope (Cy = cyclohexyl).

rings were obtained through 1,2 addition of organometallic nucleophiles to the cyclic ketoenol ether **S2**. Substrates **S3** and **S4** were synthesized by using triorganoaluminum reagents generated in situ through hydroalumination of the corresponding alkynes. **S6** was obtained by addition of the commercially available Grignard reagents to **S2**. Finally, the addition of lithium reagents, prepared in situ by lithium–bromine exchange with the corresponding vinyl bromides, afforded **S5**, **S7**, **S8** and **S9**. The bicyclic dienone **S10** was prepared according to a literature procedure.[31]

First, we applied our optimized conditions to these different substrates (Figure 2). The addition of ethyl Grignard reagents to substrates **S3**–**S6** displayed a high level of regioselectivity, affording the 1,4 adducts (**2i**–**2l**) in high enantioselectivities (Table 4, entries 1–4). The addition of the problematic methyl Grignard reagent was also tested with the substrate **S6**. The increase in the bulk of the 6 position allowed the exclusive formation of the 1,4 adduct **2m** (Table 4, entry 5). To explore the limitations of our highly regioselective catalytic system, we investigated the dienone **S7** without a substituent at the 1,6 position. To our delight the 1,4 adduct was detected as the major isomer with good enantiocontrol (Table 4, entry 6). The more challenging trienones **S8** and **S9** were also used under our reaction conditions. We were pleased to find that even with an additional electrophilic site (the 1,8 position), the 1,4 adduct was formed as a single regioisomer with excellent enantioselectivity (Table 4, entries 7 and 8).

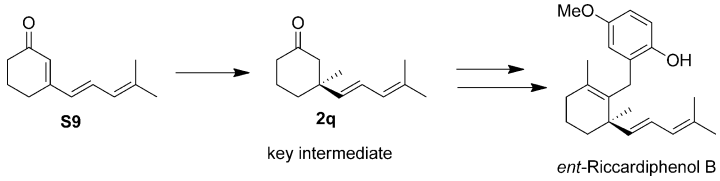
Table 4. Enantioselective 1,4 conjugate addition of Grignard reagents to various dienones **S3**–**S9**.



	Substrate	R	Prod.	**2**/**3**[a]	Conv. [%][a]	Yield [%]	*ee* **2** [%][b]
1	**S3**	Et	**2i**	>99:1	100	60	93
2	**S4**	Et	**2j**	>99:1	100	44	92
3	**S5**	Et	**2k**	>99:1	100	63	94
4	**S6**	Et	**2l**	100:0	100	69	90
5	**S6**	Me	**2m**	100:0	100	60	92
6	**S7**	Et	**2n**	90:10	100	62	88
7	**S8**	Et	**2o**	100:0	100	71	95
8	**S9**	Et	**2p**	100:0	100	70	91

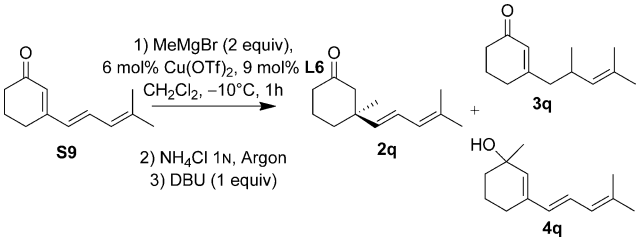
[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase.

These results encouraged us to investigate the addition of the methyl Grignard to trienone **S9**. Indeed, this transformation could allow for the formation of the chiral synthon **2q**, a key intermediate in the total synthesis of *ent*-Riccardiphenol B (Scheme 4), a natural product that was isolated from the liverwort *Riccardia Crassa* by Toyota and Asakawa[32] Two syntheses of this compound have so far been developed, by Tori et al.[33] and more recently by Hoveyda et al.[14c] We speculated that the presence of the additional conjugated double bond in the system could overcome the selectivity issue observed previously with the methyl Grignard reagent and dienone **S1**. We hypothesized that the extension of the conjugation would prevent the 1,6 addition and favor the 1,4 addition, whereas the 1,8 addition would be disfavored by the hindrance induced by the gem-dimethyl groups. Our standard reaction conditions were applied to this system; a mixture of regioisomers were detected, comprising mainly the 1,6 adduct. However, a very encouraging 31% conversion into the 1,4 adduct was observed with an enantioselectivity of 80%. The 1,2 adduct was also observed to a lesser extent (Table 5, entry 1).



Scheme 4. Application to the synthesis of *ent*-Riccardiphenol B.

Table 5. Conjugate addition of the methyl Grignard reagent to trienone **S9**.



	Conv. [%][a]	**2q**/**3q**/**4q**[a]	*ee* **2q** [%][b]
1	95	31:54:10	80
2[c]	96	26:70:0	n.d.
3[c,d]	29	8:2:19	n.d.
4[e]	90	37:24:29	85
5[f]	0	–	–
6[g]	43	21:8:14	n.d.

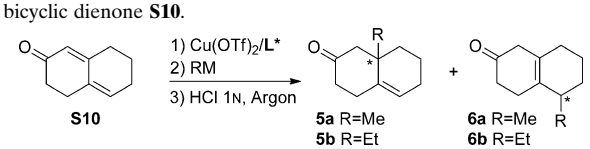
[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] The solution was twice as diluted as under the standard reaction conditions. [d] The substrate addition time was 30 min instead of 15 min. [e] Et_2O in the Grignard reagent was replaced with CH_2Cl_2. [f] 1 equivalent of $BF_3{\cdot}Et_2O$ was used as an additive. [g] MeMgI was used instead MeMgBr.

Following this promising result we started to investigate some modifications of the reaction conditions to direct the selectivity in favor of the 1,4 adduct (Table 5). Dilution of the reaction mixture afforded a cleaner reaction with no 1,2 addition being detected, although the 1,6 addition still occurred preferentially (Table 5, entry 2). Slowing down the addition time of the substrate to the catalytic system led to a drop in conversion, with a large amount of 1,2 addition product (Table 5, entry 3). Knowing the detrimental effect Et_2O had on the regioselectivity, we were encouraged to replace the Et_2O contained within the Grignard reagent with CH_2Cl_2. In this case, the 1,4 addition was favored, although the 1,2 and 1,6 addition products were still detected in substantial amounts (Table 5, entry 4). Inspired by the results reported by Yamamoto's group,[22] we used BF_3 as an additive. However, no conversion was detected under these conditions (Table 5, entry 5). Finally, MeMgI was tested as the nucleophile, generating mainly the 1,4 adduct, however, with low conversion and formation of the 1,2 product (Table 5, entry 6). After many different attempts, we were

unable to achieve good regioselectivity with reasonable conversion with the trienone **S9**.

To complete the study into the scope of the reaction with respect to substrates, the optimized reaction conditions for the 1,4 and 1,6 addition reactions were tested with bicyclic dienone **S10** (Table 6). Diethylzinc and triethylaluminum were tested in the presence of $Cu(OTf)_2$ and ligand **L2**. As expected, the 1,6 adduct was formed exclusively in both cases (Table 6, entries 1 and 2). However, low reactivity and stereocontrol were detected with diethylzinc, whereas Et_3Al gave full conversion with an enantioselectivity of 69%. Me_3Al was also tested under these conditions, displaying identical 1,6 selectivity with an enantioselectivity of 56% (Table 6, entry 3). When the addition of EtMgBr was tested under our standard reaction conditions, the 1,4 adduct was obtained with almost perfect regiocontrol, leading to the formation of bicyclic compound **5b** with an excellent enantioselectivity of 96% (Table 6, entry 4). MeMgBr gave a mixture of regioisomers, with a large amount of the 1,2 addition product (Table 6, entry 5).

Table 6. Enantioselective conjugate addition of organometallic reagents to bicyclic dienone **S10**.



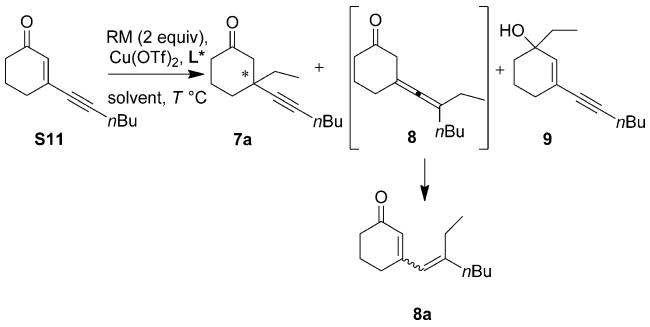
	RM	L*	Solvent	T [°C]	**5**/**6**[b]	Conv. [%][a]	Yield [%]	*ee* (**5**/**6**) [%][b]
1[c]	Et_2Zn	**L2**	Et_2O	0	0:100	11	n.d.	–/11
2[c]	Et_3Al	**L2**	Et_2O	0	0:100	100	45 (**6b**)	–/69
3[c]	Me_3Al	**L3**	Et_2O	0	0:100	100	54 (**6a**)	–/56
4[d]	EtMgBr	**L4**	CH_2Cl_2	−10	98:2	100	73 (**5b**)	96/–
5[d,e]	MeMgBr	**L4**	CH_2Cl_2	−10	n.d.	94	n.d.	n.d.

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] Reaction performed with $Cu(OTf)_2$/**L***=2:4 mol%, RM (1.2 equiv). [d] Reaction performed with $Cu(OTf)_2$/**L***=6:9 mol%, RMgBr (2 equiv). [e] Complex mixture.

Enynones: To extend our methodology to another class of substrates, we investigated the reaction of enynone **S11**.[28b] This type of polyconjugated Michael acceptor was first studied by Hulce,[34] who only observed 1,6 addition by use of a copper reagent. Hayashi et al.[35] reported the rhodium catalyzed 1,6 addition of aryltitanates to this type of substrate, which results in the formation of chiral allenes. We found two isolated examples, in different reports, of copper-catalyzed 1,4-addition reactions to this type of substrate by using diethylzinc[17] and trimethylaluminum[36] by Hoveyda et al. in the recent literature.

We initially investigated the addition of EtMgBr, Et_2Zn, and Et_3Al to enynone **S11** by using NHC ligand **L6** and phosphoramidite ligand **L2** under various conditions (Table 7). Intrigued by the potential outcome of our method with **S11**, we tested the reaction with EtMgBr under our standard reaction conditions (Table 7, entry 1). To our delight, we found that the 1,4 adduct was mainly formed with an enantioselectivity reaching 85%. This result displays similar behavior, in terms of reactivity, to the dienone analogues. We decided to perform the same reaction by using Et_2O in place of CH_2Cl_2, and were not surprised to observe a chaotic reaction with only a minor amount of the 1,4 adduct among many other products derived from the 1,2 and 1,6 additions (Table 7, entry 2). This result highlights the detrimental effect of Et_2O on the regioselectivity. The use of phosphoramidite ligand **L2** in CH_2Cl_2 led to only the 1,6 addition, affording allene **8**, which isomerized on workup into conjugated dienone **8a** (Table 7, entry 3). The same reaction performed in Et_2O led to a mixture of compounds (Table 7, entry 4). We continued our study by using diethylzinc as the organometallic reagent. Applying the standard reaction conditions (with NHC **L6**) led to very low conversion (Table 7, entry 5). However, when Et_2O was used, a ratio of 3:1 in favor of 1,4 adduct **7a** was detected with an enantioselectivity of 99% (Table 7, entry 6). Under the same reaction conditions, **L2** afforded only the 1,6 adduct (Table 7, entry 7). Finally, Et_3Al was also tested, affording mainly the 1,6 adduct (Table 7, entries 8 and 9).

Table 7. Optimization on enynone **S11**.

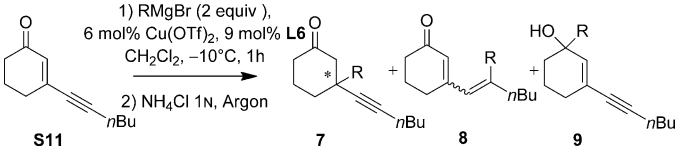


	RM	L*	Solvent	T [°C]	Conv. [%][a]	**7**/**8**/**9**[a]	*ee* **7a** [%][b]
1[c]	EtMgBr	**L6**	CH_2Cl_2	−10	100	91.5:0:8.5	85
2[c]	EtMgBr	**L6**	Et_2O	−10	100	28:n.d.:n.d.[e]	93
3[d]	EtMgBr	**L2**	CH_2Cl_2	−10	100	0:100:0	–
4[d]	EtMgBr	**L2**	Et_2O	−10	100	n.d.[e]	–
5[c]	Et_2Zn	**L6**	CH_2Cl_2	−10	10	n.d.[e]	–
6[c]	Et_2Zn	**L6**	Et_2O	−10	100	75:25:0	99
7[d]	Et_2Zn	**L2**	Et_2O	−10	60	0:100:0	–
8[c]	Et_3Al	**L5**	Et_2O	−30	100	5:95:0	n.d.
9[d]	Et_3Al	**L2**	Et_2O	−30	100	0:100:0	–

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] Reaction performed with $Cu(OTf)_2$/**L***=6:9 mol%. [d] Reaction performed with $Cu(OTf)_2$/**L***=2:4 mol%. [e] Complex mixture.

The high regioselectivity displayed with the Grignard reagent, as shown in the previous table, motivated us to examine the scope of the reaction towards nucleophiles with enynone **S11** (Table 8). After slight modification of the dilution and addition time of the EtMgBr, 1,4 adduct **7a** was obtained as a single regioisomer with an enantioselectivity of 82% (Table 8, entry 1). On the other hand, but-3-enyl magnesium bromide afforded perfect regioselectivity and an excellent enantioselectivity of up to 95% under the standard

Table 8. Enantioselective 1,4 conjugate addition of several Grignard reagents to dienone **S11**.

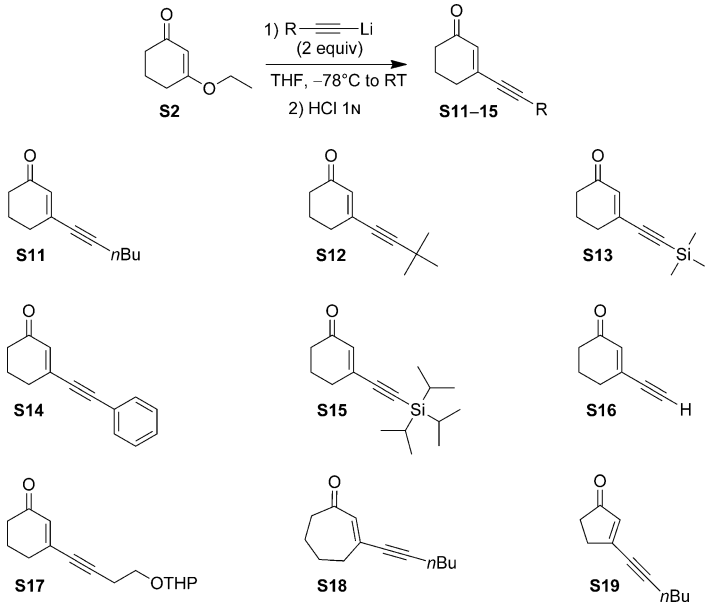


	R	Prod.	Conv. [%][a]	**7**/**8**/**9**[a]	Yield [%]	*ee* **7** [%][b]
1[c,d]	Et	**7a**	100	100:0:0	72	82
2	But-3-enyl	**7b**	100	100:0:0	90	95
3[c,d,e]	*i*Pr	**7c**	100	100:0:0	60	92
4[c,d,e]	*i*Bu	**7d**	100	93:3:4	58	89
5	Me	**7e**	100	23:77:0	n.d.	n.d.

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] The solution was twice as diluted as under the standard reaction conditions. [d] The substrate addition time was 30 min instead of 15 min. [e] Et_2O in the Grignard reagent was replaced with CH_2Cl_2.

reaction conditions (Table 8, entry 2). Isopropyl and isobutyl Grignard reagents required a slight modification of the reaction conditions. Thus, the Et_2O contained within the Grignard reagent should be replaced by CH_2Cl_2 to obtain the 1,4 adduct as the major isomer with high enantioselectivities (Table 8, entries 3 and 4). These results highlight the similar behavior of enynones and dienones with these two Grignard reagents. Despite the fact that methyl Grignard afforded 1,6 addition in the dienone series, we investigated this addition to enynone **S11**. We were not surprised to detect mainly the 1,6 adduct. However, in comparison with the dienones, the 1,4 product was detected in substantial amounts in this case (Table 8, entry 5).

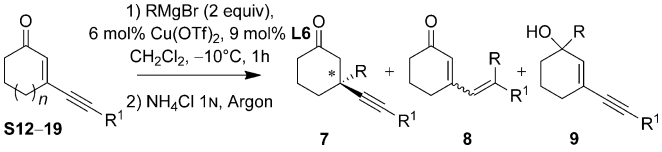
To extend the scope of this reaction, we synthesized a variety of cyclic enynones (Scheme 5). The six-membered rings **S11**–**S15** were obtained in a one-pot procedure by lithiation of the corresponding acetylene derivatives and then addition to ethoxycyclohexenone **S2**. Compound **S16** was synthesized by deprotection of enynone **S13** by using tetra-*n*-butylammonium fluoride (TBAF). The seven- and five-membered rings **S18** and **S19** were obtained through the reaction of the lithium acetylide of hexyne and the corresponding cyclic enones,[37] followed by a 1,3 rearrangement of the tertiary alcohol assisted by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).[38] Finally, the alcohol precursor of **S17** was obtained through a Sonogashira cross-coupling reaction.[39]



Scheme 5. Synthesis and substrate scope (THP = tetrahydropyranyl).

First, we investigated the addition of EtMgBr to **S12**, possessing a *tert*-butyl group. The standard reaction conditions afforded the exclusive 1,4 addition product in 79% *ee* (Table 9, entry 1). The addition of the isopropyl and isobutyl Grignard reagents to **S12** displayed the same regioselectivity with enantioselectivities of up to 93% without any modification of the standard reaction conditions (Table 9, entries 2 and 3). Trimethylsilyl (TMS)- and phenyl-substituted substrates **S13** and **S14** also gave excellent results in terms of regioselectivity with primary and secondary Grignard reagents; enantioselectivities, ranging between 78 and 96%, were detected (Table 9, entries 4–9).

Table 9. Enantioselective 1,4 conjugate addition of Grignard reagents to various enynones **S12**–**19**.



	Substrate	R	Prod.	Conv. [%][a]	**7**/**8**/**9**[a]	Yield [%]	*ee* **7** [%][b]
1	**S12**	Et	**7f**	100	100:0:0	82	79
2	**S12**	*i*Pr	**7g**	100	100:0:0	57	87
3	**S12**	*i*Bu	**7h**	100	100:0:0	87	93
4	**S13**	Et	**7i**	100	100:0:0	69	78
5	**S13**	*i*Bu	**7j**	100	100:0:0	98	95
6	**S13**	But-3-enyl	**7k**	100	100:0:0	72	91
7	**S13**	Cy	**7l**	100	95:5:0	74	96
8	**S14**	*i*Bu	**7m**	100	100:0:0	81	94
9	**S14**	But-3-enyl	**7n**	100	100:0:0	87	93
10[c,d]	**S16**	But-3-enyl	**7o**	100	50:50:0	n.d.	91
11	**S17**	But-3-enyl	**7p**	100	100:0:0	79	96
12	**S18**	But-3-enyl	**7q**	100	100:0:0	67	97
13	**S19**	Et	**7r**	100	n.d.	n.d.	36

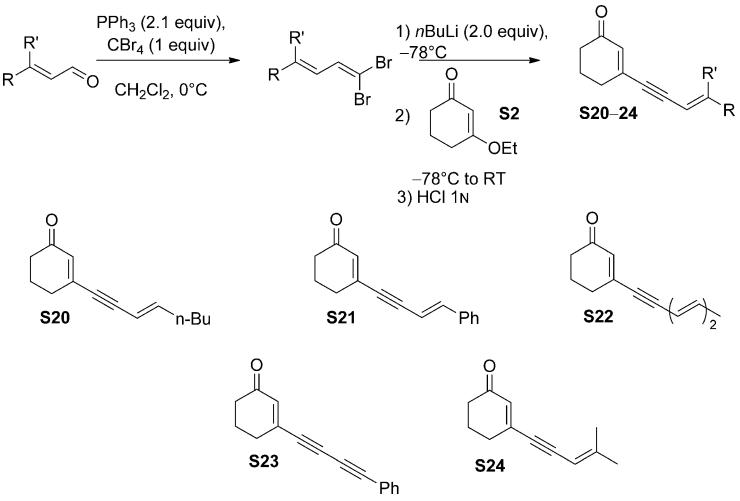
[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] The solution was twice as diluted as under the standard reaction conditions. [d] Substrate addition time was 30 min instead of 15 min.

Enynone **S16**, possessing a terminal alkyne, was synthesized to determine the limitations of the methodology. Slight modification of the methodology gave a very interesting result; we observed the formation of the 1,4 and 1,6 adducts in equal amounts (Table 9, entry 10). An enantioselectivity of 91% was detected for adduct **7o**. This result highlights the power of this catalytic system because even with the 1,6 position completely unprotected, 1,4 attack occurred. The

regioselective 1,4 A.C.A was also possible for reagents with different ring sizes. The seven-membered ring **S18** gave our best results in terms of enantioselectivity (97%) with perfect regioselectivity (Table 9, entry 12). Unfortunately, five-membered ring analogue **S19** resulted in a disordered reaction, producing a product mixture containing the 1,4 adduct in 36% *ee* (Table 9, entry 13). Finally, enynone **S17** was tested under the reaction conditions, affording only the 1,4 adduct with an enantioselectivity of 96% (Table 9, entry 11).

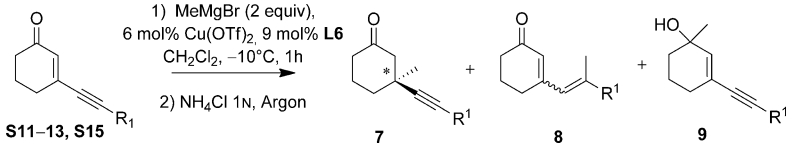
To complete the study into the scope of this reaction, we proceeded to a specific investigation of the addition of the problematic methyl Grignard reagent to various enynones (Table 10). The addition of MeMgBr to the *n*-butyl-substituted enynone **S11** exhibited the formation of the 1,4 adduct as the minor isomer (Table 10, entry 1). To drive the selectivity in favor of the 1,4 adduct, *tert*-butyl-substituted enynone **S12** was tested (Table 10, entry 2). As expected, the 1,4 addition became the dominant reaction pathway and, moreover, an enantioselectivity of 83% was detected for adduct **7t**. However, 1,2 and 1,6 addition also occurred, lowering the isolated yield. The use of the TMS-substituted enynone **S13** gave a similar regioselectivity to **S12** with an enantioselectivity of 84% (Table 10, entry 3). Finally, enynone **S15**, bearing a very bulky TIPS substituent, allowed 1,4 addition exclusively with high enantioselectivity (90%; Table 10, entry 4).

In the first section of this paper, we described the first catalytic 1,4 conjugate addition to trienones **S8** and **S9**. The high regio- and enantioselectivity of this reaction led us to examine the corresponding enynone derivatives in detail. First, we synthesized a small library of substrates through a simple two-step procedure. The corresponding aldehydes were converted into the dibromodienes by using the Corey–Fuchs methodology.[40] After treatment of the dibromodienes with BuLi, followed by addition to **S2**, the desired compounds **S20–24** were obtained in good yield (Scheme 6).



Scheme 6. Synthesis and substrate scope.

Table 10. Enantioselective 1,4 conjugate addition of MeMgBr to various enynones **S11–13** and **S15**.

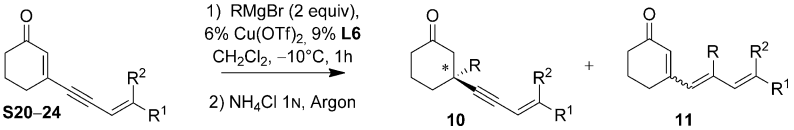


	Substrate	Prod.	Conv. [%][a]	7/8/9[a]	Yield [%]	*ee* 7 [%][b]
1	**S11**	**7s**	100	23:77:0	n.d.	n.d.
2	**S12**	**7t**	100	71:17:11	29	83
3	**S13**	**7u**	100	71:23:7	n.d.	84
4	**S15**	**7v**	100	100:0:0	78	90

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase.

The challenging substrates **S20–S24**, possessing one or even two additional unsaturated units compared with the classical enynones, were tested under the standard reaction conditions (Table 11). Our first attempt with butyl-substituted compound **S20** afforded the 1,4 adduct as a single regioisomer with a moderate enantioselectivity of 79% (Table 11, entry 1). Adducts **S21–S24** also gave perfect 1,4 selectivity, despite the possible 1,2, 1,6, and 1,8 additions pathways (Table 11, entries 2–5). Even the 10 position remained unaffected when the highly extended compound **S22** was tested, affording only product **10c** with an enantioselectivity of 87% (Table 11, entry 3). Substrate **S23**, possessing two conjugated triple bonds, resulted in perfect regioselectivi-

Table 11. Enantioselective 1,4 conjugate addition of Grignard reagents to various enynones **S20–24**.

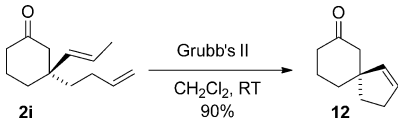


	Substrate	R	Prod.	Conv. [%][a]	10/11[a]	Yield [%]	*ee* 10 [%][b]
1	**S20**	Et	**10a**	100	100:0	60	79
2	**S21**	Et	**10b**	100	100:0	75	83
3	**S22**	Et	**10c**	100	100:0	73	87
4	**S23**	Et	**10d**	100	100:0	68	77
5	**S24**	Et	**10e**	100	100:0	81	87
6	**S24**	But-3-enyl	**10f**	100	100:0	65	93
7	**S24**	Me	**10g**	100	33:47[d]	n.d.	89
8[c]	**S24**	Me	**10g**	100	65:24[d]	n.d.	90
9	**S24**	Cy	**10h**	100	100:0	80	85
10	**S24**	*i*Pr	**10i**	100	100:0	72	90

[a] Determined by GC-MS methods. [b] Determined by chiral GC methods using a chiral stationary phase. [c] The solution was twice as diluted as under the standard reaction conditions. [d] Side product could not be identified.

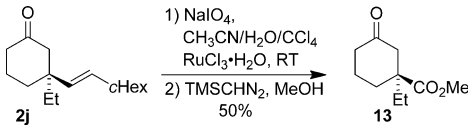
ty and an enantioselectivity of 77% (Table 11, entry 4). The scope of the reaction with respect to the nucleophile was then examined with substrate **S24**. The linear ethyl and butenyl Grignard reagents resulted in perfect regioselectivity (Table 11, entries 5 and 6). The 3-butenyl Grignard achieved a higher enantioselectivity of 93%. Secondary Grignard reagents also gave exclusively the 1,4 adducts with enantioselectivities of 90 and 85% for *i*PrMgBr and CyMgBr, respectively (Table 11, entries 9 and 10). Unfortunately, MeMgBr remained problematic with a mixture of regioisomers being detected and providing mainly the 1,6 adduct, although a significant amount of the 1,4 adduct was produced (Table 11, entry 7). Of the many unsuccessful attempts to direct the selectivity in favor of the 1,4 addition reaction, modification of the concentration afforded the best result in terms of regioselectivity, with the 1,4 adduct being obtained as the major regioisomer (Table 11, entry 8).

Synthetic applications: Next, we focused on the development of synthetic methods to demonstrate the value of our methodology by using the olefinic and acetylenic appendages of the 1,4 adduct. For example, adduct **2i** was cyclized by ring-closing metathesis (Scheme 7) to give spiro compound **12**.



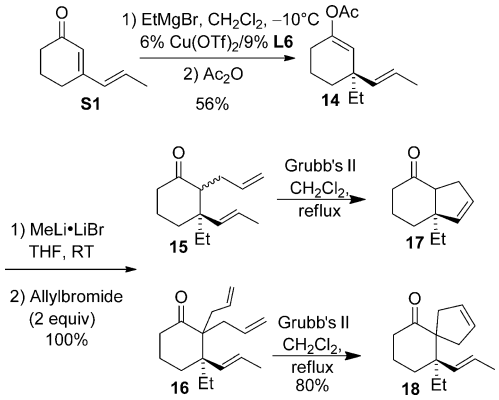
Scheme 7. Ring-closing metathesis on adduct **2i**.

Alternatively, the remaining double bond on adduct **2j** was oxidatively cleaved to give ketoester **13** (Scheme 8). As well as its synthetic versatility, this transformation allowed us to determine the *ee* value of adduct **2j**.



Scheme 8. Oxidative cleavage of adduct **2j** (TMS = trimethylsilyl).

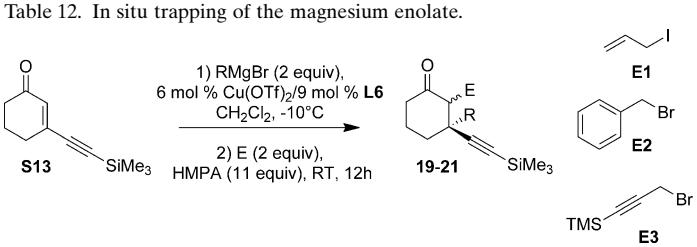
We also took advantage of the magnesium enolate intermediate resulting from the 1,4 A.C.A. by trapping it with Ac_2O (Scheme 9). Enol acetate **14** was transformed into the lithium enolate, which upon allylation gave a 3:1 ratio of monoallylated adduct **15** (as a *cis*/*trans* mixture) and bisallylated **16**. Both compounds **15** and **16** underwent a facile ring-closing methathesis reaction to yield products **17** and **18**, respectively. Although compound **15** was a mixture of isomers, a single product, **17**, was obtained; presumably the one incorporating the *cis* ring junction.



Scheme 9. Synthetic transformations of enol acetate **14**.

More recently in our laboratory, we have developed the in situ trapping of magnesium enolates with different electrophiles (allyliodide, Br_2, MeI, and benzaldehyde).[19c] Compared with the methodology described above, this methodology opens a straightforward route to an α-functionalized product. We decided to apply this useful methodology in our system and attempt to enlarge the scope of electrophiles that can be utilized (Table 12).

Table 12. In situ trapping of the magnesium enolate.



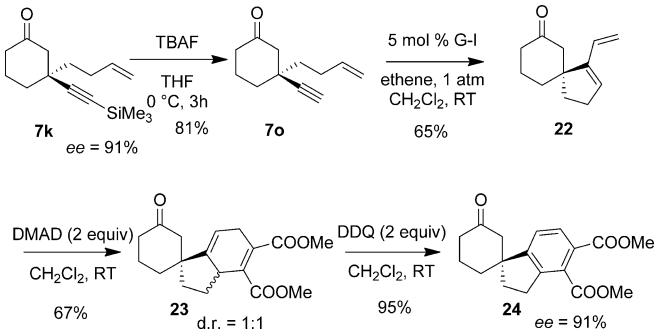
	R	Product	Conv. [%][a,b]	d.r.[a]
1	**E1**	**19**	92	83:17
2	**E2**	**20**	95	82:18
3	**E3**	**21**	82	87:13

[a] Determined by GC-MS methods. [b] The conversion was calculated from the 1,4-addition adduct.

First, we investigated the electrophilic trapping with allyl iodide (**E1**). The formation of α-alkylated product **19** proceeded at room temperature, in the presence of hexamethylphosphoramide (HMPA, 10 equiv) and the electrophile (2 equiv). A good diastereomeric ratio (d.r.) was detected, however, a small amount (< 5%) of the α′-alkylated product was also detected. Unfortunately, it was not possible to separate this isomer from the α-alkylated diastereomeric mixture. Subsequently, we explored the reactivity of benzyl bromide (**E2**) and the TMS-protected propargylic bromide **E3**. The reaction conditions gave the desired α-alkylated diastereoisomers **20** and **21**, respectively, and a small amount of the α′-alkylated products were also detected. Moreover, in all of these reactions, a small amount of the 1,4 adduct **7i** was recovered, highlighting the possible generation of

a proton source during the reaction. This observation could explain the formation of the α′-alkylated products.

In addition, applications of the triple bond remaining in products **7** were also developed. This functionality allowed for many transformations, giving access to more complex molecules. Our first experiment resulted in an ene–yne methathesis/Diels–Alder/aromatization sequence (Scheme 10). After deprotection of **7k** with TBAF, compound **7o** was submitted to the Grubbs I catalyst in the presence of an atmosphere of ethene.[41] Spirobicyclic compound **22** was formed in 65% yield. This intermediate was

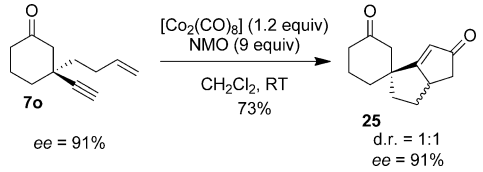


Scheme 10. Ene–yne metathesis/Diels–Alder/aromatization sequence (TBAF = tetra-*n*-butylammonium fluoride, G-I = Grubb's catalyst 1st generation, DMAD = dimethyl acetylenedicarboxylate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

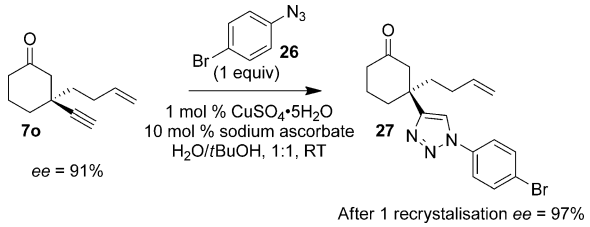
submitted to the Diels–Alder reaction by using dimethyl acetylenedicarboxylate (DMAD) as the dienophile. Unfortunately, a 1:1 diastereomeric mixture was observed for compound **23**. This system was then easily rearomatized to give compound **24** in a quantitative yield. No loss of enantioselectivity was detected with compound **24** displaying an enantioselectivity of 91%.

The synthesis of adduct **7o** encouraged us to perform the well-known Pauson–Khand reaction[42] by treating compound **7o** with cobalt octacarbonyl, followed by the addition of *N*-methylmorpholine *N*-oxide (NMO) as an inducer of decarbonylation.[43] We were glad to obtain tricyclic compound **25** in a 1:1 diastereomeric ratio (Scheme 11).

Finally, we performed the cycloaddition of azide **26** and keto–enyne **7o**, namely, the Huisgen reaction[44] (Scheme 12). The efficient methodology developed by Sharpless et al.[45] that uses catalytic amounts of copper allowed the formation of the triazole-substituted quaternary stereogenic center in **27**.



Scheme 11. Pauson–Khand reaction of adduct **7o** (NMO = *N*-methylmorpholine *N*-oxide).



Scheme 12. Huisgen reaction with adduct **7p**.

A crystalline product was obtained that enabled us to solve the crystal structure and prove that the absolute configuration of product **16** is (*R*) (Figure 3).

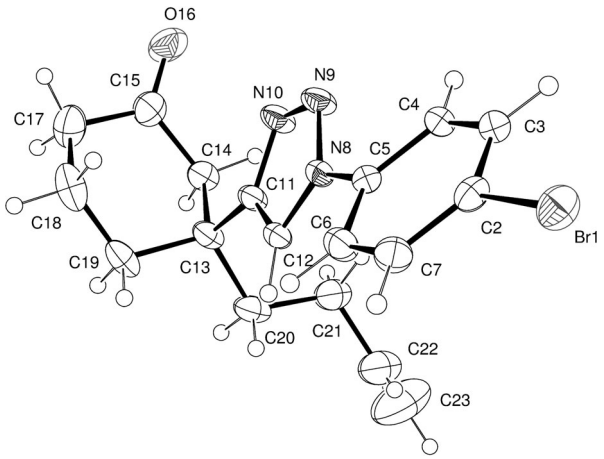


Figure 3. Single-crystal X-ray structure of compound **16**. Thermal ellipsoids shown at the 40% probability level.[46]

Mechanistic aspects: Our counterintuitive observations prompted us to attempt to get a better understanding of the mechanism of this reaction, which goes against the general trend observed with copper reagents.[21] After further investigation, we proposed a catalytic cycle that could rationalize the observed regioselectivity in the A.C.A. reaction to the polyconjugated cyclic enones described in this article (Figure 4). Our reaction conditions for the 1,4 A.C.A. reaction to the polyconjugated cyclic enones involves the addition of the substrate as the last step. This observation means that the hydroxy group of the NHC is deprotonated by the Grignard reagent, leading to the formation of a transcient complex $\mathbf{A^0}$, followed by the formation of the heterocuprate complex (Figure 4). The recent characterization of a magnesium organocuprate complex by Davies et al.[47] derived from Grignard reagents shows that they have a dimeric contact-ion-pair (CIP) structure in weakly coordinating solvents, such as Et_2O. This group found that this species is isostructural with the previously reported lithium diphenyl cuprate.[1b,48] For this reason, we propose the dimeric heterocuprate $\mathbf{A^1}$ as the copper complex in this reaction. However, the large excess of Grignard reagents cannot exclude that

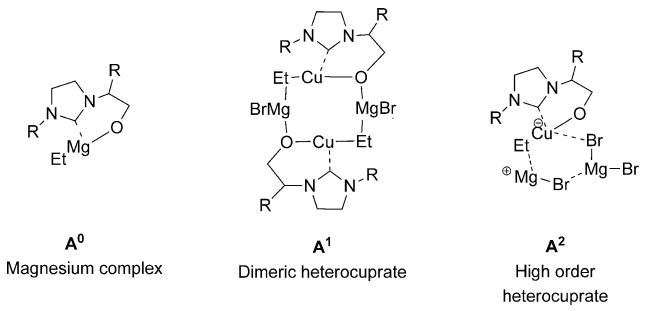


Figure 4. Carbenoid–metal complexes.

instead of having a heterocuprate complex, such as $\mathbf{A^1}$, this reaction involves the presence of a high-order heterocuprate $\mathbf{A^2}$. The formation of these two possible heterocuprates complexes ($\mathbf{A^1}$ or $\mathbf{A^2}$) appeared to be beneficial for the regioselectivity. Indeed, as described previously, when the Grignard reagent is added last, the regioselectivity becomes in favor of the 1,6 adduct. In this case, the addition of the Grignard reagent to the reaction mixture would generate a organocopper species, rather than a heterocuprate, which might explain the 1,6 selectivity. We attempted to experimentally observe complexes $\mathbf{A^1}$ or $\mathbf{A^2}$ through a ^{13}C NMR experiment in solution (see the Experimental Section) by mixing the Grignard reagent in the presence of NHC **L6** and $(CuOTf)_2{\cdot}C_6H_6$ (copper(I)). We observed a signal at 205 ppm, which probably corresponds to the chemical shift of a carbenoid/magnesium $\mathbf{A^0}$ complex, and a signal at 201 ppm, corresponding to the chemical shift of heterocuprate complex $\mathbf{A^1}$ or $\mathbf{A^2}$. The carbon atom signal of the imidazolinium salt (160 ppm) was no longer observed due to total deprotonation of the NHC by the Grignard and complete complexation to the metal.

Presumably, the addition of the dienone to complex **A** led to the formation of a π complex **B** followed by the generation of a β-cuprio(III) enolate intermediate **C** (Figure 5). At this point, two pathways can be envisaged with this species. Complex **C** can reductively eliminate to afford the 1,4 adduct, enolate **E** (pathway I) or the heterocuprate complex can migrate to the triple bond to form a new organocopper(III) intermediate **D** (pathway II), followed by reductive elimination to afford the 1,6 adduct, enolate **F**. Both enolate species **E** and **F** were transformed upon hydrolysis into the corresponding 1,4 and 1,6 adducts, respectively.

The groups of Nakamura[49] and Krause[50] have been involved in investigating the conjugate addition of organocopper reagents to polyconjugated carbonyls. Density functional calculations have been performed to explain the reason behind the formation of a remote conjugate addition product in the reaction of a lithium organocuprate (R_2CuLi) with polyconjugated carbonyl compounds. Indeed, the calculations showed that the 1,4 reductive elimination of the β-cuprio(III) intermediate is kinetically disfavored compared with the migration to the C6 position. This could be explained by the disruption of conjugation if the reductive elimination occurred at the C4 position. This observation led them to postulate that the copper migration is the rate-determining step. Moreover, the activation barrier for the 1,6 reductive elimination is lower than the activation barrier for the 1,4 reductive elimination. In our case, the 1,4 addition trend observed with our catalytic system implies that the 1,4 reductive elimination is faster than the migration to form complex **D**. We postulate that the NHC **L6**/Cu complex lowers the activation barrier of this 1,4 reductive-elimination step and thus disfavors the migration to the 1,6 position. As demonstrated by the ligand screening, the structural features of NHC **L6** are very important for the outcome of this reaction.

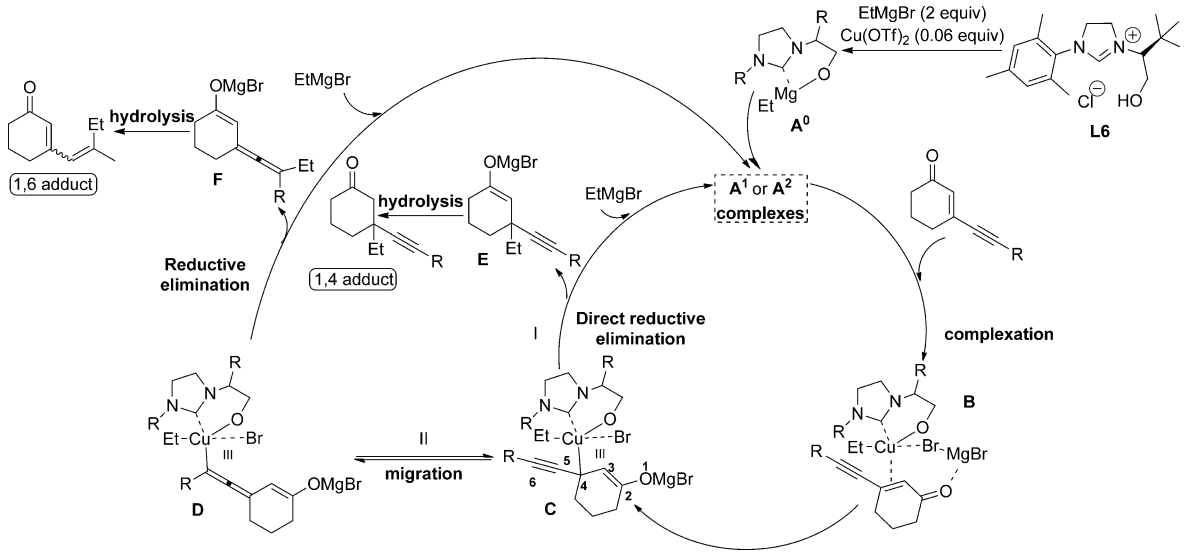


Figure 5. Proposed catalytic cycle.

Conclusion

We have developed a highly regio- and enantioselective 1,4 conjugate addition of Grignard reagents to polyconjugated cyclic enones. The exceptional and unusual 1,4 selectivity corresponds to a conjugate addition at the most hindered position, giving access to all-carbon quaternary stereogenic centers with an excellent level of enantioselectivity (99%). It is remarkable to note that experiments conducted with phosphorus or simpler NHC ligands (Arduengo's carbene) and Grignard reagents gave exclusively the 1,6 addition, whereas the use of our NHC **L6**, containing a chelating hydroxyl group, afforded the 1,4 adduct. For dienones, excellent regioselectivities and enantioselectivities (up to 99%) were obtained with primary and secondary Grignard reagents on **S1**. However, MeMgBr gave only 1,6 addition. It seems that the natural trend for 1,6 addition and the preference for the less substituted position are difficult to overcome in this case. The methodology was successfully extended to trienones, displaying perfect 1,4 selectivity. We also successfully applied our methodology to enynone derivatives. Seven-membered rings displayed the best enantioselectivity for this family of substrates (97%), reacting with perfect regiocontrol, whereas five-membered rings gave low regio- and enantioselectivity. By increasing the bulk of the 6 position, the addition of methyl Grignard reagents can be exclusively directed to 1,4 adduct formation. The scope of the reaction towards substrates with additional unsaturation attached to the triple bond was also tested, demonstrating an excellent level of regioselectivity with good enantioselectivity.

In terms of synthetic applications, the remaining C–C double bond in the 1,4 adducts allowed useful transformations, such as ring-closing metathesis, affording interesting bicyclic building blocks. We also took advantage of the formation of a magnesium enolate intermediate and trapped it with different electrophiles, allowing for the formation of useful synthons. The acetylenic appendage was also useful for synthetic transformations. Adduct **7p** was cyclized by ring-closing ene–yne metathesis and the Pauson–Khand reaction. The Huisgen reaction was also applied to this useful intermediate to confirm the absolute configuration of the 1,4 adducts. We also attempted to explain the selectivity outcome of our reaction through the elaboration of a proposed catalytic cycle highlighting reductive elimination as the rate-determining step.

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 $CHCl_3$. The evolution of the reaction was followed by GC-MS using a Hewlett Packard (EI mode) HP6890–5973 spectrometer. 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 per 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 (R_T) 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 to magnesium. Flash column chromatography was performed by using silica gel (32–63 μm, 60 Å). The syntheses of starting substrates are described in the Supporting Information.

Typical procedure for 1,4 addition reactions: A flame-dried Schlenk tube was charged with copper salt (6.0 mol%) and the chiral ImH$^+$ salt (9.0 mol%). The system was flushed with N_2 and dry CH_2Cl_2 (1.5 mL) was added. The mixture was cooled to −10°C in an ethanol cold bath. The Grignard reagent (2 equiv) in Et_2O was added dropwise to the solution over 5 min. A solution of the dienone or enynone (0.5 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was then added dropwise to the solution at −10°C over 15 min and the solution was stirred for 1 h. The reaction was hydrolyzed at the reaction temperature by addition of NH_4Cl (1 M, 3 mL) and the aqueous layer was separated and extracted further with CH_2Cl_2 (3×10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to give an oily residue. The crude was purified by flash column chromatography on a silica column with cylohexane/EtOAc to give the pure product.

(*S*,*E*)-3-Ethyl-3-(prop-1-enyl)cyclohexanone (2a): ^{1}H NMR (100 MHz, $CDCl_3$): δ=5.34 (dq, J_1=6.0, J_2=16.0 Hz, 1H), 5.15 (d, J=16 Hz, 1H), 2.46 (d, J=14.0 Hz, 1H), 2.33–2.16 (m, 2H), 2.12 (d, J=14.0 Hz, 1H), 1.84–1.76 (m, 1H), 1.69–1.61 (m, 6H), 1.37 (q, J=7.5, 2H), 0.78 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.0, 136.6, 125.3, 49.8, 44.2, 41.2, 35.2, 34.2, 21.8, 18.3, 7.9 ppm; HRMS (EI) calcd for $C_{11}H_{18}O$: 166.1357 $[M]^+$; found: 166.1360; $[\alpha]_D^{20}$=+72.24 (c=1.4 in $CHCl_3$), 95% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (75–40–1–100): R_{T_1}=36.88, R_{T_2}=39.09 min.

(*S*,*E*)-3-Butyl-3-(prop-1-enyl)cyclohexanone (2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.38–5.30 (m, 1H), 5.16 (d, J=16.5 Hz, 1H), 2.45 (d, J=14.0 Hz, 1H), 2.32–2.18 (m, 2H), 2.13 (d, J=14.0 Hz, 1H), 1.84–1.75 (m, 2H), 1.70–1.60 (m, 5H), 1.34–1.10 (m, 6H), 0.87 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3): δ=212.0, 137.1, 124.9, 50.4, 44.0, 41.6, 41.2, 35.5, 25.7, 23.3, 21.8, 18.3, 14.1 ppm; HRMS (EI) calcd for $C_{13}H_{22}O$: 194.16706 $[M]^+$; found: 194.1670; $[\alpha]_D^{20}$=+67.0 (c=1.34 in $CHCl_3$), 97.4% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (75–40–1–100): R_{T_1}=56.58, R_{T_2}=57.78 min.

(*R*,*E*)-3-(But-3-enyl)-3-(prop-1-enyl)cyclohexanone (2c): ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.83–5.72 (m, 1H), 5.35 (dq, J_1=16.0 J_2=6.0 Hz, 1H), 5.18 (d, J=16.0 Hz, 1H), 5.30–4.90 (m, 2H), 2.50 (d, J=14.0 Hz, 1H), 2.34–2.19 (m, 2H), 2.15 (d, J=14.0 Hz, 1H), 1.99–1.92 (m, 2H), 1.84–1.78 (m, 2H), 1.77–1.61 (m, 6H), 1.45–1.30 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.7, 138.9, 136.5, 125.6, 114.4, 50.1, 44.0, 41.2, 41.0, 35.6, 28.0, 21.7, 18.3 ppm; HRMS (ESI+) calcd for $C_{13}H_{21}O$: 193.1586 $[M+H]^+$; found: 193.1588; $[\alpha]_D^{20}$=+70.0 (c=0.955 in $CHCl_3$), >99% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (75–40–1–100): R_{T_1}=56.58, R_{T_2}=57.78 min.

(*S*,*E*)-3-Butyl-3-(prop-1-enyl)cyclohexanone (2e): ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.31 (dq, J_1=6.0, J_2=16.0 Hz, 1H), 5.11 (d, J=16.0 Hz, 1H), 2.50 (d, J=14.0 Hz, 1H), 2.34–2.19 (m, 2H), 2.15 (d, J=14.0 Hz, 1H), 1.99–1.92 (m, 2H), 1.84–1.78 (m, 2H), 1.77–1.61 (m, 6H), 1.45–1.30 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.0, 137.5, 125.0, 51.4, 50.7, 44.6, 41.2, 36.3, 25.2, 25.1, 24.0, 21.7, 18.3 ppm; HRMS (EI) calcd for $C_{13}H_{22}O$: 194.1671 $[M]^+$; found: 194.1667; $[\alpha]_D^{20}$=+61.2 (c=1.26 in $CHCl_3$), 98.7% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing HYDRODEX B3-P (70–50–1–120): R_{T_1}=98.34, R_{T_2}=98.94 min.

(*S*,*E*)-3-Isopropyl-3-(prop-1-enyl)cyclohexanone (2f): ^{1}H NMR (400 MHz, $CDCl_3$): 5.32 (dq, $J_1=6.0$, $J_2=16.0$ Hz, 1H), 5.14 (d, $J=16.0$ Hz, 1H), 2.49 (dt, $J_1=2.0$, $J_2=14.0$ Hz, 1H,), 2.31–2.24 (m, 1H), 2.19–2.12 (m, 1H), 2.11 (d, $J=14.0$ Hz, 1H), 1.85–1.62 (m, 7H), 1.54 (sept, $J=6.8$ Hz, 1H), 0.83 (d, $J=2.8$ Hz, 3H), 0.81 ppm (d, $J=2.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.5$, 134.2, 126.8, 47.6, 46.9, 41.2, 37.1, 33.6, 21.8, 18.5, 17.5, 17.0 ppm; HRMS (EI) calcd for $C_{12}H_{20}O$: 180.1514 $[M]^+$; found: 180.1513; $[\alpha]_D^{20}=+88.14$ ($c=1$ in CH_3Cl), 95.5% *ee*. The enantiomeric excess was determined by GC analysis employing LIPODEX-E (100–12): $R_{T_1}=8.31$, $R_{T_2}=9.37$ min.

(*S*,*E*)-3-Cyclohexyl-3-(prop-1-enyl)cyclohexanone (2g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.28$–5.23 (m, 1H), 5.14 (d, $J=16.2$ Hz, 1H), 2.49 (d, $J=16.2$ Hz, 1H), 2.29–2.24 (m, 1H), 2.19–2.11 (m, 2H), 1.84–1.61 (m, 11H), 1.24–1.10 (m, 5H), 0.94–0.84 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.5$, 135.2, 126.4, 47.8, 47.5, 46.8, 41.3, 33.3, 27.3, 27.0, 26.9, 26.8, 26.6, 21.6, 18.4 ppm; HRMS (EI) calcd for $C_{15}H_{24}O$: 220.1826 $[M]^+$; found: 220.1827; $[\alpha]_D^{20}=+74.2$ ($c=1$ in CH_3Cl), 86% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=99.88$, $R_{T_2}=100.67$ min.

(*S*,*E*)-3-Ethyl-3-(pent-1-enyl)cyclohexanone (2i): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.30$ (td, $J_1=6.5$, $J_2=16.0$ Hz, 1H), 5.12 (d, $J=16.0$ Hz, 1H), 2.31–2.16 (m, 2H), 2.10 (d, $J=14.0$ Hz, 1H), 2.00–1.82 (m, 2H), 1.83–1.73 (m, 2H), 1.68–1.60 (m, 2H), 1.40–1.30 (m, 4H), 0.85 (t, $J=7.5$ Hz, 3H), 0.77 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 212.0, 135.6, 130.9, 49.8, 44.2, 41.2, 35.3, 35.0, 34.3, 22.7, 21.8, 13.6, 7.9 ppm; HRMS (ESI+) calcd for $C_{13}H_{23}O$: 195.1743 $[M+H]^+$; found: 195.1749; $[\alpha]_D^{20}=+59.4$ ($c=0.745$ in $CHCl_3$), 93% *ee*. The enantiomeric excess was determined by GC analysis employing HYDRODEX-B-6TDM (80–1–150): $R_{T_1}=45.20$, $R_{T_2}=45.89$ min.

(*S*,*E*)-3-(2-Cyclohexylvinyl)-3-ethylcyclohexanone (2j): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.26$ (dd, $J_1=7.0$, $J_2=16.0$ Hz, 1H), 5.07 (d, $J=16.0$ Hz, 1H), 2.45 (d, $J=14.0$ Hz, 1H), 2.32–2.12 (m, 2H), 2.09 (d, $J=14.0$ Hz, 1H), 1.98–1.84 (m, 1H), 1.83–1.73 (m, 2H), 1.72–1.58 (m, 7H), 1.36 (q, $J=7.5$ Hz, 2H), 1.43–0.96 (m, 5H), 0.76 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 211.9, 137.0, 132.7, 49.8, 43.9, 41.2, 41.1, 35.3, 34.2, 33.4, 33.3, 26.2, 26.1, 21.8 7.9 ppm; HRMS (ESI+) calcd for $C_{16}H_{26}ONa$: 257.1875 $[M+Na]^+$; found: 257.1869; $[\alpha]_D^{20}=+57.67$ ($c=1.09$ in $CHCl_3$), 92% *ee*. The enantiomeric excess was determined on the corresponding δ-keto ester **13** by GC analysis employing LIPODEX-E (60–1–110): $R_{T_1}=47.94$, $R_{T_2}=49.31$ min.

***(S,E)*-3-Ethyl-3-styrylcyclohexanone (2k)**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.19 (m, 5H), 6.29 (d, $J=16.5$ Hz, 1H), 5.96 (d, $J=16.5$ Hz, 1H), 2.63 (d, $J=14.2$ Hz, 1H), 2.35–2.23 (m, 3H), 1.89–1.74 (m, 4H), 1.55–1.46 (m, 2H), 0.84 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=211.4$, 137.3, 135.8, 130.0, 128.6, 127.3, 126.2, 49.7, 44.7, 41.2, 35.3, 34.2, 21.9, 8.1 ppm; HRMS (EI) calcd for $C_{16}H_{20}O$: 228.1514 $[M]^+$; found: 228.1516; $[\alpha]_D^{20}=+53.4$ ($c=1$ in CH_3Cl), 94% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel OJ column, method: MeOH 0%–2–1–15, 5 °C): $R_{T_1}=4.27$, $R_{T_2}=5.08$ min.

(*S*)-3-Ethyl-3-(2-methylprop-1-enyl)cyclohexanone (2l): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.88$ (s, 1H), 2.50 (d, $J=13.5$ Hz, 1H), 2.32–2.22 (m, 2H), 2.16 (d, $J=13.5$ Hz, 1H), 1.97–1.88 (m, 1H), 1.85–1.80 (m, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.64–1.45 (m, 2H), 0.81 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=212.2$, 133.6, 128.3, 52.9, 44.4, 41.2, 35.7, 33.2, 28.3, 22.3, 19.1, 8.4 ppm; HRMS (EI) calcd for $C_{12}H_{20}O$: 180.1514 $[M]^+$; found: 180.1515; $[\alpha]_D^{20}=+57.6$ ($c=1$ in CH_3Cl), 88% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=53.78$, $R_{T_2}=54.58$ min.

(*S*)-3-Methyl-3-(2-methylprop-1-enyl)cyclohexanone (2m): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.03$ (s, 1H), 2.46 (d, $J=13.5$ Hz, 1H), 2.29–2.21 (m, 2H), 2.19 (d, $J=13.5$ Hz, 1H), 1.97–1.81 (m, 3H), 1.70 (d, $J=1.0$ Hz, 3H), 1.67 (d, $J=1.0$ Hz, 3H), 1.65–1.55 (m, 1H), 1.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=212.9$, 133.2, 130.4, 55.2, 41.0, 40.5, 37.8, 28.1, 27.4, 22.6, 19.2 ppm; HRMS (EI) calcd for $C_{11}H_{18}O$: 166.1357 $[M]^+$; found: 166.1356; $[\alpha]_D^{20}=+48.16$ ($c=0.995$ in $CHCl_3$), 92% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (80–25): $R_{T_1}=16.71$, $R_{T_2}=19.87$ min.

(*S*)-3-Ethyl-3-(prop-1-en-2-yl)cyclohexanone (2n): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.96$ (s, 1H), 4.71 (s, 1H), 2.65 (d, $J=14.4$, 1H), 2.37–2.27 (m, 1H), 2.25–2.15 (m, 1H), 2.12 (d, $J=14.4$ Hz, 1H), 1.91–1.84 (m, 1H), 1.83–1.77 (m, 1H), 1.74–1.66 (m, 1H), 1.63 (s, 3H), 1.61–1.51 (m, 1H), 1.39–1.30 (m, 2H), 0.71 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): 211.8, 146.8, 114.6, 49.9, 47.3, 41.0, 33.9, 31.3, 21.4, 18.8, 7.7 ppm; HRMS (EI) calcd for $C_{11}H_{18}O$: 166.1357 $[M]^+$; found: 166.1357; $[\alpha]_D^{20}=+33.6$ ($c=1$ in CH_3Cl), 88% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=53.78$, $R_{T_2}=54.58$ min.

(*S*)-3-Ethyl-3-[(1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl]cyclohexenone (2o): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.46$–7.22 (m, 5H), 6.78 (dd, $J=15.7$, 10.2 Hz, 1H), 6.56 (d, $J=15.7$ Hz, 1H), 6.18 (dd, $J=15.7$, 10.2 Hz, 1H), 5.61 (d, $J=15.7$ Hz, 1H), 2.60 (d, $J=14.1$ Hz, 1H), 2.42–2.21 (m, 3H), 1.95–1.71 (m, 3H), 1.51 (q, $J=7.3$ Hz, 2H), 1.33–1.23 (m, 1H), 0.87 ppm (t, $J=7.4$, 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=211.5$, 140.3, 137.4, 131.5, 130.7, 129.1, 128.7, 127.4, 126.3, 49.7, 44.9, 41.3, 35.2, 34.3, 22.0, 8.1 ppm; HRMS (EI) calcd for $C_{18}H_{22}O$: 254.1671 $[M]^+$; found: 254.1668; $[\alpha]_D^{20}=+21.4$ ($c=1$ in CH_3Cl), 95% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AS column, method: MeOH 0%–2–1–15, 5 °C): $R_{T_1}=5.51$, $R_{T_2}=5.88$ min.

(*S*,*E*)-3-Ethyl-3-(4-methylpenta-1,3-dien-1-yl)cyclohexenone (2p): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.13$ (dd, $J=15.5$, 10.7 Hz, 1H), 5.77 (d, $J=10.4$ Hz, 1H), 5.27 (d, $J=15.6$ Hz, 1H), 2.51 (d, $J=14.1$ Hz, 1H), 2.43–2.00 (m, 3H), 1.80 (d, $J=4.6$ Hz, 1H), 1.74 (d, $J=3.8$ Hz, 6H), 1.69 (d, $J=5.6$ Hz, 1H), 1.48–0.83 (m, 4H), 0.78 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=211.8$, 136.7, 134.6, 126.9, 125.0, 49.9, 44.8, 41.3, 35.3, 34.3, 26.1, 21.9, 18.5, 8.1 ppm; HRMS (EI) calcd for $C_{14}H_{22}O$: 206.1671 $[M]^+$; found: 206.1670; $[\alpha]_D^{20}=+23.4$ ($c=1$ in CH_3Cl), 91% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=84.67$, $R_{T_2}=85.27$ min.

8a-Ethyl-3,4,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one (5b): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.68$ (brs, 1H), 2.54–2.42 (m, 1H), 2.41–2.26 (m, 4H), 2.19 (dd, $J_1=2.0$, $J_2=13.5$ Hz, 1H), 2.08–1.92 (m, 2H), 1.77–1.66 (m, 1H), 1.64–1.20 (m, 5H), 0.77 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.0$, 139.1, 124.2, 53.2, 42.4, 40.8, 33.6, 31.4, 29.9, 25.7, 19.2, 7.7 ppm; HRMS (EI) calcd for $C_{12}H_{18}O$: 178.1356 $[M]^+$; found: 178.1358; $[\alpha]_D^{20}=-12.9$ ($c=1.29$ in $CHCl_3$), 96% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (80–1–120): $R_{T_1}=29.73$, $R_{T_2}=32.57$ min.

3-Ethyl-3-(hex-1-yn-1-yl)cyclohexanone (7a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.50$ (d, $J=2.04$ Hz, 1H), 2.39–2.23 (m, 1H), 2.20–2.00 (m, 5H), 1.99–1.80 (m, 2H), 1.50–1.30 (m, 7H), 1.00 (t, $J=7.36$ Hz, 3H), 0.87 ppm (t, $J=7.08$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=210.1$, 85.0, 82.2, 52.8, 41.0, 40.8, 35.9, 35.1, 31.1, 22.8, 21.8, 18.3, 13.6, 8.8 ppm; HRMS (EI) calcd for $C_{14}H_{22}O$: 229.1564 $[M+Na]^+$; found: 229.1564; $[\alpha]_D^{25}=+50.08$ ($c=1$ in $CHCl_3$), 82% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=78.24$, $R_{T_2}=78.98$ min.

3-(But-3-en-1-yl)-3-(hex-1-yn-1-yl)cyclohexanone (7b): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=5.83$–5.79 (m, 1H), 5.00–4.93 (m, 2H), 2.45 (d, $J=13.55$ Hz, 1H), 2.35 (m, 1H), 2.20–2.02 (m, 7H), 2.00–1.80 (m, 2H), 1.65–1.50 (m, 3H), 1.45–1.30 (m, 4H), 0.88 ppm (t, $J=7.25$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.7$, 138.5, 114.6, 85.4, 82.0, 53.1, 41.6, 41.0, 40.2, 36.3, 31.1, 28.9, 22.7, 21.8, 18.3, 13.6 ppm; HRMS (EI) calcd for $C_{16}H_{24}O$: 255.1719 $[M+Na]^+$; found: 255.1719; $[\alpha]_D^{25}=+32.8$ ($c=1$ in $CHCl_3$), 95% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=95.99$, $R_{T_2}=96.41$ min.

3-(Hex-1-yn-1-yl)-3-isopropylcyclohexanone (7c): ^{1}H NMR (400 MHz, $CDCl_3$): 2.50 (d, $J=2.04$ Hz, 1H), 2.34–2.32 (m, 1H), 2.20–2.05 (m, 5H), 2.00–1.89 (m, 2H), 1.60–1.50 (m, 2H), 1.45–1.30 (m, 4H), 1.00 (m, 6H), 0.87 ppm (t, $J=1.52$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=210.5$, 85.8, 80.8, 51.0, 44.5, 40.9, 37.3, 33.9, 31.2, 22.8, 21.8, 18.3, 18.1, 17.7,

13.6 ppm; HRMS (EI) calcd for $C_{15}H_{24}O$: 243.3402 $[M+Na]^+$; found: 243.3400; $[\alpha]_D^{25}=+56.8$ ($c=1$ in $CHCl_3$), 92% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=85.48$, $R_{T_2}=86.85$ min.

3-(Hex-1-yn-1-yl)-3-isobutylcyclohexanone (7d): ^{1}H NMR: (500 MHz, $CDCl_3$): 2.50 (d, $J=1.9$ Hz, 1H), 2.40–2.21 (m, 1H), 2.20–2.03 (m, 5H), 1.99–1.80 (m, 3H), 1.65–1.50 (m, 1H), 1.48–1.30 (m, 6H), 0.98–0.95 (m, 6H), 0.87 ppm (t, $J=7.25$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 210.0, 85.1, 82.7, 53.8, 51.1, 40.9, 39.9, 37.0, 31.0, 24.9, 24.66, 24.62, 22.6, 21.8, 18.3, 13.6 ppm; HRMS (EI) calcd for $C_{16}H_{26}O$ 257.1876 $[M+Na]^+$; found: 247.1876; $[\alpha]_D^{25}=+48.3$ ($c=1$ in $CHCl_3$), 95% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=90.44$, $R_{T_2}=90.74$ min.

3-(3,3-Dimethylbut-1-yn-1-yl)-3-ethylcyclohexanone (7f): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.43$–2.39 (m, 1H), 2.37–2.30 (m, 1H), 2.2–2.00 (m, 3H), 1.95–1.80 (m, 2H), 1.55–1.40 (m, 2H), 1.28–1.20 (m, 1H), 1.10 (s, 9H), 0.90 ppm (t, $J=7.32$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 210.0, 94.1, 80.4, 52.8, 41.0, 40.5, 35.9, 35.0, 31.3, 27.3, 22.8, 8.8 ppm; HRMS (EI) calcd for $C_{14}H_{22}O$: 229.1563 $[M+Na]^+$; found: 229.1561; $[\alpha]_D^{25}=+36.5$ ($c=1$ in $CHCl_3$), 79% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=116.03$, $R_{T_2}=116.50$ min.

3-(3,3-Dimethylbut-1-yn-1-yl)-3-isopropylcyclohexanone (7g): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.43$–2.39 (m, 1H), 2.37–2.30 (m, 1H), 2.20–2.10 (m, 2H), 2.09–2.00 (m, 1H), 1.98–1.85 (m, 2H), 1.65–1.55 (m, 1H), 1.52–1.48 (m, 1H), 1.10 (s, 9H), 0.96 ppm (q, $J=6.65$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): 210.4, 94.8, 79.1, 51.0, 44.1, 40.9, 37.1, 33.9, 31.3, 27.4, 22.7, 18.0, 17.6 ppm; HRMS (EI) calcd for $C_{15}H_{24}O$: 220.1827 $[M]^-$; found: 220.1830; $[\alpha]_D^{25}=+45.2$ ($c=1$ in CH_3Cl), 87% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=60.76$, $R_{T_2}=63.41$ min.

3-(3,3-Dimethylbut-1-yn-1-yl)-3-isobutylcyclohexanone (7h): ^{1}H NMR (500 MHz, $CDCl_3$): 2.40 (d, $J=13.25$ Hz, 1H), 2.36–2.33 (m, 1H), 2.23–2.10 (m, 2H), 1.95–1.80 (m, 3H), 1.55–1.45 (m, 1H), 1.40–1.30 (m, 2H), 1.10 (s, 9H), 0.96 ppm (t, $J=6.3$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$209.9, 93.9, 81.1, 53.8, 51.0, 40.9, 39.5, 37.0, 31.1, 31.0, 27.3, 24.9, 24.57, 24.56, 22.6 ppm; HRMS (EI) calcd for $C_{16}H_{26}O$: 257.1876 $[M+Na]^+$; found: 257.1879; $[\alpha]_D^{25}=+39.4$ ($c=1$ in CH_2Cl_2), 93% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=$ 68.92, $R_{T_2}=69.95$ min.

3-Isobutyl-3-[(trimethylsilyl)ethynyl]cyclohexanone (7j): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.50$–2.40 (m, 1H). 2.39–2.30 (m, 1H), 2.20–2.10 (m, 2H), 2.09–2.00 (m, 1H), 1.95–1.80 (m, 3H), 1.60–1.50 (m, 1H), 1.45–1.35 (m, 2H), 1.08–0.90 (m, 6H), 0.08 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.2. 109.6, 88.9, 53.2, 50.3, 40.8, 40.4, 36.6, 24.9, 24.53, 24.50, 22.4, 0.1 ppm; HRMS (EI) calcd for $C_{15}H_{26}OSi$: 273.1645 $[M+Na]^+$; found: 273.1648; $[\alpha]_D^{25}=+40.4$ ($c=1$ in CH_3Cl), 95% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=72.12$, $R_{T_2}=72.80$ min.

3-(But-3-enyl)-3-[2-(trimethylsilyl)ethynyl]cyclohexanone (7k): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.88$–5.78 (m, 1H), 5.75–5.06 (m, 2H), 2.50 (d, 1H, $J=12$ Hz), 2.38–2.35 (d, 1H, $J=12$ Hz), 2.24–2.02 (m, 5H), 1.97–1.90 (m, 2H), 1.63–1.54 (m, 3H), 0.10 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.0, 138.3, 114.7, 108.6, 89.2, 52.6, 40.9, 40.7, 35.9, 28.9, 22.5, 0.1 ppm; HRMS (EI) calcd for $C_{15}H_{24}OSi$: 247.1518 $[M-H]$; found: 247.1517; $[\alpha]_D^{20}=+34.9$ ($c=1$ in CH_3Cl), 91% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=76.32$, $R_{T_2}=76.97$ min.

(*S*)-3-Cyclohexyl-3-[2-(trimethylsilyl)ethynyl]cyclohexanone (7l): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.47$ (d, 1H, $J=12$ Hz), 2.36 (d, 1H, $J=$ 16 Hz), 2.21 (d, 1H, $J=16$ Hz), 2.09–2.05 (m, 2H), 1.96–1.91 (m, 2H), 1.86–1.77 (m, 4H), 1.67–1.53 (m, 3H), 1.27–1.10 (m, 6H), 0.11 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 210.0, 108.5, 89.7, 50.4, 46.6, 44.7, 41.0, 33.3, 35.9, 27.7, 27.4, 26.6, 26.55, 26.4, 22.5, 0.2 ppm; HRMS (ESI) calcd for $C_{15}H_{24}OSi$: 277.1982 $[M-H]$; found: 277.1985; $[\alpha]_D^{20}=+19.1$ ($c=1$ in CH_3Cl), 96% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (Hydrodex B-3P, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=96.05$, $R_{T_2}=96.62$ min.

(*R*)-3-Isobutyl-3-(2-phenylethynyl)cyclohexanone (7m): ^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.25 (m, 5H), 2.63 (d, $J=13.8$ Hz, 1H), 2.42 (d, $J=13.8$ Hz, 1H), 2.31–2.16 (m, 3H), 2.05–1.95 (m, 2H), 1.71–1.66 (m, 1H), 1.54–1.52 (m, 1H), 1.05–1.02 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 131.6, 128.2, 127.9, 123.4, 92.6, 85.1, 53.4, 50.7, 41.0, 40.4, 36.9, 26.7, 25.1, 24.6, 24.5, 22.7 ppm; HRMS (EI) calcd for $C_{18}H_{22}O$: 254.1671 $[M]^+$; found: 254.1673; $[\alpha]_D^{20}=+51.7$ ($c=1$ in CH_3Cl), 94% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=$ 111.10, $R_{T_2}=111.74$ min.

(*R*)-3-(But-3-enyl)-3-(2-phenylethynyl)cyclohexanone (7n): ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.35 (m, 2H), 7.28–7.27 (m, 3H), 5.82–5.81 (m, 1H), 5.05 (dd, 1H, $J=13.6$ Hz), 2.62 (d, $J=13.6$ Hz, 1H), 2.44–1.97 (m, 7H), 1.73–1.67 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 131.6, 128.3, 128.2, 123.2, 114.9, 91.7, 85.3, 52.8, 41.3, 41.0, 40.8, 36.2, 29.0, 27.0, 22.8 ppm; HRMS (EI) calcd for $C_{18}H_{20}O$: 251.1436 $[M-H]$; found: 251.1433; $[\alpha]_D^{20}=+50.4$ ($c=1$ in CH_3Cl), 95% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%–2–1–15, 5°C), $R_{T_1}=5.15$, $R_{T_2}=$ 5.67 min.

(*R*)-3-(But-3-enyl)-3-ethynylcyclohexanone (7o): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.85$–5.75 (m, 1H), 5.05–4.93 (m, 2H), 2.50 (d, $J=12.0$ Hz, 1H), 2.39–2.34 (m, 1H), 2.26–2.18 (m, 5H), 2.13–2.05 (m, 1H), 1.98–1.92 (m, 2H), 1.64–1.56 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.0, 138.0, 114.9, 86.3, 72.9, 52.6, 41.0, 40.9, 40.0, 35.8, 28.7, 22.5 ppm; HRMS (EI) calcd for $C_{12}H_{16}O$: 176.1201 $[M]^+$; found: 176.1189; $[\alpha]_D^{20}=+26.4$ ($c=1$ in CH_3Cl). The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=66.22$, $R_{T_2}=66.47$ min.

(*R*)-3-(But-3-enyl)-3-[4-(tetrahydro-2*H*-pyran-2-yloxy)but-1-ynyl]cyclohexanone (7p): ^{1}H NMR (400 MHz, $CDCl_3$): 5.87–5.77 (m, 1H), 5.05–4.94 (m, 2H), 4.61 (s, 1H), 3.88–3.83 (m, 1H), 3.78–3.72 (m, 1H), 3.52–3.44 (m, 2H), 2.48–2.35 (m, 3H), 2.24–2.04 (m, 5H), 1.95–1.90 (m, 2H), 1.85–1.78 (m, 1H), 1.73–1.47 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.5, 138.4, 114.6, 98.8, 83.1, 82.0, 66.1, 62.1, 53.0, 41.5, 41.0, 40.2, 36.2, 30.6, 28.9, 25.5, 22.7, 20.2, 19.4 ppm; HRMS (EI) calcd for $C_{19}H_{28}O_3$: 324.4136 $[M+Na]^+$; found: 324.4138; $[\alpha]_D^{20}=+50.4$ ($c=1$ in CH_3Cl), 96% *ee*. The enantiomeric excess was determined on the deprotected alcohol by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=39.67$, $R_{T_2}=40.39$ min.

(*R*)-3-(But-3-enyl)-3-(hex-1-ynyl)cycloheptanone (7q): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.86$–5.76 (m, 1H), 5.04–4.93 (m, 2H), 2.63–2.58 (m, 4H), 2.23–2.14 (m, 4H), 1.96–1.82 (m, 4H), 1.51–1.34 (m, 8H), 0.89 ppm (t, 3H, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 212.4, 138.5, 114.5, 85.8, 82.4, 55.0, 43.8, 43.1, 42.6, 36.7, 31.2, 29.2, 26.5, 24.1, 22.0, 18.4, 13.6 ppm; HRMS (EI) calcd for $C_{17}H_{26}O$: 245.1905 $[M-H]$; found: 245.1907; $[\alpha]_D^{20}=+84.0$ ($c=1$ in CH_3Cl), 97% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=96.45$, $R_{T_2}=96.76$ min.

(*S*)-3-(3,3-Dimethylbut-1-yn-1-yl)-3-methylcyclohexanone (7t): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.45$–2.35 (m, 1H), 2.33–2.27 (m, 1H), 2.20–2.02 (m, 2H), 1.99–1.79 (m, 2H), 1.70–1.55 (m, 2H), 1.20 (s, 3H), 1.10 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.7, 92.6, 82.0, 54.7, 40.6, 38.0, 35.9, 31.3, 30.3, 29.7, 22.9 ppm; HRMS (EI) calcd for $C_{13}H_{20}O$: 215.2870 $[M+Na]^+$; found: 215.2870; $[\alpha]_D^{25}=+27.3$ ($c=1$ in $CHCl_3$), 83% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}), $R_{T_1}=41.53$, $R_{T_2}=43.00$ min.

(*S*)-3-Methyl-3-[2-(triisopropylsilyl)ethynyl]cyclohexanone (7v): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.48$ (d, $J=13.7$ Hz, 1H), 2.39–2.32 (m, 1H), 2.26–2.08 (m, 3H), 1.97–1.88 (m, 2H), 1.64–1.60 (m, 8.3 Hz, 1H), 1.32 (s,

3H), 1.08–0.93 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): 208.9, 112.1, 83.1, 54.2, 40.5, 37.8, 37.0, 29.5, 22.8, 18.6, 11.1 ppm; HRMS (EI) calcd for $C_{18}H_{32}OSi$: 292.2222 $[M]^+$; found: 292.2225; $[\alpha]_D^{20}=+44.3$ ($c=1$ in CH_3Cl), 90% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=98.97$, $R_{T_2}=98.97$ min.

(*S*,*E*)-3-Ethyl-3-(oct-3-en-1-yn-1-yl)cyclohexenone (10a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.02$ (dt, $J=15.8$, 7.0 Hz, 1H), 5.41 (dt, $J=15.8$, 1.6 Hz, 1H), 2.48 (dt, $J=13.6$, 1.8 Hz, 1H), 2.40–2.33 (m, 1H), 2.26–2.16 (m, 2H), 2.10–2.01 (m, 3H), 1.98–1.87 (m, 2H), 1.63–1.48 (m, 3H), 1.36–1.23 (m, 4H), 0.99 (t, $J=7.4$ Hz, 3H), 0.87 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=209.8$, 144.3, 109.4, 90.1, 83.6, 52.5, 41.3, 41.1, 35.8, 34.9, 32.7, 30.9, 22.8, 22.3, 14.0, 9.0 ppm; $[\alpha]_D^{20}=+49.3$ ($c=1$ in CH_3Cl), 79% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (LIPODEX-E column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=75.9$, $R_{T_2}=77.01$ min.

(*S*,*E*)-3-Ethyl-3-(4-phenylbut-3-en-1-yn-1-yl)cyclohexenone (10b): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.36$–7.22 (m, 5H), 6.85 (d, $J=16.3$ Hz, 1H), 6.13 (d, $J=16.2$ Hz, 1H), 2.55 (dt, $J=13.6$, 1.9 Hz, 1H), 2.46–2.37 (m, 1H), 2.32–2.19 (m, 2H), 2.17–2.05 (m, 1H), 2.03–1.92 (m, 2H), 1.71–1.53 (m, 3H), 1.05 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=209.7$, 140.8, 136.5, 128.8, 128.5, 126.2, 108.3, 94.3, 84.1, 52.5, 41.7, 41.1, 35.8, 35.0, 22.9, 9.1 ppm; HRMS (EI) calcd for $C_{18}H_{20}O$: 252.1514 $[M]^+$; found: 252.1514; $[\alpha]_D^{20}=+55.7$ ($c=1$ in CH_3Cl), 83% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AS column, method: MeOH 0%–2–1–15, 5°C): $R_{T_1}=5.62$, $R_{T_2}=6.29$ min.

(*S*)-3-Ethyl-3-[(3*E*,5*E*)-hepta-3,5-dien-1-yn-1-yl]cyclohexenone (10c): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.32$ (dd, $J=15.6$, 10.7 Hz, 1H), 5.97–5.86 (m, 1H), 5.62 (td, $J=13.7$, 6.8 Hz, 1H), 5.30 (d, $J=15.6$ Hz, 1H), 2.41–2.31 (m, 1H), 2.25 (d, $J=15.0$ Hz, 1H), 2.15–2.05 (m, 3H), 1.86–1.78 (m, 2H), 1.63 (d, $J=6.7$ Hz, 3H), 1.49–1.39 (m, 3H), 0.88 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.7$, 141.6, 132.0, 131.0, 108.5, 93.5, 84.2, 52.4, 41.5, 41.0, 35.7, 34.9, 22.8, 18.4, 8.9 ppm; HRMS (EI) calcd for $C_{15}H_{20}O$: 216.1514 $[M]^+$; found: 216.1512; $[\alpha]_D^{20}=+39.9$ ($c=1$ in CH_3Cl), 87% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (DEX CB column, method: 140–100, 45 cm s^{-1}): $R_{T_1}=48.33$, $R_{T_2}=49.32$ min.

(*S*)-3-Ethyl-3-(phenylbuta-1,3-diyn-1-yl)cyclohexenone (10d): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.50$–7.27 (m, 1H), 2.57 (dt, $J=13.9$, 1.8 Hz, 1H), 2.48–2.37 (m, 1H), 2.31–2.19 (m, 1H), 2.16–1.93 (m, 1H), 1.74–1.54 (m, 1H), 1.05 ppm (t, $J=7.5$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=208.8$, 132.6, 129.1, 128.5, 128.4, 121.9, 86.1, 73.9, 69.1, 51.9, 41.8, 41.0, 35.5, 34.6, 22.7, 9.0 ppm; HRMS (EI) calcd for $C_{18}H_{18}O$: 250.1358 $[M]^+$; found: 250.1357; $[\alpha]_D^{20}=+56.2$ ($c=1$ in CH_3Cl), 77% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AS column, method: MeOH 0%–2–1–15, 5°C): $R_{T_1}=6.49$, $R_{T_2}=7.45$ min.

(*S*)-3-Ethyl-3-(4-methylpent-3-en-1-yn-1-yl)cyclohexenone (10e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.20$ (s, 1H), 2.49 (d, $J=13.6$ Hz, 1H), 2.40–2.33 (m, 1H), 2.26–2.16 (m, 2H), 2.15–2.01 (m, 1H), 1.98–1.88 (m, 2H), 1.81 (s, 3H), 1.74 (s, 3H), 1.59–1.51 (m, 3H), 1.01 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=209.8$, 147.8, 134.0, 105.1, 93.8, 82.9, 52.7, 41.6, 41.1, 35.9, 35.1, 24.8, 22.9, 20.9, 9.0 ppm; HRMS (EI) calcd for $C_{14}H_{20}O$: 204.1514 $[M]^+$; found: 204.1513; $[\alpha]_D^{20}=+59.6$ ($c=1$ in CH_3Cl), 87% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (Hydrodex B-3P, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=84.03$, $R_{T_2}=84.67$ min.

(*R*)-3-(But-3-enyl)-3-(4-methylpent-3-en-1-ynyl)cyclohexanone (10f): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.88$–5.78 (m, 1H), 5.21 (s, 1H), 5.06–4.94 (m, 2H), 2.52 (d, $J=12$ Hz, 1H), 2.40–2.35 (m, 1H), 2.27–2.19 (m, 4H), 2.16–2.07 (m, 1H), 1.99–1.93 (m, 2H), 1.82 (s, 3H), 1.76 (s, 3H), 1.66–1.59 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.4$, 148.0, 138.4, 114.7, 105.0, 93.4, 83.1, 53.0, 41.5, 41.0, 40.9, 36.3, 29.0, 24.7, 22.8, 20.9 ppm; HRMS (EI) calcd for $C_{16}H_{22}O$: 230.1671 $[M]^+$; found: 230.1659; $[\alpha]_D^{20}=+62.9$ ($c=1$ in CH_3Cl), 93% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (LIPODEX-E column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=92.30$, $R_{T_2}=92.89$ min.

(*S*)-1-(4-Methylpent-3-en-1-yn-1-yl)-[1,1′-bi(cyclohexan)]-3-one (10h): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.22$ (s, 1H), 2.52 (d, $J=13.4$ Hz, 1H), 2.41–2.33 (m, 1H), 2.26 (d, $J=13.4$ Hz, 1H), 2.23–2.01 (m, 2H), 2.00–1.93 (m, 2H), 1.91–1.84 (m, 2H), 1.82 (s, 3H), 1.81–1.76 (m, 2H), 1.75 (s, 3H), 1.69–1.55 (m, 2H), 1.27–1.07 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=210.4$, 147.6, 105.3, 93.3, 83.8, 50.9, 47.3, 44.9, 41.2, 33.8, 28.0, 27.7, 26.7, 26.6, 26.5, 24.8, 22.9, 21.0 ppm; HRMS (EI) calcd for $C_{18}H_{26}O$: 258.1984 $[M]^+$; found: 258.1984; $[\alpha]_D^{20}=+56.1$ ($c=1$ in CH_3Cl), 85% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%–2–1–15, 5°C, $R_{T_1}=5.11$, $R_{T_2}=5.57$ min.

(*S*)-3-Isopropyl-3-(4-methylpent-3-en-1-ynyl)cyclohexanone (10i): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.22$ (s, 1H), 2.53 (d, $J=16$ Hz, 1H), 2.39–2.35 (m, 1H), 2.25–2.09 (m, 3H), 1.99–1.94 (m, 2H), 1.82 (s, 3H), 1.76 (s, 3H), 1.72–1.55 (m, 2H), 1.03–0.98 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=210.2$, 147.6, 105.2, 92.5, 83.7, 51.0, 45.3, 40.9, 37.4, 34.0, 24.7, 22.8, 20.9, 18.2, 17.85 ppm; HRMS (EI) calcd for $C_{15}H_{22}O$: 218.1671 $[M]^+$; found: 218.1670; $[\alpha]_D^{20}=+75.5$ ($c=1$ in CH_3Cl), 90% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (HYDRODEX B-6-TBDM column, method: 60–0–1–170–5, 45 cm s^{-1}): $R_{T_1}=91.59$, $R_{T_2}=92.59$ min.

(*S*)-Spiro[4.5]dec-1-en-7-one (12): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.71$–5.69 (m, 1H), 5.56–5.54 (m, 1H), 2.39–2.30 (m, 5H), 2.23 (d, $J=13.5$ Hz, 1H), 1.97–1.77 (m, 3H), 1.69–1.62 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=211.5$, 137.6, 130.4, 53.8, 52.6, 41.3, 36.4, 35.2, 31.3, 23.6 ppm; HRMS (EI) calcd for $C_{10}H_{14}O$: 150.1045 $[M]^+$; found: 150.1044; $[\alpha]_D^{20}=-49.5$ ($c=1.485$ in $CHCl_3$).

7a-Ethyl-3,3a,5,6,7,7a-hexahydroinden-4-one (17): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.72$ (d, $J=11.0$ Hz, 1H), 5.51–5.44 (m, 1H), 2.60–2.51 (m, 2H), 2.48 (dd, $J_1=2.0$, $J_2=18.0$ Hz, 1H), 2.37–2.30 (m, 1H), 2.21 (d, $J=18.0$ Hz, 1H), 2.11–1.93 (m, 3H), 1.65–1.58 (m, 1H), 1.38 (q, $J=7.5$ Hz, 2H), 0.88 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=216.1$, 138.6, 127.1, 52.1, 46.5, 36.5, 36.1, 35.4, 34.1, 24.7, 8.2 ppm; HRMS (EI) calcd for $C_{11}H_{16}O$: 164.1201 $[M]^+$; found: 164.1202; $[\alpha]_D^{20}=+53.19$ ($c=0.97$ in $CHCl_3$).

(*R*,*E*)-10-Ethyl-10-(prop-1-enyl)spiro[4.5]dec-2-en-6-one (18): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.60$–5.57 (m, 1H), 5.50–5.46 (m, 1H), 5.39–5.31 (dq, $J_1=6.5$, $J_2=16.0$ Hz, 1H), 5.16 (dd, $J_1=1.5$, $J_2=16.0$ Hz, 1H), 3.05–2.98 (m, 1H), 2.66–2.60 (m, 1H), 2.49 (dd, $J_1=2.0$, $J_2=14.0$ Hz, 1H), 2.32 (m, 1H), 2.26 (d, $J=14.0$ Hz, 1H), 2.00 (m, 1H), 1.77–1.60 (m, 8H), 1.33 (q, $J=7.5$, 2H), 0.77 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=216.1$, 136.6, 128.9, 126.9, 125.1, 54.9, 47.5, 44.3, 42.5, 41.3, 35.4, 34.0, 32.4, 18.4, 8.0 ppm; HRMS (EI) calcd for $C_{15}H_{22}O$: 218.1671 $[M]^+$; found: 218.1671; $[\alpha]_D^{20}=+3.11$ ($c=1.57$ in $CHCl_3$).

(*S*)-2-Allyl-3-ethyl-3-[2-(trimethylsilyl)ethynyl]cyclohexanone (19): ^{1}H NMR (500 MHz, $CDCl_3$) for the major diastereoisomer: $\delta=5.96$–5.75 (m, 1H), 5.05–4.91 (m, 2H), 2.66–2.56 (m, 1H), 2.42–2.36 (m, 1H), 2.28–2.20 (m, 2H), 2.04–1.87 (m, 4H), 1.77–1.63 (m, 2H), 1.53 (m, 1H), 0.98 (t, $J=7.4$ Hz, 3H), 0.12 ppm (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.9$, 137.7, 115.3, 107.9, 89.4, 58.2, 45.4, 40.8, 33.9, 32.0, 29.7, 22.9, 8.7, 0.1 ppm; HRMS (EI) calcd for $C_{16}H_{26}OSi$: 262.1753 $[M]^+$; found: 262.1753.

(*S*)-2-Benzyl-3-ethyl-3-[2-(trimethylsilyl)ethynyl]cyclohexanone (20): ^{1}H NMR (400 MHz, $CDCl_3$) for the major diastereoisomer: $\delta=7.27$–7.10 (m, 5H), 3.30–3.21 (m, 1H), 2.76 (dd, $J=14.3$, 2.6 Hz, 1H), 2.51 (dd, $J=9.1$, 2.5 Hz, 1H), 2.44–2.40 (m, 1H), 2.24–2.14 (m, 1H), 2.06–1.82 (m, 4H), 1.72–1.55 (m, 2H), 1.02 (t, $J=7.4$ Hz, 3H), 0.16 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.3$, 141.8, 129.1, 128.3, 125.8, 107.8, 89.7, 60.5, 46.1, 41.2, 34.4, 32.5, 30.8, 23.2, 8.8, 0.2 ppm; HRMS (EI) calcd for $C_{20}H_{28}OSi$: 312.1909 $[M]^+$; found: 312.1907.

(*S*)-3-Ethyl-3-[2-(trimethylsilyl)ethynyl]-2-[3-(trimethylsilyl)prop-2-ynyl]-cyclohexanone (21): ^{1}H NMR (500 MHz, $CDCl_3$) for the major diastereoisomer: $\delta=2.96$ (m, 1H), 2.53–2.50 (m, 1H), 2.46–2.42 (m, 1H), 2.35–2.28 (m, 1H), 2.27–2.21 (m, 1H), 2.02–1.91 (m, 4H), 1.88–1.83 (m, 1H), 1.71–1.63 (m, 1H), 1.01 (t, $J=7.4$ Hz, 3H), 0.11 (s, 9H), 0.10 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 207.5, 107.1, 106.8, 90.2, 84.5, 57.7, 46.5, 41.0, 34.5, 32.5, 23.1, 15.6, 8.9, 0.1 ppm; HRMS (EI) calcd for $C_{19}H_{32}OSi_2$: 332.1991 $[M]^+$; found: 332.1991.

(*R*)-1-Vinylspiro[4.5]dec-1-en-7-one (22): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25–6.18 (dd, 1H, J_1 = 12.0, J_2 = 16.0 Hz), 5.79 (s, 1H), 5.44 (d, 1H, J = 16.0 Hz), 5.09 (d, J = 12.0 Hz, 1H), 2.56 (d, J = 16.0 Hz, 1H), 2.37–2.24 (m, 4H), 2.12–1.99 (m, 3H), 1.84–1.72 (m, 2H), 1.69–1.62 (m, 1H), 1.53 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 146.9, 130.5, 128.2, 115.1, 53.8, 50.3, 41.3, 35.4, 34.4, 29.4, 23.3 ppm; HRMS (EI) calcd for $C_{12}H_{16}O$: 176.1201 $[M]^+$; found: 176.1200; $[\alpha]_D^{20} = -43.8$ (c = 1 in CH_3Cl).

(*R*)-Dimethyl-3-oxo-2′,3′-dihydrospiro(cyclohexane-1,1′-indene)-4′,5′-dicarboxylate (24): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.95 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 13.8 Hz, 1H), 2.45–2.41 (m, 2H), 2.36 (d, J = 13.8 Hz, 1H), 2.10–2.03 (m, 2H), 1.97 (q, J_1 = 13.8, J_2 = 6.8 Hz, 2H), 1.91–1.86 (m, 1H), 1.77–1.73 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 210.1, 169.0, 166.7, 154.3, 141.7, 131.3, 128.9, 127.9, 123.8, 52.6, 52.3, 52.2, 51.8, 41.2, 36.5, 35.5, 28.5, 22.9. HRMS (EI) calcd for $C_{12}H_{16}O$: 339.12029 $[M+Na]^+$; found: 339.12010; $[\alpha]_D^{20} = -25.2$ (c = 1 in CH_3Cl); $[\alpha]_D^{20} = -25.6$ (c = 1 in CH_3Cl), 92% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AD column, method: MeOH 0%–2–1–15, 5°C): R_{T_1} = 10.30, R_{T_2} = 11.86 min.

(1*R*)-3a′,4′-Dihydro-2′*H*-spiro(cyclohexane-1,1′-pentalene)-3,5′(3′*H*)-dione (25): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (s, 1H), 5.80 (s, 1H), 3.05–3.03 (m, 2H), 2.63–2.56 (m, 2H), 2.50–2.28 (m, 8H), 2.19–2.04 (m, 5H), 2.01–1.78 (m, 11H), 1.26–1.16 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.35, 210.24, 209.54, 209.00, 194.58, 194.29, 124.60, 123.23, 52.07, 51.10, 46.83, 46.61, 45.14, 44.79, 42.71, 42.63, 41.01, 41.00, 39.46, 37.64, 36.17, 34.21, 29.46, 29.29, 23.78, 23.08 ppm; $[\alpha]_D^{20} = -22.5$ (c = 1 in CH_3Cl), 90% *ee*. The enantiomeric excess was determined by chiral GC on a chiral stationary phase (LIPODEX-E column, method: 60–0–1–170–20, 45 cm s^{-1}): 1st diastereoisomer: R_{T_1} = 112.07, R_{T_2} = 113.88 min; 2nd diastereoisomer: R_{T_1} = 115.56, R_{T_2} = 116.91 min.

(*R*)-3-[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]-3-(but-3-enyl)cyclohexanone (26): ^{1}H NMR (500 MHz, DMSO): δ = 8.69 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 5.80–5.75 (m, 1H), 5.00–4.91 (m, 2H), 2.84 (d, J = 14 Hz, 1H), 2.59 (d, J = 14 Hz, 1H), 2.43–2.30 (m, 1H), 2.28–2.25 (m, 2H), 2.06–2.01 (m ,1H), 1.93–1.73 (m, 5H), 1.67–1.62 ppm (m, 1H); ^{13}C NMR (126 MHz, DMSO): δ = 210.42, 153.57, 139.33, 136.82, 133.67, 122.63, 121.94, 121.18, 115.58, 51.07, 42.50, 41.14, 41.04, 34.75, 28.51, 22.19 ppm; $[\alpha]_D^{20} = +26.4$ (c = 1 in CH_3Cl), 96% *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AD column, method: MeOH 0%–2–1–15, 5°C): R_{T_1} = 18.48, R_{T_2} = 19.71 min.

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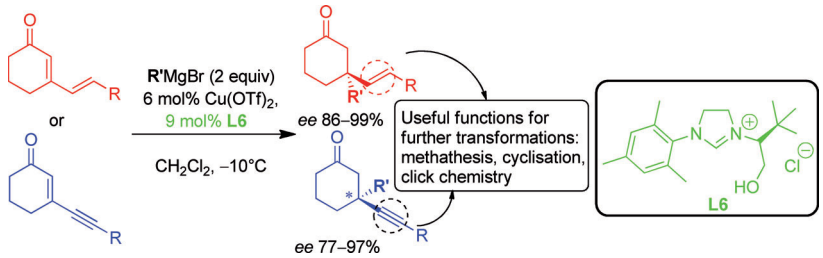
Asymmetric Synthesis

M. Tissot, D. Poggiali, H. Hénon, D. Müller, L. Guénée, M. Mauduit,* A. Alexakis** ..... ▮▮▮▮–▮▮▮▮

VIP

Formation of Quaternary Stereogenic Centers by NHC–Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Polyconjugated Cyclic Enones



Along came poly: The copper-catalyzed conjugate addition of Grignard reagents to polyconjugated cyclic enones allows for the formation of all-carbon chiral quaternary centers (see scheme). An *N*-heterocyclic carbene (NHC) acts as an efficient chiral ligand for this transformation. High enantioselectivities (up to 99%) and regioselectivities (1,4 selectivity) were obtained for a broad range of substrates and nucleophiles.

