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Enantio- and Regioselective Conjugate Addition of Organometallic Reagents to Linear Polyconjugated Nitroolefins

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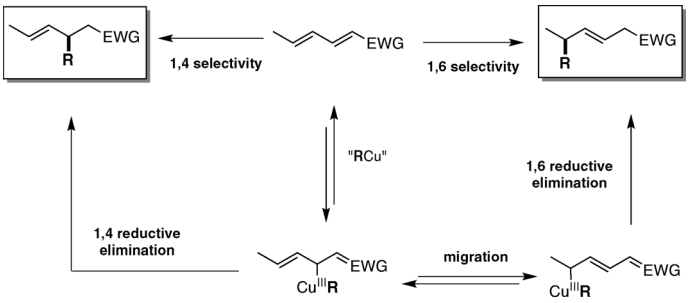
Abstract: The copper-catalysed conjugate addition of trialkylaluminium and dialkylzinc reagents to polyconjugated nitroolefins (nitrodiene and nitroenyne derivatives) is reported. A reversed Josiphos ligand **L7** allows for the selective 1,4- or 1,6-addition with high enantioselectivities.

Keywords: asymmetric catalysis · conjugate addition · copper · ligand effects · phosphine ligands

Introduction

In the field of copper-catalysed asymmetric conjugate addition (ACA), many methodologies have been developed towards a variety of activated alkenes, allowing for the formation of tertiary and quaternary carbon stereocentres.[1] Stereoselectivity and regioselectivity are two important factors in this transformation. Use of appropriate reaction conditions, as well as the correct choice of catalyst are essential for a successful reaction profile. Recent reports on ACA have documented the development of enantioselective conjugate addition to polyconjugated substrates.[2] In particular, the issue of regioselectivity has been emphasised because of the presence of several electrophilic sites allowing for 1,2-, 1,4-, 1,6- or even 1,8-addition reactions. In the first example, as reported by Fillion, 1,6-addition of diorganozinc to diactivated Meldrum's acid has been detailed.[3] Two years later, Feringa achieved a similar 1,6-selectivity for the addition of methylmagnesium bromide to dienoates, displaying an excellent level of regio- and enantioselectivity.[4] Furthermore, Mauduit and Alexakis developed the addition of diorganozinc reagents to cyclic dienones by using a Cu–diphenylphosphinoazomethinylate salt (DIPPAM) complex. This methodology afforded exclusively the 1,6-adducts with excellent enantioselectivities.[5] The preference for the 1,6-selectivity appeared to concur with the general trend observed by Naef, Krause and others.[6] Nakamura and Krause have explored the mechanism of the ACA of organocopper reagents to polyconjugated carbonyls.[7,8] Density function calculations have also been performed to rationalise the preference of lithium organocuprate (R_2CuLi) towards the formation of the remote 1,6-conjugate addition product with polyconjugated carbonyl compounds. Calculations indicated that 1,4-reductive elimination of the copper(III) intermediate is kinetically disfavoured compared with migration to the 6-position. This result could be explain by the loss of conjugation due to reductive elimination at the 4-position, which could suggest that the migration is the rate-determining step.

In 2008, we discovered that the selectivity can be altered in favour of 1,4-addition. Indeed, we reported that the combined use of a NHC ligand and $Cu(OTf)_2$ as the catalyst allowed for the conjugate addition of Grignard reagents to cyclic dienones with 1,4-selectivity, leading to the formation of enantioenriched quaternary stereogenic centres.[9] The efficiency of this methodology has also been demonstrated with a variety of polyconjugated cyclic enones (enynones, trienones), allowing for the formation of valuable synthons.[10] This selectivity outcome has been previously observed by Yamamoto, who reported that the use of an organocopper reagent ($RCu{\cdot}BF_3$) led to 1,4-addition with acyclic dienoate.[11] The 1,4- and 1,6-selectivities observed with copper reagents suggest that copper encourages a regiodivergent process as a result of migration of the copper complex (Scheme 1).



Scheme 1. Regiodivergence with copper reagents.

Furthermore, Krause observed that Gilman cuprates display an unusual 1,4-selectivity with nitroenynes.[12] This type of substrate has been studied by the Alexakis group in the context of organocatalytic reactions.[13]

Nitroolefins have also been shown to be valuable substrates for copper-catalysed ACA.[14] In 2010, we revealed

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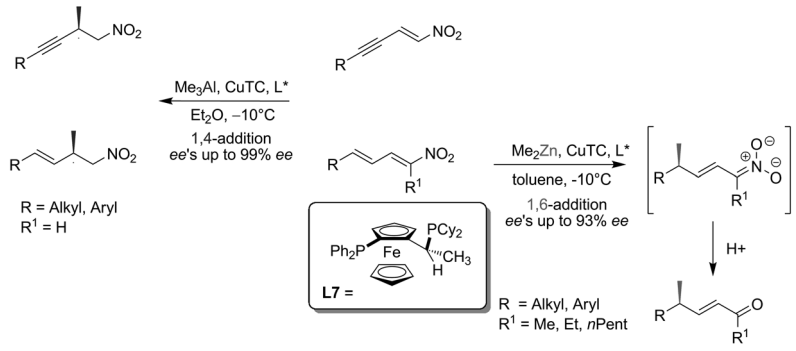
the first conjugate addition of trimethylaluminium to polyconjugated nitroolefins leading to the exclusive formation of the 1,4-adduct.[15] A reversed Josiphos ligand **L7** in combination with CuTC gave high enantioselectivities.

Interestingly, the use of nitrodienoates led to 1,6-addition. In this report we detail the full extent of this work, including improvements to enantioselectivity for the 1,4-addition and the development of a 1,6-selective ACA of dimethylzinc (Scheme 2).

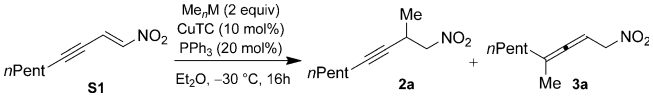


Scheme 2. Summary of the study.

Results and Discussion

1,4-Selective conjugate addition: We first screened three organometallic reagents to evaluate their reactivity and regioselectivity with nitroenyne **S1**. Triphenylphosphine and CuTC were used as catalyst, and the reactions were performed in Et_2O at −30 °C (Table 1). These preliminary experiments revealed the exclusive 1,4-addition of the Grignard reagent, delivering the adduct **2a**, whereas trimethylaluminium afforded a mixture of regioisomers, with a preference for the 1,4-adduct (Table 1, entries 1 and 2). This trend seems to relate to the hardness of the metal: Zn leads tend towards 1,6-addition, whereas the harder Mg provides exclusively the 1,4 adduct. This trend has already been observed with dienones and enynones.[10b]

Table 1. Screening of Organometallic reagents.



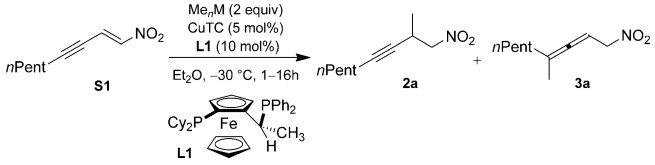
Entry	Me_nM	Conv. [%][a]	**2a**/**3a**[a]
1	MeMgBr	100	100:0
2	Me_3Al	100	68:31
3	Me_2Zn	100	18:82

[a] Determined by GC-MS analysis.

Finally, dimethylzinc reacted mainly in a 1,6-addition fashion, producing allene **3a** (Table 1, entry 3). These results highlighted a difference in terms of regioselectivity that was dependent on the nature of the organometallic reagents.

We decided to examine this reaction further in the presence of a chiral ligand. We first tested the Josiphos ligand **L1**, which has demonstrated excellent regio- and enantiocontrol in the addition of Grignard reagents to dienoates (Table 2).[4] As observed previously, methylmagnesium bromide displayed perfect selectivity in favour of the 1,4-adduct **2a**. However, no enantioselectivity was detected in the presence of chiral ligand **L1** (Table 2, entry 1). We continued with dimethylzinc and detected almost an equal amount of 1,4- and 1,6-addition products. High enantioselectivity was detected for the 1,4-adduct (86% *ee*), whereas, no enantioselectivity was recorded for the allene compound **3a** derived from 1,6-addition (Table 2, entry 2). This outcome could be due to the ease of racemisation of allenes in the presence of organocopper or cuprate catalytic species.[16] We persevered with trimethylaluminium, and found that exclusive 1,4-addition took place with a good enantioselectivity of 86% *ee*. These results highlight the influence that the ligand has on the regiocontrol of the reaction that favoured the 1,4-addition process. However, the reaction did not go to completion, even after 16 h (Table 2, entry 3). Increasing the reaction temperature to −10 °C led to a quantitative reaction with an enantioselectivity of 87% *ee* (Table 2, entry 4).

Table 2. Organometallic screening for the ACA to nitroenyne **S1**.



Entry	Me_nM	Conv. [%][a]	**2a**/**3a**[a]	*ee* **2a**/**3a** [%][b]
1	MeMgBr	100	100:0	0:–
2	Me_2Zn	100	42:58	86:0
3	Me_3Al	27	100:0	86:–
4[c]	Me_3Al	100	100:0	87:–

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Reaction performed at −10 °C.

With the encouraging regioselective and enantioselective results obtained with trimethylaluminium, we carried out a screening of ferrocene-based phosphine ligands (Figure 1). Other types of phosphorus ligands, such as phosphoramidites were evaluated, however, they did not demonstrate high enantiocontrol. The phosphorus atom directly attached to the cyclopentadiene cycle is defined as $\mathbf{P^1}$ and the second as $\mathbf{P^2}$. We initiated our study with ligand **L2**, which differs from **L1** by the substituents on the $\mathbf{P^2}$ phosphorus atom. In particular, the presence of a cyclohexyl group instead of phenyl substituents results in increased electron density on the phosphorus atom ($\mathbf{P^2}$). The 1,4-addition dominated in

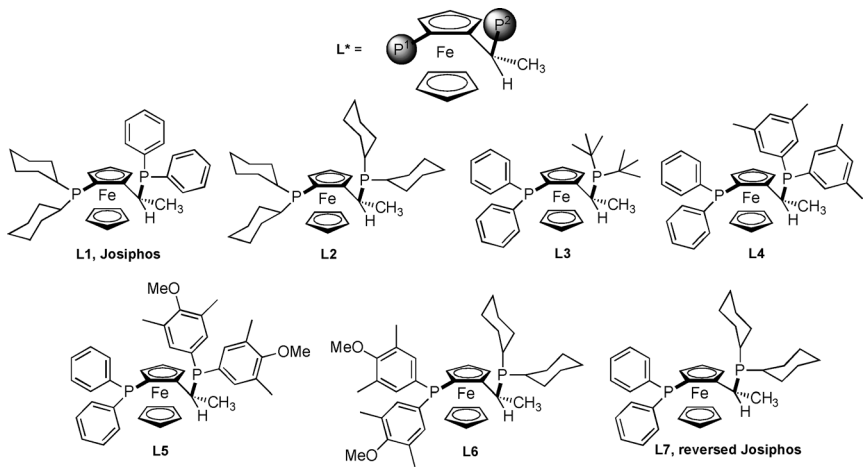
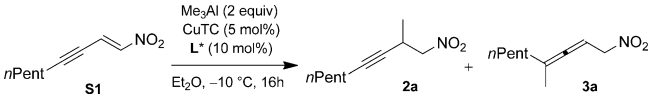


Figure 1. Selected ferrocene-based phosphine ligands.

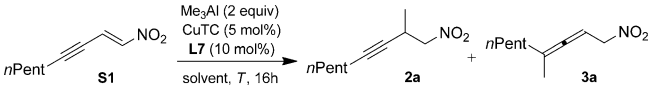
Table 3. Screening of ferrocene-based phosphine ligands.



Entry	L*	Conv. [%][a]	**2a**/**3a**[a]	*ee* **2a** [%][b]
1	**L1**	100	100:0	86
2	**L2**	100	94:6	62
3	**L3**	97	100:0	65
4	**L4**	62	99:1	60
5	**L5**	100	94:6	14
6	**L6**	100	100:0	92
7	**L7**	98	100:0	95

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

Table 4. Optimisation of the reaction conditions.



Entry	Solvent	*T* [°C]	Conv. [%][a]	**2a**/**3a**[a]	*ee* **2a** [%][b]
1	Et_2O	−10	100	100:0	95
2[c]	Et_2O	−10	100	100:0	95
3	CH_2Cl_2	−10	100	100:0	9
4	THF	−10	100	100:0	94
5	THF	−30	100	100:0	94
6[c]	THF	−78	100	100:0	99

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Reaction performed with CuTC/**L7** = 5:5.25 mol% in 10 min.

this reaction, with a small amount of 1,6-addition product being observed. However, a drop in enantioselectivity was also observed, with a final enantiomeric excess of 62% being observed (Table 3, entry 2). We then tested ligand **L3**, with phenyl (**P**^{1}) and *tert*-butyl (**P**^{2}) substituents. A unique 1,4-addition was detected with a moderate 65% *ee* (Table 3, entry 3). Ligands **L4** and **L5**, despite being quite similar in structure, differed greatly in terms of enantioselectivity, affording 60 and 14% *ee*, respectively (Table 3, entries 4 and 5).

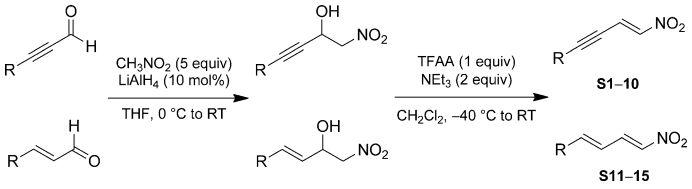
With ligand **L6**, an excellent enantioselectivity of 92% *ee* was observed. This result was further improved through the use of the reversed Josiphos ligand **L7**, which delivered an enantiomeric excess reaching 95% (Table 3, entry 7).

This screening of ligands was particularly difficult to interpret, however, despite highlighting the importance of the right combination of substituents on **P**^{1} and **P**^{2}. The best ligands **L6** and **L7**, possessed the same cyclohexyl substituents on the **P**^{2} atom, and an aromatic substituent on **P**^{1}. Nevertheless, at this point it was difficult to conclude whether enantioselectivity was induced by steric or electronic factors.

With the best ligand **L7** in hand, we examined the reaction conditions for this transformation in terms of solvent, temperature and catalyst loading. First, it was found that the ratio of CuTC/**L7** could be reduced to 5:5.25 without loss of enantioselectivity (Table 4, entry 2). Solvent screening indicated that use of dichloromethane gave a significant drop in terms of enantioselectivity, displaying only 9% *ee*, whereas use of tetrahydrofuran (THF) afforded an excellent enantioselectivity of 94% *ee*, which was almost as high as that obtained with diethyl ether (Table 4, entries 3 and 4). As demonstrated in Table 2, when the reaction was performed at −30°C in diethyl ether, the reaction did not go to completion. However, in THF, the reaction proceeded quantitatively with the same level of enantioselectivity being observed to that when the reaction was performed at −10°C (Table 4, entry 5). Furthermore, excellent enantioselectivity was observed when the reaction was performed at −78°C in THF (99% *ee*, Table 4, entry 6).

To conclude this section, we want to add that, following a screening of ligands, ligand **L7** gave the best results for this highly regio- and enantioselective 1,4-addition to nitroenynes. Two sets of conditions were developed and these were used in the subsequent studies described below. Conditions A involved the use of Et_2O as solvent at a temperature of −10°C, whereas conditions B involved the use of THF at −78°C.

For the next section, we describe our endeavours to validate the optimised reaction conditions for the addition of a variety of trialkyaluminium reagents and several nitroenynes, nitrodienes analogues and classical nitro-olefins. The reaction conditions used to synthesise the polyconjugated nitro-olefins (nitroenynes/nitrodienes) have already been optimised in our laboratory.[13] Initially, a Henry reaction between α,β-unsaturated aldehydes and nitromethane, catalysed by lithium aluminium hydride, afforded the nitro-alco-



Scheme 3. Synthesis of polyconjugated nitro-olefins.

hols.[17] Subsequent dehydration produced the polyconjugated Michael acceptors (**S1**–**S15**; Scheme 3).

Having synthesised a library of nitroenynes (Figure 2), we applied two sets of reaction conditions using the reversed Josiphos ligand **L7**. First, we successfully reproduced our

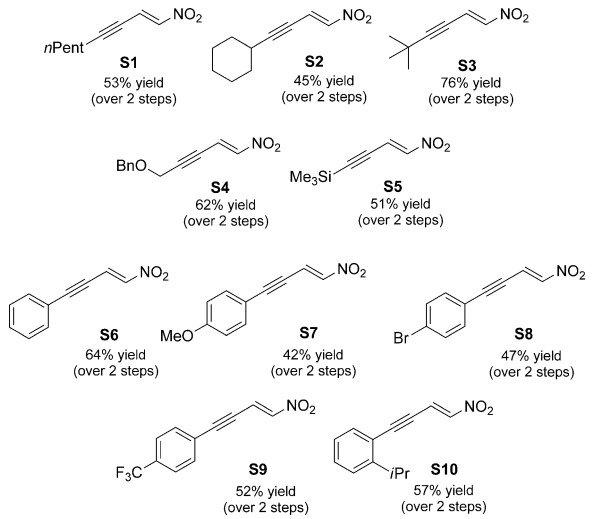


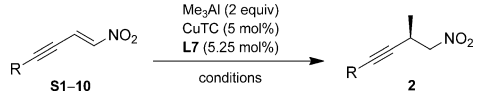
Figure 2. Nitroenynes **S1**–**10**.

two previous results with the aliphatic nitroenyne **S1** and, as demonstrated before, conditions B (using THF) afforded the best *ee* of 99%. Under conditions A, the enantioselectivity reached 95% *ee* (Table 5, entries 1 and 2). Both conditions promoted formation of the 1,4-adduct in good yield of up to 68%.

We further pursued the use of aliphatic substrates **S2**–**4** under conditions A. Perfect regioselectivities were observed in favour of the 1,4-adduct, with the degree of enantioselectivity ranging from 90 to 95% *ee* (Table 5, entries 3–5). The reaction with nitroenyne **S5**, bearing a trimethylsilyl (TMS) substituent, was carried out under both conditions. When the reaction was performed in Et_2O at −10°C (conditions A), 95% *ee* was reached, whereas in THF at −78°C (conditions B), the enantioselectivity increased to 99% *ee* (Table 5, entries 6 and 7). We continued our investigation with aromatic nitroenynes, such as **S6**. Again, use of conditions B gave the best enantioselectivities (up to 97% *ee*; Table 5, entries 8 and 9).

When an electron-rich aromatic system was probed through the use of the *p*-OMe substituted substrate **S7**, the enantioselectivity dropped to 83% *ee* under conditions A, whereas use of conditions B gave 90% *ee* (Table 5, entries 10 and 11).

Table 5. Scope of the reaction with nitroenynes **S1**–**10**.

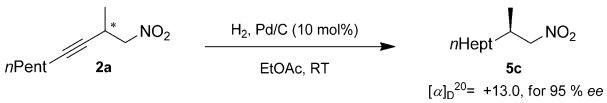


Entry	Substrate	Cond.[c]	Prod.	Conv. [%][a]	Yield [%]	*ee* **2** [%][b]
1	**S1**	A	**2a**	100	56	95
2	**S1**	B	**2a**	100	68	99
3	**S2**	A	**2b**	100	74	90
4	**S3**	A	**2c**	100	55	95
5	**S4**	A	**2d**	100	65	93
6	**S5**	A	**2e**	100	69	95
7	**S5**	B	**2e**	100	66	99
8	**S6**	A	**2f**	100	70	94
9	**S6**	B	**2f**	100	59	97
10	**S7**	A	**2g**	100	54	83
11	**S7**	B	**2g**	100	60	90
12	**S8**	A	**2h**	100	64	95
13	**S9**	A	**2i**	100	52	90
14	**S9**	B	**2i**	100	49	94
15	**S10**	A	**2j**	100	62	88

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Conditions A: Et_2O, −10°C; conditions B: THF, −78°C.

We then examined the use of substrates with electron-poor aromatic substituents. Under conditions A, *p*-bromophenyl-substituted nitroenyne **S8** afforded 95% *ee* (Table 5, entry 12). We next tested substrate **S9**, with a *p*-trifluoromethylphenyl substituent, and found that 90% *ee* was achieved under conditions A, and this was increased to 94% *ee* under conditions B (Table 5, entries 13 and 14). Finally, the scope of the reaction was further examined with substrate **S10**, bearing an isopropyl group at the *ortho* position. Surprisingly, with this substrate, the *ee* dropped to 88% under conditions A, probably as a result of steric hindrance (Table 5, entry 15).

To determine the absolute configuration of the conjugate adduct, **2a** was converted into compound **5c** upon hydrogenation. The *R* configuration was established by comparison of the optical rotation of **5c** to the previously reported value for this compound (Scheme 4).[18]

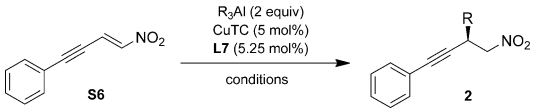


Scheme 4. Determination of the absolute configuration of **2a**.

We then proceeded to include a variety of trialkylaluminium reagents. First, when triethylaluminium was tested under conditions A, exclusive 1,4-addition was achieved, albeit with a moderate 62% *ee* (Table 6, entry 1). Under conditions B, the reaction did not proceed (Table 6, entry 2), demonstrating a significant difference in reactivity potential between trimethyl- and triethylaluminium reagents. Increasing the temperature to −50°C gave the 1,4-adduct with 53% *ee* (Table 6, entry 3).

We decided to continue our study of the nucleophiles with **S6** under conditions A. By using tri-*n*-butyl- and tri-*n*-

Table 6. ACA of trialkylaluminium reagents to nitroenyne **S6**.



Entry	R	Cond.[c]	Prod.	Conv. [%][a]	Yield [%]	*ee* **2** [%][b]
1	Et	A	**2k**	100	53	62
2	Et	B	**2k**	0	–	–
3	Et	B[d]	**2k**	100	–	53
4	*n*Bu	A	**2l**	100	65	71
5	*n*Pr	A	**2m**	100	68	60
6	*i*Bu	A	**2n**	100	55	6

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Conditions A: Et_2O, −10 °C; conditions B: THF, −78 °C. [d] Reaction performed at −50 °C.

propylaluminium, product **2** was obtained in 71 and 60 % *ee*, respectively (Table 6, entries 4 and 5). Finally, use of the triisobutylaluminium reagent led to almost complete loss of asymmetric induction. Others have already reported the detrimental effect of using highly hindered trialkylaluminium reagents in ACA employing nitroalkenes as Michael acceptors.[19]

We then turned our attention to nitrodienes as polyconjugated nitro-olefins. Substrates **S11–15** were synthesised by using the same reaction conditions used for nitroenynes (Figure 3). First, nitrodiene **S11** was examined under conditions A and it was found that the reaction afforded exclusively the 1,4-adduct **4a** with 88 % *ee* (Table 7, entry 1), which allowed for preferential enantiocontrol with the nitroenyne analogue **S6** (95 % *ee* under conditions A).

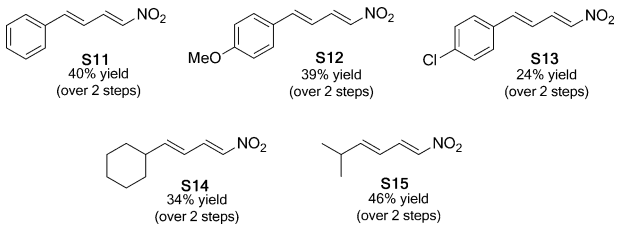


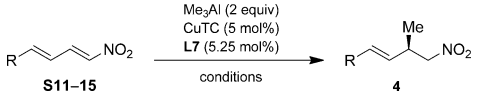
Figure 3. Nitrodienes **S11–15**.

We also examined the reaction under conditions B, however, no reaction was observed (Table 7, entry 2). When the reaction was performed at −30 °C in THF, an 81 % *ee* was detected (Table 7, entry 3). Conversely, with nitroenynes, use of conditions A led to higher enantioselectivity.

The enantioselectivities observed with nitroenynes and nitrodienes were some of the best results that have been achieved in the ACA to nitro-olefins, according to the literature.[14] These reports encouraged us to test two sets of conditions with simple nitro-olefins, which were either commercially available or prepared in our laboratory (Table 8).

Initial attempts, using nitrostyrene **S16** under conditions A, led to a surprisingly low enantioselectivity of only 53 % *ee*, and the application of conditions B did not result in any reaction (Table 8, entries 1 and 2). A low enantioselectivity (24 % *ee*) was also reported with **S17**, bearing a cyclohexyl group. However, using the *n*-heptyl-substituted nitroolefin **S18**, afforded a good enantioselectivity of 82 % *ee*. Determination of the optical rotation of 1,4-adduct **5c** confirmed that the absolute configuration was *R* ($[\alpha]_D^{20} = +4.6$), by comparison with literature data.[18] This information indicated that, under the same catalytic conditions, facial attack of the nucleophilic species is the same for nitroenynes (Scheme 4) and nitrolefins. We hypothesised that with nitrodienes, the same facial approach is favoured.

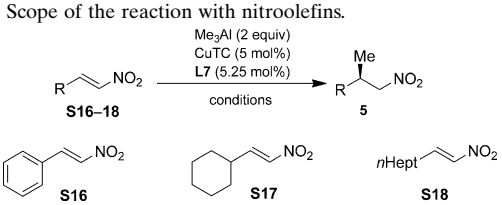
Table 7. Scope of the reaction with nitrodienes.



Entry	Substrate	Cond.[c]	Prod.	Conv. [%][a]	Yield [%]	*ee* **4** [%][b]
1	**S11**	A	**4a**	100	70	88
2	**S11**	B	**4a**	0	–	–
3	**S11**	B[d]	**4a**	80	n.d.[e]	81
4	**S12**	A	**4b**	100	50	77
5	**S13**	A	**4c**	100	55	84
6	**S14**	A	**4d**	100	59	90
7	**S15**	A	**4e**	100	67	90

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Conditions A: Et_2O, −10 °C; conditions B: THF, −80 °C. [d] Reaction performed at −30 °C. [e] n.d. = not determined.

Table 8. Scope of the reaction with nitroolefins.

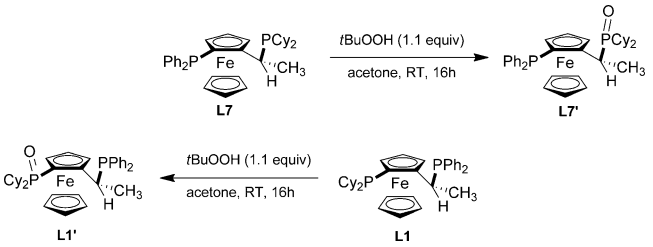


Entry	Substrate	Cond.[c]	Prod.	Conv. [%][a]	*ee* **5** [%][b]
1	**S16**	A	**5a**	100	53
2	**S16**	B	**5a**	0	–
3	**S17**	A	**5b**	100	24
4	**S18**	A	**5c**	100	82

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Conditions A: Et_2O, −10 °C; conditions B: THF, −78 °C.

Charette reported that use of the Me-Duphos monoxide ligand was very effective in the enantioselective copper-catalysed conjugate addition of dialkylzinc reagents to nitroalkenes.[14h] Interestingly, he demonstrated that use of the hemilabile Me-Duphos monoxide ligand led to good stereocontrol, although, conversely, the nonoxidised ligand displayed no enantioselectivity. To test this hemilability concept, we synthesised the monoxide ligands of **L1** and **L7** (Scheme 5).

We then applied the four ligands **L1**, **L1′**, **L7** and **L7′** in the addition of trimethylaluminium to nitroenyne **S3** under reaction conditions A (Table 9). Our first observation was that **L1** and **L7** displayed stereocontrol, whereas the *ee* was zero for the oxidised ligands **L1′** and **L7′**. Consequently, we did not observe a positive hemilability effect as described by Charette. Moreover, this observation highlighted that stereoselectivity required two chelating phosphorus atoms (**P1**



Scheme 5. Mono-oxidation of **L1** and **L7**.

and **P2**). This also appeared to be important for the reactivity, because very low conversion was obtained after one hour with the oxidised ligands.

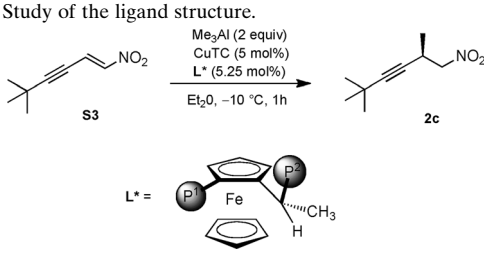
1,6-Selective conjugate addition: Wendisch and Mikami used nitroenoates as Michael acceptors. They reported a copper-catalysed ACA with respect to the nitro group.[14b,i] The strong inductive effect of the nitro group favoured conjugate addition, despite addition onto the ester group. Inspired by this work, nitrodienoates **S19**–**20** were synthesised according to the procedure used for polyconjugated nitro-olefins (Scheme 2).

As expected, conjugate addition proceeds with respect to the nitro group. Grignard reagents afforded 1,4-adduct **6** exclusively without enantioselectivity (Table 10, entry 1). Interestingly, dimethylzinc and trimethylaluminium displayed unusual regioselectivities. We previously reported that, compared with dimethylzinc, trimethylaluminium gave a larger ratio of 1,4- to 1,6-addition in favour of the 1,4-product. However, in this case, the tendency is reversed because the aluminium reagent displayed a ratio of 1,4- to 1,6-addition product of 45:55, whereas the zinc reagent afforded the 1,4-product mainly (ratio of 64:36; Table 10, entries 2 and 3). High enantioselectivities were detected for both the 1,4- (93% *ee*) and 1,6- (91% *ee*) adducts upon the addition of trimethylaluminium reagents, showing the high versatility of the catalyst.

By using THF at −78°C (conditions B), almost exclusive formation of the 1,6-adduct was achieved, with an enantioselectivity reaching 90% *ee* (Table 10, entry 4). Applying these conditions to substrate **S20**, led to a ratio of 1,4- to 1,6-addition products of 5:95 and an enantioselectivity reaching 91% *ee* (Table 10, entry 5). This switch in regioselectivity was unexpected, but could be rationalised by invoking a coordination of the carbonyl moiety to the catalyst, which, in turn, favours the migration step. However, it is important to note that better regioselectivity was observed in more highly coordinating solvents such as THF.

To demonstrate the versatility of the nitro group in synthesis, we transformed the 1,6-addition product **7a** into lactam **8** through a reduction/cyclisation tandem reaction (Scheme 6). This transformation did not lead to any erosion of the enantioselectivity, delivering the heterocycle in 91% *ee*.

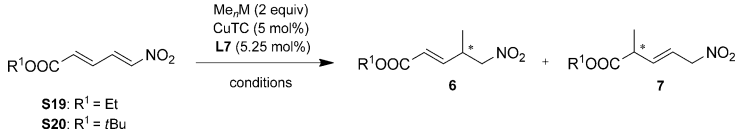
Table 9. Study of the ligand structure.



Entry	Ligand	Conv. [%][a]	*ee* **2c** [%][b]
1	**L7**	100	95
2	**L1**	28	65
3	**L7′**	10	0
4	**L1′**	8	0

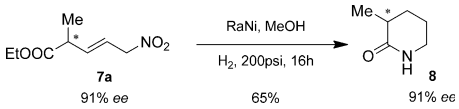
[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase.

Table 10. ACA to nitrodienoate **S19**–**20**.



Entry	Substrate	Me_nM	Cond.[c]	Conv. [%][a]	**6**/**7**[a]	Yield [%]	*ee* [%][b] **6**	**7**
1	**S19**	MeMgBr	A	100	100:0	–	0	–
2	**S19**	Me_2Zn	A	100	64:36	n.d.	92	76
3	**S19**	Me_3Al	A	100	45:55	n.d.	93	91
4	**S19**	Me_3Al	B	100	3:97	68 (**7a**)	n.d.	90
5	**S20**	Me_3Al	B	100	5:95	71 (**7b**)	n.d.	91

[a] Determined by GC-MS analysis. [b] Determined by chiral GC analysis using a chiral stationary phase. [c] Conditions A: Et_2O, −10°C; conditions B: THF, −78°C.



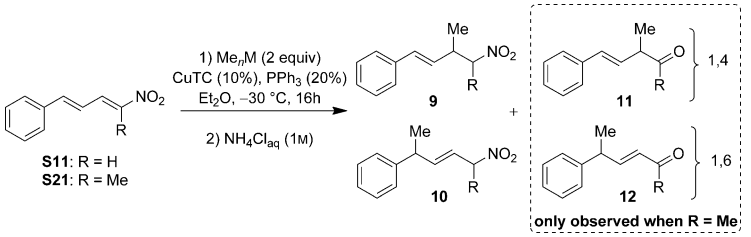
Scheme 6. Synthesis of lactam **8**.

In 2002, Hoveyda discovered that the asymmetric conjugate addition of diethylzinc to cyclic nitro-olefin afforded the chiral α-substituted cyclohexanone through a Nef transformation.[14e]

Concerning ACA to nitrodienes and nitroenynes, we never observed this type of transformation, even under strongly acidic conditions, suggesting that this reaction worked specifically with α-substituted nitro-olefins.

Because we were interested in the influence of α-substitution on polyconjugated nitro-olefins for the ACA, and also wanted to examine the potential to convert the conjugate addition products directly into carbonyl derivatives, we decided to examine α-substituted nitrodienes. Our investigation started with an investigation of three organometallic reagents: methyl magnesium bromide, trimethylaluminium, and dimethylzinc, with nitrodiene **S11** and α-substituted nitrodiene **S21** to establish the effect of α-substitution on regioselectivity (Table 11); CuTC and PPh_3 were chosen as catalyst.

Table 11. Screening of the organometallic reagents with **S11** and **S21**.



Entry	Substrate	Me$_n$M	Conv. [%][a]	**9**/**10**[a]
1	**S11**	MeMgBr	100	85:15
2[b]	**S21**	MeMgBr	100	60:40
3	**S11**	Me$_3$Al	100	58:42
4[b]	**S21**	Me$_3$Al	100	20:80
5[c]	**S11**	Me$_2$Zn	100	13:86
6[b][c]	**S21**	Me$_2$Zn	100	5:95

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Nef product formation. [c] Reaction performed at −10 °C.

With the most reactive methyl magnesium bromide reagent, the reaction proceeded in favour of the 1,4-addition product with **S11**, in a ratio 85:15 (Table 11, entry 1). Interestingly, when the same reaction conditions were applied to α-substituted nitrodiene **S21**, the 1,6-addition product was formed in higher amounts, demonstrating the influence of the α-substitution on regioselectivity. As expected, partial formation of the Nef products **11** and **12**, derived from both 1,4- and 1,6-additions, were detected. We then probed the use of trimethylaluminium as the organometallic reagent, observing that the α-substitution again influenced the regioselective outcome. We noted that the ratio of 1,4-addition to 1,6-addition shifted from 58:42 with **S11** to 20:80 with **S21**. Interestingly, transformation into the Nef adduct was more significant; this outcome is probably due to the Lewis acid character of the aluminium reagents, which promoted an aluminium nitronate, which, in turn, favoured the Nef reaction.

Finally, we tested the conjugate addition of dimethylzinc. In this case, 1,6-addition occurred preferentially with **S11** (Table 11, entry 5) and almost exclusively with **S21** (Table 11, entry 6). The Nef transformation occurred quantitatively with **S21**, producing α,β-unsaturated ketone **12** (Table 11, entry 6).

Encouraged by the last result, we examined different conditions with dialkylzinc reagent and chiral phosphorus ligands (Figure 4).

When dimethylzinc was employed in the presence of the reversed Josiphos ligand **L7**, CuTC, with diethyl ether as solvent (conditions A), chiral enone **12** was obtained as the major isomer with 80% *ee* (Table 12, entry 1). When diethyl ether was replaced by dichloromethane, a mixture of 1,4- and 1,6-adduct was observed in a **11**/**12** ratio of 12:88. Moreover, low levels of enantiocontrol was observed for the 1,6-addition product **12** (Table 12, entry 2). With toluene as solvent, a clean reaction was observed, with exclusive formation of the Nef adduct in 91% *ee* (Table 12, entry 3). It is important to note that the conditions use for the hydrolysis step is crucial for the Nef reaction, as already reported.[14e] Use of NH_4Cl_{aq} (1 M) resulted in complete conversion into the Nef product, whereas use of HCl_{aq} (1 M) resulted in only partial conversion. To improve the enantioselectivity, a ligand screening was performed with phosphoramidite and phosphine amine ligands, using toluene as solvent (**L8**, **L9** and **L10**) (Figure 4). With the phosphoramidite ligand **L8**, an equal mixture of 1,4- and 1,6-addition adducts were obtained, demonstrating that the regioselectivity was also dependent on the ligand and, moreover, the 1,6-Nef product displayed a moderate enantioselectivity of 73% *ee* (Table 12, entry 4).

The more elaborate phosphoramidite **L9**, was also used, affording mainly the 1,6-adduct in excellent 93% *ee* (Table 12, entry 5). Finally, Simplephos ligand **L10**, which is a ligand developed in the Alexakis laboratory,[20] afforded exclusively the 1,6-adduct with an enantioselectivity of 89% *ee* (Table 12, entry 6). We decided to pursue the reaction further with the ferrocene-based phosphine ligand **L7** and decreased the reaction temperature to −30 °C. Unfortunately, the conversion dropped

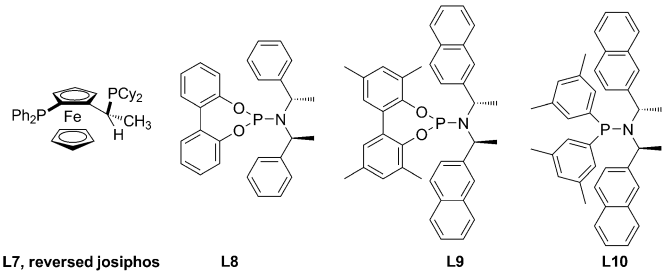
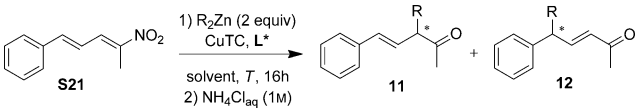


Figure 4. Selected chiral ligands.

Table 12. Optimisation of the 1,6-ACA of dialkylzinc reagents to **S21**.



Entry	R$_2$Zn	Solvent	*T* [°C]	L*	Conv. [%][a]	**11**/**12**[a]	*ee* **12** [%][b]
1[c]	Me$_2$Zn	Et$_2$O	−10	**L7**	100	<1:99	80
2[c]	Me$_2$Zn	CH$_2$Cl$_2$	−10	**L7**	100	12:88	20
3[c]	Me$_2$Zn	toluene	−10	**L7**	100	<1:99	91
4[d]	Me$_2$Zn	toluene	−10	**L8**	100	50:50	73
5[d]	Me$_2$Zn	toluene	−10	**L9**	100	11:89	93
6[d]	Me$_2$Zn	toluene	−10	**L10**	100	<1:99	89
7[c]	Me$_2$Zn	toluene	−30	**L7**	10	<1:99	n.d.
8[c]	Et$_2$Zn	toluene	−30	**L7**	100	<1:99	29
9[c]	Et$_2$Zn	toluene	−10	**L7**	100	<1:99	6
10[c,e]	Et$_2$Zn	toluene	−30	**L9**	100	n.d.	62

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by chiral SFC analysis using a chiral stationary phase. [c] Reaction performed with CuTC/**L** = 5:5.25 mol%. [d] Reaction performed with CuTC/**L** = 5:10 mol%. [e] Partial transformation into the Nef product.

dramatically (Table 12, entry 7). With the more reactive diethylzinc under the same reaction conditions, however, a low enantioselectivity of 29% *ee* was detected (Table 12, entry 8). Increasing the temperature to −10°C afforded an almost racemic mixture (Table 12, entry 9). A screening of other ligands was undertaken to improve these poor results but, unfortunately, we were only able to increase the *ee* to 62% by using **L9**. The regioselectivity was not perfect and transformation into the Nef product was only partially achieved (Table 12, entry 10).

Having established the appropriate conditions for the tandem 1,6-ACA/Nef reaction, we synthesised a small library of α-substituted nitrodienes **S21**–**S27**, using the same methodology that was previously used for the synthesis of nitroenynes and nitrodienes. Linear nitroalkanes were utilised instead of nitromethane to perform the Henry reaction. However, this reaction required a longer reaction time to generate the substrates in good yields (Figure 5).

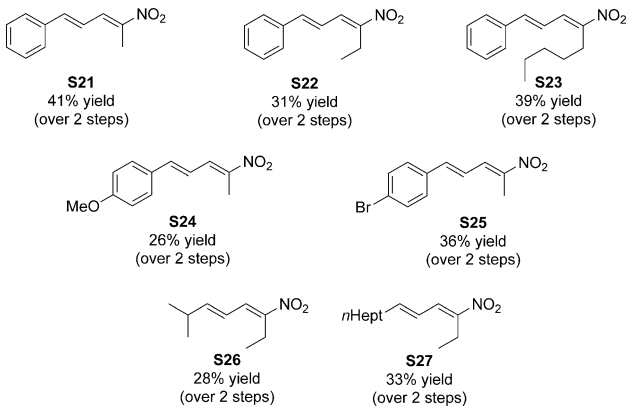
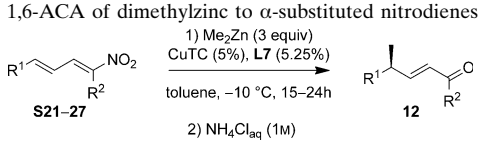


Figure 5. α-Substituted nitrodienes **S21**–**S27**.

We began to explore the scope of the reaction with respect to the electrophiles by using a variety of alkyl chain lengths at the α-position. Nitrodienes **S21**, **S22** and **S23** afforded the 1,6-addition products exclusively with similar levels of enantioselectivity (up to 92% *ee*) and good yields (Table 13, entries 1–3). The optimised reaction conditions were then applied to nitrodiene **S24**, bearing an aryl substituent with an electron-donating substituent at the *para*-position.

The 1,6-addition reaction proceeded with high enantiocontrol (93% *ee*) (Table 13, entry 4). The substrate analogue **S25**, with the *para*-bromo phenyl substituent, was also tested, affording the 1,6-adduct with a slightly lower enantioselectivity of 91% *ee* (Table 13, entry 5). This demonstrated that electronic factors do not exert a significant influence on the stereoselectivity of the reaction. Finally, we probed the use of aliphatic substrates **S26** and **S27**. Again, the reaction displayed excellent regiocontrol and complete formation of the Nef adduct. The enantioselectivities reached 92 and 80% *ee*, respectively (Table 13, entries 6 and 7). This investigation showed that the α-substituted nitrodienes were converted into the 1,6-Nef adduct in one pot, with high regio- and enantioselectivities.

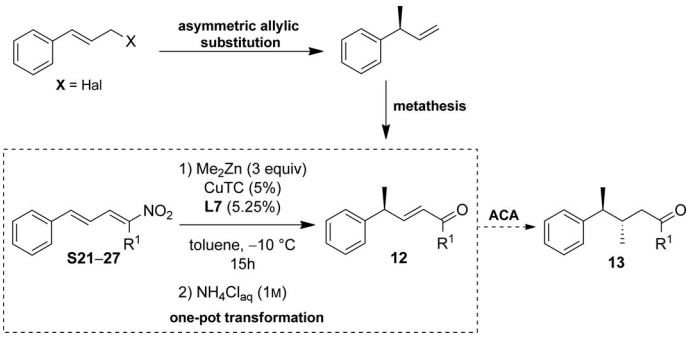
Table 13. 1,6-ACA of dimethylzinc to α-substituted nitrodienes **S21**–**S27**.



Entry	Substrate	Prod.	Conv. [%][a]	Yield [%]	*ee* **12** [%][b]
1	**S21**	**12a**	100	56	89
2	**S22**	**12b**	100	70	92
3	**S23**	**12c**	100	74	92
4	**S24**	**12d**	100	55	93
5	**S25**	**12e**	100	64	91
6	**S26**	**12f**	100	62	92
7	**S27**	**12g**	100	65	80

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by chiral SFC analysis using a chiral stationary phase.

The *S* configuration of **12a** was established by comparison of the optical rotation with the reported value for this compound.[21] This efficient one-pot transformation allowed direct access to enantioenriched α,β-unsaturated ketone **12** (Scheme 7). These types of chiral compounds are usually synthesised through two-step procedures[21,22] involving asymmetric allylic alkylation (AAA) followed by cross metathesis.[23] From a synthetic point of view, an additional asymmetric conjugate addition on the enone **12** could potentially deliver vicinal dialkyl arrays such as **13**, as already demonstrated by Feringa.[21]



Scheme 7. Iterative 1,6-/1,4-ACA.

Conclusion

We have described a highly regioselective and enantioselective ACA of trimethylaluminum reagents to nitroenynes and nitrodienes using ferrocene-based phosphine ligand **L7** and CuTC as the catalytic system. The reaction proceeded exclusively in a 1,4-additon fashion. Whereas Me_3Al afforded high levels of enantioselectivities up to 99% *ee*, other trialkylaluminium reagents reached up to 71% *ee*. Interestingly, we discovered that the regioselectivity could be switched to 1,6-addition by applying a slight modification in the substrate design. In fact, the use of nitrodienoate allowed pref-

erential formation of the 1,6-adduct with an enantioselectivity of up to 91% *ee*. Finally, we turned our attention to α-substituted nitrodienes. Initially, by comparison with classic nitrodienes, we observed that this substitution pattern influenced the regioselectivity in favour of the 1,6-addition product. However, by using a similar catalytic system, with ligand **L7** and CuTC, the addition of dimethylzinc promoted exclusive 1,6-addition. Moreover, the resulting 1,6-nitronate can be directly converted into the α,β-unsaturated ketone upon acidic work-up, through a Nef reaction. This reaction was applied to a small library of α-substituted nitrodienes and delivered valuable α,β-unsaturated ketones in good enantioselectivities of up to 93% *ee*. Surprisingly, the addition of diethylzinc was more problematic, displaying low enantioselectivity and only partial conversion into the Nef product.

Experimental Section

General remarks: All reactions were conducted in 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 with a Büchi rotary evaporator. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$, and chemical shift (δ) are given in ppm relative to residual $CHCl_3$. Evolution of the reaction was followed by GC-MS with a Hewlett Packard (EI mode) HP6890–5973. Optical rotations were measured at 20°C in a 1 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration c given as g/100 mL). 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), final temperature (°C), retention time (t_R in min). All Grignard reagents except ethyl and methyl magnesium bromide (Aldrich) were synthesised in Et_2O by addition of the corresponding bromide onto magnesium. Flash chromatography was performed by using silica gel 32–63 mm (60 Å). Syntheses of starting substrates are described in the Supporting Information.

General procedure 1: 1,4-ACA of trialkylaluminium reagents to polyconjugated nitro-olefins (methods A and B): A flame-dried Schlenk tube was charged with CuTC (5 mol%) and the chiral ligand (5.25 mol%). Et_2O (method A) or THF (method B) (3 mL) was added and the mixture was stirred at RT for 30 min before being cooled to −10°C (method A) or −78°C (method B). Trialkylaluminium (0.7–2 M in hexane or heptane, 2 equiv.) was added dropwise over 1 min by using a syringe. The solution was stirred for 5 min, and the nitro compound (0.5 mmol, 2 equiv.) was then added dropwise into either Et_2O (method A) or THF (method B) (0.5 mL). The reaction mixture was stirred for an additional 1 h at −10°C (method A) or 12 h at −78°C (method B). The flask was removed from the cooling bath and an aq. solution of tartaric acid (1 M, 2 mL) was added slowly. The reaction mixture was stirred for 0.5 h, then the latter was extracted with Et_2O. The organic phase was dried over magnesium sulfate, concentrated, and the crude product was purified by chromatography. Gas chromatography or supercritical fluid chromatography on a chiral stationary phase revealed the enantiomeric excess.

2-Methyl-1-nitronon-3-yne (2a): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2a** (56%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (dd, J = 12.0, 7.2 Hz, 1H), 4.28 (dd, J = 12.0, 7.6 Hz, 1H), 3.28 (m, 1H), 2.11 (td, J = 7.1, 2.3 Hz, 2H), 1.44 (m, 2H), 1.30 (m, 4H), 1.24 (d, J = 7.1 Hz, 3H), 0.88 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.2, 80.5, 78.6, 31.3, 28.7, 25.9, 22.5, 18.8, 14.3 ppm; HRMS (EI): m/z calcd for $C_{10}H_{16}$: 136.1252 $[M-HNO_2]^+$; found: 136.1254. $[\alpha]_D^{25}$ = +8.49 (c = 1, $CHCl_3$) for 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}): t_{R1} = 67.63, t_{R2} = 67.92 min.

(3-Methyl-4-nitrobut-1-yn-1-yl)cyclohexane (2b): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2b** (74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (dd, J = 11.9, 7.3 Hz, 1H), 4.29 (dd, J = 12.1, 7.6 Hz, 1H), 3.29 (m, 1H), 2.31 (m, 1H), 1.23–1.74 ppm (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.1, 80.4, 32.7, 28.9, 25.9, 25.6, 24.7, 18.6 ppm. HRMS (EI): m/z calcd for $C_{11}H_{16}$: 148.1252 $[M-HNO_2]^+$; found: 148.1252. $[\alpha]_D^{25}$ = +9.0 (c = 1, $CHCl_3$) for 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}): t_{R1} = 84.52, t_{R2} = 84.85 min.

2,2-Dimethyl-5-(nitromethyl)hex-3-yne (2c): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2c** (55%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.39 (dd, J = 11.8, 7.0 Hz, 1H), 4.28 (dd, J = 11.8, 7.6 Hz, 1H), 3.27 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 1.17 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 92.3, 80.3, 65.4, 31.0, 27.2, 25.4, 18.5 ppm; HRMS (EI): m/z calcd for C_9H_{14}: 122.1096 $[M-HNO_2]^+$; found: 122.1096; $[\alpha]_D^{25}$ = +13.7 (c = 1, $CHCl_3$) for 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}): t_{R1} = 51.33, t_{R2} = 51.93 min.

1-[(4-Methyl-5-nitropent-2-ynyloxy)methyl]benzene (2d): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2d** (65%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 5H), 4.56 (s, 2H), 4.46 (dd, J = 12.1, 7.3 Hz, 1H), 4.34 (dd, J = 12.1, 7.1 Hz, 1H), 4.14 (d, J = 2.0 Hz, 2H), 3.39 (m, 1H), 1.31 ppm (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 128.5, 128.2, 128.0, 85.0, 79.6, 79.3, 71.7, 57.3, 25.5, 18.1 ppm; HRMS (EI): m/z calcd for $C_{13}H_{13}O$: 185.0966 $[M-H_2NO_2]^+$; found: 185.0965; $[\alpha]_D^{25}$ = +7.3 (c = 1, $CHCl_3$) for 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}): t_{R1} = 58.51, t_{R2} = 60.03 min.

Trimethyl(3-methyl-4-nitrobut-1-ynyl)silane (2e): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2e** (69%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (dd, J = 12.0, 6.7 Hz, 1H), 4.31 (dd, J = 12.4, 8.1 Hz, 1H), 3.35 (m, 1H), 1.27 (d, J = 7.1 Hz, 3H), 0.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.2, 88.1, 79.6, 26.2, 18.1, −0.1 ppm; HRMS (CI): m/z calcd for $C_8H_{16}NO_2Si$: 186.0950 $[M+H]^+$; found: 186.0951; $[\alpha]_D^{25}$ = +12.3 (c = 1, $CHCl_3$) for 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}): t_{R1} = 37.67, t_{R2} = 38.62 min.

1-(3-Methyl-4-nitrobut-1-ynyl)benzene (2f): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2f** (70%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2H), 7.29 (m, 3H), 4.55 (dd, J = 12.1, 7.1 Hz, 1H), 4.42 (dd, J = 12.4, 7.6 Hz, 1H), 3.56 (m, 1H), 1.38 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 128.4, 128.3, 122.5, 87.5, 83.4, 79.6, 26.0, 18.2 ppm; HRMS (EI): m/z calcd for $C_{11}H_{11}NO_2$: 189.0790 $[M]^+$; found: 189.0792; $[\alpha]_D^{25}$ = +24.1 (c = 1, $CHCl_3$) for 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}): t_{R1} = 95.12, t_{R2} = 95.58 min.

1-Methoxy-4-(3-methyl-4-nitrobut-1-ynyl)benzene (2g): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2g** (54%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.53 (dd, J = 12.1, 7.1 Hz, 1H), 4.40 (dd, J = 12.1, 7.6 Hz, 1H),3.80 (s, 1H), 3.53 (m, 1H), 1.36 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 133.2, 114.6,

113.9, 86.1, 83.3, 79.9, 55.3, 26.1, 18.3 ppm; HRMS (EI): *m/z* calcd for $C_{12}H_{13}NO_3$: 219.0895 $[M]^+$; found: 219.0898; $[\alpha]_D^{25} = +20.2$ ($c = 1$, $CHCl_3$) for 83% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 5.59$, $t_{R2} = 5.99$ min.

1-Bromo-4-(3-methyl-4-nitrobut-1-ynyl)benzene (2h): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2h** (64%) as a pale-yellow crystal. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$ (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 8.6$ Hz, 2H), 4.53 (dd, $J = 12.4$, 7.6 Hz, 1H), 4.41 (dd, $J = 12.1$, 7.3 Hz, 1H), 3.54 (m, 1H), 1.37 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 133.1$, 131.5, 122.6, 121.4, 88.7, 82.4, 79.5, 26.0, 18.0 ppm; HRMS (EI): *m/z* calcd for $C_{11}H_{10}BrNO_2$: 266.9895 $[M]^+$; found: 266.9893; $[\alpha]_D^{25} = +20.8$ ($c = 1$, $CHCl_3$) for 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}): $t_{R1} = 137.76$, $t_{R2} = 138.43$ min.

1-(3-Methyl-4-nitrobut-1-yn-1-yl)-4-(trifluoromethyl)benzene (2i): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2i** (52%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 8.3$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 4.55 (dd, $J = 12.1$, 7.3 Hz, 1H), 4.44 (dd, $J = 12.1$, 7.1 Hz, 1H), 3.58 (m, 1H), 1.40 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 132.0$, 126.4, 125.3, 125.2, 122.5, 90.1, 82.2, 79.4, 26.0, 18.0 ppm; HRMS (EI): *m/z* calcd for $C_{12}H_{10}F_3NO_2$: 257.0664 $[M]^+$; found: 257.0667; $[\alpha]_D^{25} = +16.2$ ($c = 1$, $CHCl_3$) for 90% *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}): $t_{R1} = 70.90$, $t_{R2} = 71.39$ min.

1-Isopropyl-2-(3-methyl-4-nitrobut-1-ynyl)benzene (2j): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2j** (62%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 7.8$ Hz, 1H), 7.23–7.30 (m, 2H), 7.11 (m, 1H), 4.56 (dd, $J = 12.1$, 7.3 Hz, 1H), 4.44 (dd, $J = 12.1$, 7.32 Hz, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 1.41 (d, $J = 6.8$ Hz, 3H), 1.25 ppm (d, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.6$, 132.5, 128.8, 125.5, 124.9, 121.3, 91.1, 82.2, 79.8, 31.5, 26.3, 23.0, 18.3 ppm; HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259 $[M]^+$; found: 231.1258; $[\alpha]_D^{25} = +15.3$ ($c = 1$, $CHCl_3$) for 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}): $t_{R1} = 106.90$, $t_{R2} = 107.35$ min.

[3-(Nitromethyl)pent-1-yn-1-yl] (2k): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2k** (53%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (m, 2H), 7.30 (m, 3H), 4.55 (dd, $J = 12.1$, 7.5 Hz, 1H), 4.47 (dd, $J = 12.4$, 7.3 Hz, 1H), 3.41 (m, 1H), 1.58–1.74 (m, 2H), 1.14 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 131.8$, 128.4, 128.3, 122.7, 86.4, 84.5, 78.4, 33.0, 25.4, 11.3 ppm; HRMS (EI): *m/z* calcd for $C_{12}H_{13}NO_2$: 203.0946 $[M]^+$; found: 203.0948; $[\alpha]_D^{25} = -4.5$ ($c = 1$, $CHCl_3$) for 62% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 4.41$, $t_{R2} = 4.85$ min.

[3-(Nitromethyl)hept-1-yn-1-yl]benzene (2l): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2l** (65%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (m, 2H), 7.30 (m, 3H), 4.54 (dd, $J = 12.1$, 7.8 Hz, 1H), 4.46 (dd, $J = 12.1$, 7.1 Hz, 1H), 3.46 (m, 1H), 0.92–1.63 (m, 6H), 0.94 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 131.8$, 128.4, 128.3, 122.7, 86.7, 84.4, 78.8, 31.8, 31.5, 29.0, 22.3, 14.0 ppm; HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259; found: 231.1261; $[\alpha]_D^{25} = -13.7$ ($c = 1$, $CHCl_3$) for 71% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 4.70$, $t_{R2} = 5.30$ min.

[3-(Nitromethyl)hex-1-yn-1-yl]benzene (2m): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2m** (68%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (m, 2H), 7.30 (m, 3H), 4.54 (dd, $J = 12.1$, 7.6 Hz, 1H), 4.46 (dd, $J = 12.4$, 7.1 Hz, 1H), 3.48 (m, 1H), 1.49–1.68 (m, 4H), 0.99 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 131.8$, 128.4, 128.3, 122.7, 86.6, 84.4, 78.8, 34.12, 31.3, 20.2, 13.7 ppm; HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO_2$: 217.1103 $[M]^+$; found: 217.1105; $[\alpha]_D^{25} = -7.7$ ($c = 1$, $CHCl_3$) for 60% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 9.63$, $t_{R2} = 10.21$ min.

[5-Methyl-3-(nitromethyl)hex-1-yn-1-yl]benzene (2n): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **2n** (55%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.40 (m, 2H), 7.30 (m, 3H), 4.54 (dd, $J = 12.1$, 7.8 Hz, 1H), 4.44 (dd, $J =$ 12.1, 6.8 Hz, 1H), 3.51 (m, 1H), 1.96 (m, 1H), 1.59 (m, 1H), 1.32 (m, 1H), 0.99 ppm (t, $J = 7.6$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 131.8, 128.4, 128.3, 122.7, 86.6, 84.3, 79.1, 41.0, 29.9, 26.0, 23.3, 21.4 ppm; HRMS (EI): *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259 $[M]^+$; found: 231.1262; $[\alpha]_D^{25} = -2.1$ ($c = 1$, $CHCl_3$) for 6% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 6.29$, $t_{R2} = 6.90$ min.

1-[(*E*)-3-Methyl-4-nitrobut-1-enyl]benzene (4a): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **4a** (70%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.30 (m, 4H), 7.27–7.23 (m, 1H), 6.50 (d, $J = 16$ Hz, 1H), 6.05 (dd, $J = 15.9$, 7.8 Hz, 1H), 4.38 (m, 2H), 3.22 (m, 1H), 1.23 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.4$, 131.8, 128.8, 128.6, 127.8, 126.3, 80.9, 36.4, 17.5 ppm; HRMS (EI): *m/z* calcd for $C_{11}H_{13}NO_2$: 191.0946 $[M]^+$; found: 191.0949; $[\alpha]_D^{25} = +79.7$ ($c = 1$, $CHCl_3$) for 88% *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}): $t_{R1} = 73.07$, $t_{R2} = 73.51$ min.

1-Methoxy-4-[(*E*)-3-methyl-4-nitrobut-1-enyl]benzene (4b): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **4b** (50%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.44 (d, $J = 15.9$ Hz, 1H), 5.90 (dd, $J = 15.6$, 7.8 Hz, 1H), 4.36 (m, 2H), 3.80 (s, 3H), 3.19 (m, 1H), 1.21 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.3$, 131.2, 129.2, 127.5, 126.6, 113.9, 81.1, 55.3, 36.5, 17.6 ppm. HRMS (EI): *m/z* calcd for $C_{12}H_{15}NO_3$: 221.1052 $[M]^+$; found: 221.1054; $[\alpha]_D^{25} = +70.5$ ($c = 1$, $CHCl_3$) for 77% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OB column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 8.77$, $t_{R2} = 9.48$ min.

(*E*)-Ethyl 2-methyl-5-nitropent-3-enoate (4c): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **4c** (55%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.06$ (d, $J =$ 8.6 Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 5.93 (d, $J = 15.8$ Hz, 1H), 5.90 (dd, $J = 15.9$, 7.8 Hz, 1H), 3.53 (m, 2H), 2.65 (m, 1H), 0.62 ppm (d, $J = 15.8$, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.9$, 133.4, 130.7, 129.5, 128.7, 127.5, 80.8, 36.4, 17.5 ppm; HRMS (EI): *m/z* calcd for $C_{11}H_{12}ClNO_2$: 225.0557 $[M]^+$; found: 225.0557; $[\alpha]_D^{25} = +63.0$ ($c = 1$, $CHCl_3$) for 84% *ee*. The enantiomeric excess was determined by SFC on a chiral stationary phase (Chiralcel OB column, method: MeOH 0%-2–1–15, 5°C): $t_{R1} = 7.17$, $t_{R2} = 7.63$ min.

(*E*)-(3-Methyl-4-nitrobut-1-en-1-yl)cyclohexane (4d): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **4d** (59%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.49$ (dd, $J = 15.4$, 6.6 Hz, 1H), 5.21 (dd, $J = 15.4$, 6.6 Hz, 1H), 4.25 (m, 2H), 2.95 (m, 1H), 1.88 (m, 1H), 1.62–1.72 (m, 6H), 1.03–1.29 ppm (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.1$, 126.7, 81.5, 40.5, 36.3, 32.9, 26.1, 26.0, 17.8 ppm; HRMS (EI): *m/z* calcd for $C_{11}H_{18}$: 150.1409 $[M-HNO_2]^+$; found: 150.1407; $[\alpha]_D^{25} = +27.6$ ($c = 1$, $CHCl_3$) for 90% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (LIPO-

DEX E column, method: 60–20–1–170–5, 45 cm s^{-1}): t_{R1} = 67.07, t_{R2} = 67.68 min.

(*E*)-(3-Methyl-4-nitrobut-1-en-1-yl) (4e): The reaction was performed according to general procedure 1. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **4e** (67%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (dd, J = 15.4, 6.8 Hz, 1H), 5.21 (dd, J = 15.4, 6.8 Hz, 1H), 4.25 (m, 2H), 2.95 (m, 1H), 2.22 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 ppm (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 126.2, 81.5, 36.1, 31.0, 22.4, 22.3, 17.7 ppm; HRMS (EI): m/z calcd for C_8H_{14}: 110.1096 $[M-HNO_2]^+$; found: 110.1096; $[\alpha]_D^{25}$ = +24.9 (c = 1, $CHCl_3$) for 90% *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}): t_{R1} = 13.41, t_{R2} = 14.03 min.

General procedure 2: Copper-catalysed 1,6-ACA of trialkylaluminium reagents to polyconjugated nitrodienoates (method B): A flame-dried Schlenk tube was charged with copper salt (5 mol%) and the chiral ligand (5.25 mol%). THF (3 mL) was added and the mixture was stirred at RT for 30 min. The mixture was stirred for 30 min before being cooled to −80 °C. Trimethylaluminium (2 M in hexane, 2 equiv.) was added dropwise over 1 min by using a syringe. The solution was stirred for 5 min, and the nitro compound (0.5 mmol) was then added in one portion. The reaction mixture was stirred for an additional 12 h at −78 °C. The flask was removed from the cooling bath, and an aq. solution of tartaric acid (1 M, 2 mL) were added slowly. The reaction mixture was stirred for 0.5 h, then the latter was extracted with diethyl ether. The organic phase was dried over magnesium sulfate, concentrated, and the crude product was purified by chromatography. Gas chromatography on a chiral stationary phase revealed the enantiomeric excess.

(*E*)-Ethyl 2-methyl-5-nitropent-3-enoate (7a): The reaction was performed according to general procedure 2. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **7a** (68%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (dd, J = 15.6, 7.6 Hz, 1H), 5.86 (m, 1H), 4.91 (d, J = 7.0 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.22 (m, 1H), 1.31 (d, J = 7.1 Hz, 3H), 1.26 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 139.2, 120.0, 77.0, 61.1, 42.5, 16.8, 14.2 ppm; HRMS (EI): m/z calcd for $C_8H_{13}NO_4$: 187.0845 $[M^+]$; found: 187.0845; $[\alpha]_D^{25}$ = +6.4 (c = 1, $CHCl_3$) for 90% *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}): t_{R1} = 45.57, t_{R2} = 46.27 min.

(*E*)-*tert*-Butyl 2-methyl-5-nitropent-3-enoate (7b): The reaction was performed according to general procedure 2. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **7b** (71%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dd, J = 15.6, 7.6 Hz, 1H), 5.84 (m, 1H), 4.91 (d, J = 6.8 Hz, 2H), 3.13 (m, 1H), 1.43 (s, 12H), 1.27(d, J=7.3 Hz, 3H), 1.26 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 139.8, 119.6, 81.2, 43.5, 28.0, 26.9, 16.8 ppm; HRMS (EI): m/z calcd for $C_{10}H_{17}NO_4$: 215.1158 $[M^+]$; found: 215.1158; $[\alpha]_D^{25}$ = +8.9 (c = 1, $CHCl_3$) for 91% *ee*. The enantiomeric excess was determined by GC on a chiral stationary phase (LIPODEX E column, method: 60–20–1–170–5, 45 cm s^{-1}): t_{R1} = 62.34, t_{R2} = 63.19 min.

3-Methylpiperidin-2-one (8): RaNi (0.28 mL) was added to a solution of 1,6-adduct **7a** (0.187 g, 1.00 mmol) in MeOH (11.5 mL). The mixture was hydrogenated at 200 psi for 48 h, then the catalyst was filtered and the filtrate was concentrated. The crude product was purified by chromatography (methanol/diethyl ether, 3:97) to afford **8** (65%) as a brown oil. ^{1}H NMR (400 MHz, C_6H_6): δ = 6.25 (br s, 1H), 3.29 (m, 2H), 2.36 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.47 (m, 1H), 1.20 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 139.8, 119.6, 81.2, 43.5, 28.0, 26.9, 16.8 ppm; HRMS (EI): m/z calcd for $C_6H_{11}NO$: 113.0841 $[M]^+$; found: 113.0843; $[\alpha]_D^{25}$ = +38.5 (c = 1, $CHCl_3$).

General procedure 3: Copper-catalysed 1,6-ACA of dialkylzinc reagents to polyconjugated α-substituted nitro-olefins: A flame-dried Schlenk tube was charged with CuTC (0.025 mmol, 0.05 equiv) and the chiral ligand (0.0262 mmol, 0.0525 equiv). Toluene (3 mL) was added and the mixture was stirred at RT for 10 min, before being cooled to −10 °C. Dialkylzinc (1–1.2 M in hexane or toluene, 1.5 mmol, 3 equiv) was added dropwise over 1 min by using a syringe. The solution was stirred for 5 min, then the nitro compound (0.5 mmol, 1 equiv) in a solution of toluene (1 mL) was added dropwise. The reaction mixture was stirred for 24 h at −10 °C. Finally, the reaction was quenched at 0 °C with an aq. solution of NH_4Cl (1 M, 2 mL) during 10 min. The latter was extracted three times with diethyl ether, then the organic phase was dried over magnesium sulfate, concentrated, and the crude product was purified by chromatography. Gas chromatography or supercritical fluid chromatography on a chiral stationary phase revealed the enantiomeric excess.

(*S*,*E*)-6-Phenylhept-4-en-3-one (12b): The reaction was performed according to general procedure 3. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **12a** (56%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 2H), 7.29–7.17 (m, 3H), 6.92 (dd, J = 16.0, 6.6 Hz, 1H), 6.07 (d, J = 16.0 Hz, 1H), 3.64 (m, 1H), 2.25 (s, 3H), 1.45 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.96, 151.72, 143.28, 129.69, 128.80, 127.36, 126.88, 42.27, 27.03, 20.20 ppm; HRMS (EI): m/z calcd for $C_{12}H_{14}O$: 188.1201 $[M]^+$; found: 188.1200; $[\alpha]_D^{20}$ = −15.6 (c = 1, CH_3Cl) for 89% of *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel OB column, method: MeOH 2%-2–1–15, 40 °C): t_{R1} = 7.48, t_{R2} = 7.92 min.

(*S*,*E*)-2-Phenyldec-3-en-5-one (12c): The reaction was performed according to general procedure 3. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **12c** (74%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2H), 7.26–7.22 (m, 1H), 7.21–7.17 (m, 2H), 6.95 (dd, J = 15.9, 6.7 Hz, 1H), 6.08 (d, J = 15.9 Hz, 1H), 3.62 (m, 1H), 2.52 (t, J = 7.4 Hz, 2H), 1.73–1.55 (m, 2H), 1.44 (d, J = 7.0 Hz, 3H), 1.39–1.11 (m, 4H), 0.88 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.08, 150.35, 143.44, 128.80, 128.73, 127.33, 126.78, 42.23, 40.20, 31.49, 23.92, 22.46, 20.29, 13.92 ppm; HRMS (EI): m/z calcd for $C_{16}H_{22}O$: 230.1671 $[M]^+$; found: 230.1671; $[\alpha]_D^{20}$ = −8.4 (c = 1, CH_3Cl) for 92% of *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel ID column, method: MeOH 2%-2–1–15, 40 °C): t_{R1} = 6.29, t_{R2} = 8.00 min.

(*S*,*E*)-5-(4-Methoxyphenyl)hex-3-en-2-one (12d): The reaction was performed according to general procedure 3. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **12d** (55%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 8.6 Hz, 2H), 6.94–6.86 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.05 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.59 (m, 1H), 2.24 (s, 3H), 1.41 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.95, 158.46, 152.06, 135.26, 129.40, 128.28, 114.14, 55.29, 41.41, 26.99, 20.25 ppm. HRMS (EI): m/z calcd for $C_{13}H_{16}O_2$: 204.1150 $[M]^+$; found: 204.1152; $[\alpha]_D^{20}$ = −11.0 (c = 1, CH_3Cl) for 93% of *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel OD column, method: MeOH 2%-2–1–15, 40 °C): t_{R1} = 7.92, t_{R2} = 8.41 min.

(*S*,*E*)-5-(4-Bromophenyl)hex-3-en-2-one (12e): The reaction was performed according to general procedure 3. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **12e** (64%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.86 (dd, J = 16.0, 6.6 Hz, 1H), 6.05 (d, J = 16.0 Hz, 1H), 3.84–3.41 (m, 1H), 2.24 (s, 3H), 1.42 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.61, 150.71, 142.22, 131.86, 129.87, 129.08, 120.68, 41.67, 27.14, 20.09 ppm; HRMS (EI): calcd for $C_{12}H_{13}BrO$: 252.0150 $[M]^+$; found: 252.0149; $[\alpha]_D^{20}$ = −13.4 (c = 1, CH_3Cl) for 91% of *ee*. The enantiomeric excess was determined by chiral SFC on a chiral stationary phase (Chiralcel AD column, method: MeOH 2%-2–1–15, 40 °C): t_{R1} = 9.05, t_{R2} = 9.64 min.

(*R*,*E*)-6-Methyltridec-4-en-3-one (12g): The reaction was performed according to general procedure 3. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 98:2) to afford **12g** (65%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (dd, J = 16.0, 7.9 Hz, 1H), 6.05 (d, J = 15.9 Hz, 1H), 2.57 (q, J = 7.4 Hz, 2H), 2.42–2.16 (m, 1H), 1.46- 1.20 (m, 12H), 1.10 (t, J = 7.3 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 0.91–0.81 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.49, 152.52, 128.25, 36.73, 36.16, 33.23, 31.83, 29.61, 29.21, 27.24, 22.64, 19.51, 14.08, 8.22 ppm; HRMS (EI): calcd for $C_{14}H_{26}O$: 210.1984

$[M]^+$; found: 210.1984; $[\alpha]_D^{20} = -18.2$ ($c = 1$, CH_3Cl) for 80% of *ee*. The enantiomeric excess was determined by chiral GC on a chiral stationary phase (Lipodex E column, method: 60–0–1–100–200, 45 $cm\,s^{-1}$): $t_{R1} =$ 230.42, $t_{R2} = 231.87$ min.

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