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One-Pot Asymmetric Conjugate Addition−Trapping of Zinc Enolates by Activated Electrophiles

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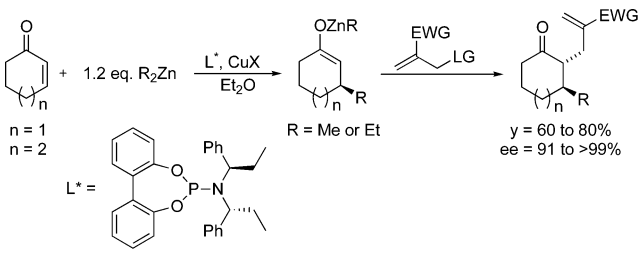

The copper-catalyzed asymmetric conjugate addition of dialkyl zinc leads to homochiral zinc enolates. These intermediates were trapped in situ with activated allylic electrophiles, without the need of additional palladium catalysis. High *trans* selectivity (85/15 to 100/0) and excellent enantioselectivities (up to 99%) could be attained. The functionalized nature of the electrophiles makes the new synthons potential candidates for further elaboration.

Introduction

The copper-catalyzed conjugate addition is a very useful reaction to control carbon−carbon bond formation on the β position of enones.[1−3] Recent years have seen tremendous advances in the asymmetric variant of this reaction with ee's greater than 99%, using as little as 0.5 mol % of copper salt and 1 mol % of chiral ligand.[4,5] When the primary organometallic is a dialkyl zinc species, these reactions end up with the formation of a zinc enolate that is, usually, simply hydrolyzed. However, these enolates may be trapped with a variety of electrophiles, thus creating a second stereocenter, α to the carbonyl group. Although the concept of conjugate addition−enolate trapping is not new[6] and has been extensively applied to the synthesis of natural products,[7] it has scarcely been used with the particularly poorly reactive homochiral zinc enolates.[8] Thus, in addition to silylation,[9] aldol reactions may be performed with aldehydes,[10,11] acetals, or orthoformate,[12] and α-halogenation can be done by addition of halogenating agents.[13] Alkyl iodides react under forcing conditions (10−20 equiv and HMPA),[14,15] whereas allylic acetates react with added Pd catalyst.[10,11] Allyl bromide itself reacts very sluggishly without Pd catalysis.

In the course of our studies on the reactivity of zinc enolates,[16,17] we considered that more reactive allylic halides could be good candidates for this trapping. Particularly, we thought that Pd catalysis might not be needed, the present copper catalyst being enough. The chosen substrates all share the same characteristic: an electron-withdrawing group in vinylic position and a leaving group in allylic position (Figure 1). Although the reaction proceeds probably by a conjugate addition−elimination mechanism, they are usually considered as allylic substitutions.[18,19]

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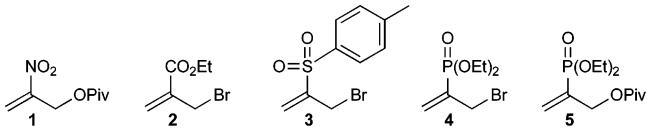

FIGURE 1. Electrophiles used to trap zinc enolates.

TABLE 1. Conjugate Addition−Trapping with Electrophiles

entry	$E^{\oplus}$	trapping conditions (°C)	**8**	**9**	**10**
1	**1**	+20	51%	49%	0%
2	**1**	−30	82%	18%	0%
3	**2**	−30	13%	56%	31%
4	**3**	+20	36%	64%	0%
5	**3**	−30	12%	77%	11%
6	**4**	+20	45%	55%	0%
7	**4**	−30	36%	64%	0%
8	**5**	+20	11%	10%	78%

Results and Discussion

The synthesis of **1**−**5** was done according to known procedures or by modifications of described ones (see Experimental Section for details). The asymmetric conjugate addition was first performed under our usual conditions[4,16,20,21] (1.2 equiv of Et_2Zn, 1% $CuOTf_2$, 2% **L1**, Et_2O, −30 °C), then the electrophiles **1**−**5** were added (1.2 equiv), and the mixture was either maintained at −30 °C (15 h) or warmed to room temperature for 6 h.

As anticipated, the conversion of the conjugate addition is quantitative. The resulting zinc enolate is reactive enough in most cases, as can be seen by the amount of the hydrolyzed conjugate adduct **10** left (see Table 1). Even at −30 °C, substrates **1** and **4** react quantitatively, without any metal catalyst other than the present copper salt. Only pivalate **5** is much less reactive than its corresponding bromide **4**. However, the most striking observation was the large amount of ethyl adducts **9**. In the previously reported Pd-catalyzed allylations with allyl acetate, such products were never noticed, probably because of the volatility of the resulting 1-pentene.[10,11] The ratio of the desired product **8** versus the ethyl adduct **9** varies with the temperature of the trapping reaction. Except for **1** (entries 1 and 2), low temperature has a detrimental effect. Changing the solvent of the second step from Et_2O to CH_2Cl_2, toluene, or THF did not alter fundamentally these results.

The large amounts of undesired product **9** could not result only from the 20% excess of Et_2Zn used. Indeed, a control experiment with 0.8 equiv of Et_2Zn was performed, in which case no Et_2Zn is anymore available (Scheme 2). The fact that 43% of **9d** is still present could only be explained by the respective reactivity, on **7**, of the ethyl group and the enolate, both linked to Zn.[10,11] This is rather unusual, as on the trapping with aldehydes or acetals, to form the aldol product, the transfer of the ethyl group was never observed.[5,10−12,22−24]

TABLE 2. Trapping in the Presence of Additional Catalysts

entry	$E^{\oplus}$	catalyst	**8**[c]	**9**[c]	unreacted $E^{\oplus}$[c]	**10**[c]
1[a]	**4**	2% Pd	44%	15%	41%	trace
2[b]	**5**	2% Pd	36%	7%	57%	trace
3[b]	**2**	2% Pd	9%	28%	41%	22%
4[b]	**2**	2% Ni	4%	28%	49%	19%

[a] Trapping proceeds at −30 °C. [b] Trapping proceeds at room temperature. [c] ^1H NMR or ^{31}P NMR ratio.

It possibly could be argued that palladium catalysis may help in a better discrimination of the transfer of the ethyl group versus the enolate. To check this point, we repeated some experiments (according to Scheme 1) with added $Pd(PPh_3)_4$ or $Ni(acac)_2$, 2 mol %, with trapping at −30 °C. As can be seen from Table 2 there is indeed some improvement with substrates **4** and **5** but not with **2**, with either Pd or Ni.

As the most interesting alkyl group in natural product synthesis is the methyl group, we tested the same reaction with Me_2Zn (Scheme 3). An additional advantage in such a reaction would be the differential reactivity on the mixed zinc enolate. While the reactivity of the enolate part would essentially be the same as previously, the reactivity of the Me group is notoriously lower than that of the Et group.[4,11] The results are shown in Table 3. Indeed, as compared to the results with Et_2Zn (Tables 1 and 2), the ratio of the desired product **12** versus the product of the methyl transfer **13** is significantly better. Thus **12a** was obtained in 85% yield instead of 51% for **8a**. The same trend is observed with the other electrophiles. Only substrate **5** was not tested, as its reactivity was much poorer than that of its sister substrate **4**. We have also tested the influence of Pd catalysis (with $Pd(PPh_3)_4$). Although larger amount of unreacted electrophile were observed, the ratio of **12** versus **13** is greatly improved, particularly for substrates **2**, **3**, and **4** (compare entries 2 and 6, 2 and 7, 4 and 8).

As our goal was to avoid additional catalyst, we sought a simpler solution. The obtained products **8** and **9**, and **12** and **13**, are easily separable on column chromatography. Therefore, we just added more of the electrophile, 1.5−2.4 equiv instead of 1.2. Another modification was done in order to improve the enantioselectivity of the first step, the asymmetric conjugate addition. This was to replace $Cu(OTf)_2$ by copper thiophene carboxylate (CuTC).[20,25,26] In addition, we also tested cycloheptenone **15** as starting enone. The results obtained according to Scheme 4 are shown in Table 4.

In all cases, the isolated yield of the alkylated product is good. Only with the phosphonate derivatives **8d** and **12d** were the products not fully separated from the ethylated or methylated products **9d** or **13d**. The enantioselectivity was measured on the final product, and it is excellent in all cases. In fact, the true enantiodetermining step is the conjugate addition. The other very important point is the *trans*/*cis* ratio of the final product. Although the most thermodynamically stable isomer, the selective formation of the *trans* product results from the allylation from the least sterically hindered face of the enolate. This is agreement with all previous results of the literature on such tandem conjugate addition−enolate trapping.[7]

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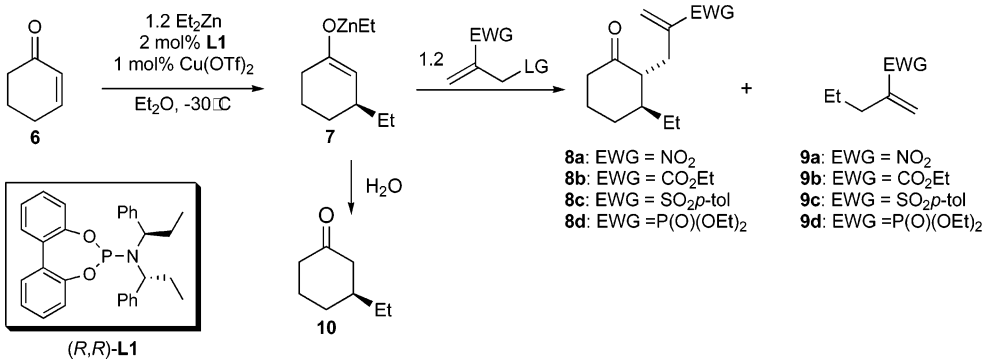
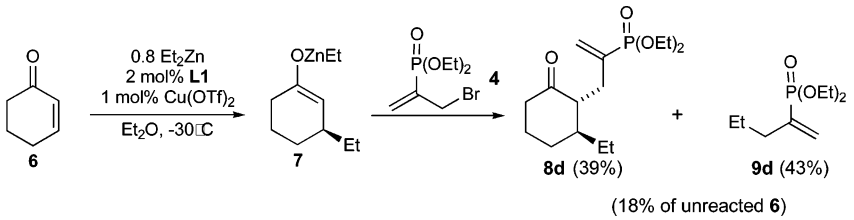
SCHEME 1. Conjugate Addition of Diethyl Zinc−Trapping with Electrophiles



SCHEME 2. Control Experiment with Default of Et_2Zn



SCHEME 3. Conjugate Addition of Dimethyl Zinc−Trapping with Electrophiles

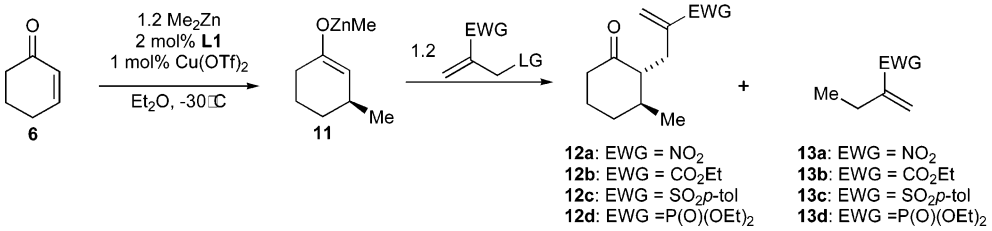
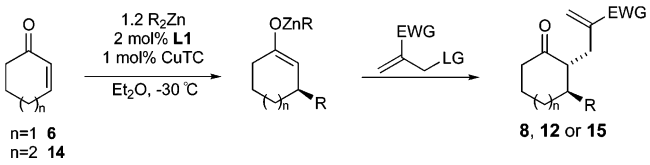


TABLE 3. Addition of Me_2Zn−Trapping with 1−4

entry	E⊕	catalyst	**12**[c]	**13**[c]	unreacted E⊕[c]
1[a]	**1**		85%	15%	0%
2[b]	**2**		37%	47%	16%
3[a]	**3**		24%	29%	47%
4[a]	**4**		52%	48%	trace
5[a]	**1**	2% Pd	88%	12%	0%
6[b]	**2**	2% Pd	65%	14%	21%
7[a]	**3**	2% Pd	32%	21%	47%
8[a]	**4**	2% Pd	62%	11%	27%

[a] Trapping proceeds at −30 °C. [b] Trapping proceeds at room temperature. [c] ^{1}H NMR or ^{31}P NMR ratio.

SCHEME 4. Conjugate Addition−Trapping with Electrophiles under Optimized Conditions



In summary, the allylic alkylation of the zinc enolates, resulting from an asymmetric copper-catalyzed conjugate addition of dialkyl zinc, could be performed with activated allylic substrates, in high yields and enantioselectivities. The reaction is done as a one-pot procedure, and there is no need to have an additional catalyst. The isolated yields are good, the enantioselectivities are excellent, and the *trans*/*cis* ratio is very good. The resulting functionalized compounds are useful synthetic intermediates and their application in natural product synthesis is under way.

TABLE 4. Results According to Scheme 4

entry	*n*	R_2Zn	E⊕ (equiv)	product	yield[a]	*trans*/*cis*[b]	ee[c]
1	1	Et_2Zn	**1** (1.5)	**8a**	72%	95/5	99.1%
2	1	Et_2Zn	**2** (2.4)	**8b**	70%	91/9	98.7%
3	1	Et_2Zn	**3** (2.4)	**8c**	60%	78/22[f]	98.7%
4	1	Et_2Zn	**4** (2.4)	**8d**	65%[g]	88/12	>98%[d]
5	1	Me_2Zn	**1** (1.5)	**12a**	80%	90/10	98.5%
6	1	Me_2Zn	**2** (2.4)	**12b**	74%	94/6	98.9%
7	1	Me_2Zn	**3** (2.4)	**12c**	73%	89/11	99.1%
8	1	Me_2Zn	**4** (2.4)	**12d**	67%[g]	nd	>98%[d]
9	2	Et_2Zn	**1** (1.5)	**15a**	68%	>98%	90.8%
10	2	Et_2Zn	**2** (2.4)	**15b**	72%	>98%	94.6%

[a] Isolated yield. [b] Determined by GC−MS. [c] Determined by chiral GC or SFC on the final products for major dia. [d] Determined on the conjugate addition step. [f] Measured by ^{1}H NMR. [g] Not fully separated from **9d** or **13d**.

Experimental Section

2′-Nitro-2′-propen-1′-yl 2,2-dimethylpropanoate (1). According to the literature[27,28] the following modifications were done. A mixture of crude 2-nitropropane-1,3-diol (99.2 g, 813 mmol, 1

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equiv) in 325 mL of CH_2Cl_2 was vigorously stirred and heated to reflux. Pivaloyl chloride (250 mL, 2 mol, 2.5 equiv) was added in 3 h, and the HCl evolution was monitored by a bubbler. After the end of introduction, the mixture was left still 1 h under reflux, then it was cooled to room temperature, and left overnight with stirring. The solvent and most of the rest of PivCl were removed by evaporation to give crude 2′-nitrotrimethylene bis(2,2-dimethylpropanoate). All the crude was distilled under vacuum. PivCl and PivOH distill first and then a mixture of PivOH, **1**, and 2′-nitrotrimethylene bis(2,2-dimethylpropanoate). A second distillation and then a third distillation were done affording 94.50 g of pure compound **1** (62% yield, bp 82−84 °C).

3-(5,5-Dimethylpropanoate)-2-propenyl-diethylphosphonate (5). According to the literature[29] the following modifications were done. Pivaloyl chloride (2.25 mL, 2 equiv) was added to a solution of the corresponding allylic alcohol (1.75 g, 9 mmol, 1 equiv) in 5 mL of CH_2Cl_2 at room temperature. This mixture was then heated to reflux for 2 h and cooled at room temperature. The solvent and the excess of acid chloride were removed by evaporation, and the crude product was purified by chromatography (silica, AcOEt/MeOH, 9/1). This gave pure phosphonate **5** as a colorless liquid (1.02 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, J = 22.5 Hz, J = 1.2 Hz, 1H), 5.98 (dd, J = 46.0 Hz, J = 1.2 Hz, 1H), 4.69 (d, J = 7.8 Hz, 2H,), 4.10 (m, 4H), 1.32 (t, 6H, J = 7.1 Hz), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 134.8 (d, J = 177.2 Hz), 130.1 (d, J = 6.6 Hz), 62.6 (d, J = 18.1 Hz), 62.0 (d, J = 5.0 Hz), 38.8, 27.1, 16.2 (d, J = 5.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.78. IR ($CDCl_3$) ν (cm^{-1}) 2983, 1729, 1480, 1153 (large), 1028 (large), 973. LRMS (EI, 70 eV, m/z) 279 $(M + H)^{+\bullet}$, 193 $(M - OPiv)^{+\bullet}$, 57 (base peak). HRMS m/z $M^{+\bullet}$ calcd for $C_{12}H_{23}O_5P$ 278.1283, found 278.1264.

Allyl(p-tolyl)sulfane. According to the literature[30] the following modifications were done. *p*-Thiocresol (24.8 g, 200 mmol, 1 equiv) was added at 50 °C with stirring to a solution of NaOEt (8.7 g of Na, 200 mmol, 1 equiv in 112 mL of absolute ethanol). This mixture was cooled to 0 °C, and allyl chloride (33 mL, 400 mmol, 2 equiv) was added in 15 min. The reaction mixture was stirred for 1 h at 0 °C, then the water−ice bath was removed, and stirring was continued for 19 h at room temperature. The solvent was evaporated and the residue was taken up in Et_2O and water. The organic layer was washed with water dried with anhydrous $MgSO_4$ and evaporated. The product was purified by distillation under vacuum affording allyl(*p*-tolyl)sulfane as a colorless liquid (30.0 g, 90% yield). Bp (∼1 mmHg) 76−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 5.89 (ddt, J = 9.8 Hz, J = 7.1 Hz, J = 7.1 Hz, 1H), 5.09 (m, 2H), 3.53 (d, J = 7.1 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 133.8, 132.0, 130.6, 129.5, 117.4, 37.8, 21.0. IR (neat) ν (cm^{-1}) 3080, 3019, 2979, 2919, 1636, 1492, 915, 801. LRMS (EI, 70, eV m/z) 164 ($M^{+\bullet}$, base peak), 149, 123. HRMS m/z $M^{+\bullet}$ calcd for $C_{10}H_{12}S$ 164.0660, found 164.0657.

1-(9,10-Dibromo-propane-8-sulfonyl)-4-methyl-benzene. According to the literature[30] the following modifications were done. To a solution of allyl(*p*-tolyl)thioether (26 g, 158 mmol, 1 equiv) in 140 mL of CCl_4 cooled to −10 °C was added in 2 h a solution of bromine (8.13 mL, 158 mmol, 1 equiv) in 70 mL of CCl_4, keeping the temperature below −10 °C. The slightly orange solution was allowed to reach room temperature and was added in 40 min to a suspension of *m*-CPBA (93.9 g, 379 mmol, 2.4 equiv) in 800 mL of methylene chloride at −10 °C. The bath was then removed, and stirring was continued for 24 h at room temperature. The mixture was diluted with ether and saturated $NaHCO_3$, and the organic layer was washed several times with aqueous $NaHCO_3$. Drying with anhydrous $MgSO_4$ and evaporation of the solvent gave crude dibromo sulfone in nearly quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 3.84 (m, 4H), 3.54 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 134.0, 130.2, 129.0, 65.5, 26.4, 21.7. IR ($CDCl_3$) ν (cm^{-1}) 3033, 2975, 2926, 2261, 1597, 1324 (large), 1150 (large). LRMS (EI, 70, eV m/z) 356 ($M^{+\bullet}$), 277 $(M - {}^{79}Br)^{+\bullet}$, 275 $(M - {}^{81}Br)^{+\bullet}$, 91 (base peak). HRMS m/z $(M - {}^{79}Br)^{+\bullet}$ calcd for $C_{10}H_{12}O_2S^{81}Br$ 276.9721, found 276.9715. $(M - {}^{81}Br)^{+\bullet}$ calcd for $C_{10}H_{12}O_2S^{79}Br$ 274.9741, found 274.9761.

1-(9-Bromo-prop-8-ene-8-sulfonyl)-4-methyl-benzene (3). According to the literature[30] the following modifications were done. The above crude dibromo sulfone (5.4 g, 15 mmol, 1 equiv) was dissolved in a mixture composed of 30 mL of dry ether and 20 mL of dry CH_2Cl_2. Once the solution became clear, anhydrous NaOAc (5.7 g, 69 mmol, 4.6 equiv) was added at room temperature and the reaction was followed by ^{1}H NMR. Once the conversion was complete, the reaction mixture was filtered, and the solvent removed by evaporation. This gave crude **3** in nearly quantitative yield and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 6.59 (s, 1H), 6.21 (s, 1H), 4.09 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 145.1, 135.6, 130.0, 128.5, 128.3, 25.2, 21.6. IR ($CDCl_3$) ν (cm^{-1}) 2927, 2260, 1597, 1318 (large), 1149 (large). LRMS (EI, 70, eV m/z) 276 ($M^{+\bullet}$), 274 ($M^{+\bullet}$), 195 $(M - Br)^{+\bullet}$, 91 (base peak). HRMS m/z $(M - Br)^{+\bullet}$ calcd for $C_{10}H_{11}O_2S^{81}Br$ 275.9643, found 275.9640; calcd for $C_{10}H_{11}O_2S^{79}Br$ 273.9663, found 273.9673.

General Procedure for Asymmetric Conjugate Addition with Diethylzinc (ACA1). Dry ether (2 mL) was added to a dry round-bottom flask containing copper thiophene carboxylate (CuTC) (3.8 mg, 0.02 mmol, 1%) and ligand (*R*,*R*)-**L1** (18.8 mg, 0.04 mmol, 2%) under Ar. This mixture was stirred for 20 min at room temperature and was cooled to −30 °C. After 20 min, diethylzinc solution (1.0 M in hexane, 2.4 mL, 2.4 mmol, 1.2 equiv) was added, followed 20 min later by 2-cyclohexenone **6** (193 μL, 2 mmol, 1 equiv) or 2-cycloheptenone **14** (220.2 mg, 2 mmol, 1 equiv). The solution was stirred until complete consumption of the starting material (usually 2−5 h).

General Procedure for Asymmetric Conjugate Addition with Dimethylzinc (ACA2). Dry ether (2 mL) was added to a dry round-bottom flask containing copper thiophene carboxylate (CuTC) (7.7 mg, 0.04 mmol, 2%) and ligand (*R*,*R*)-**L1** (37.4 mg, 0.08 mmol, 4%) under Ar. This mixture was stirred for 20 min at room temperature and was cooled to 0 °C. After 20 min, dimethylzinc solution (2.0 M in toluene, 1.2 mL, 2.4 mmol, 1.2 equiv) was added, followed 20 min later by 2-cyclohexenone **6** (193 μL, 2 mmol, 1 equiv). The solution was stirred until complete consumption of the starting material (usually 2−5 h).

General Procedure for Quench, after Addition of the Electrophiles 1−5. The mixture was hydrolyzed with HCl 10% and ether. The aqueous layer was washed three times with ether. The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo.

(3)-Ethyl-(2)-[(8-nitro)-allyl]-cyclohexanone (8a). Following the general procedure ACA1 for the first step, the nitroolefin **1** (562.2 mg, 3.0 mmol, 1.5 equiv) was then added. The cooling bath was removed, and the mixture was stirred for 6 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, pentane/Et_2O 8/2), to afford the desired compound **8a** as a slightly yellow oil (305.6 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 5.73 (s, 1H), 2.95 (dd, J = 20.1 Hz, J = 12.8 Hz, 1H), 2.79 (dd, J = 15.2 Hz, 2.3 Hz, 1H), 2.41 (m, 2H), 2.29 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.53 (m, 5H), 0.96 (t, J = 10.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 156.6, 119.8, 53.3, 45.7, 41.9, 29.7, 27.2, 26.1, 26.0, 10.3. IR ($CDCl_3$) ν (cm^{-1}) 2971, 1735, 1706, 1526, 1147 (broad). LRMS (EI, 70 eV, m/z) 211 $M^{+\bullet}$, 166 $(M - NO_2)^{+\bullet}$, 57 (base peak). HRMS m/z $(M - NO_2)^{+\bullet}$ calcd for $C_{11}H_{17}O$ 165.1279, found 165.1265. $[\alpha]^{20}_D$ = +12.5 (c 1.00, $CHCl_3$). ee of 99.1% was measured by chiral SFC

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with a chiracel AD column (program: 2% MeOH-5′ 1−10%, 200 bar, 2 mL/min, 30 °C). t_R: 3.28 and 3.74.

Ethyl 2-((2-ethyl-6-oxocyclohexyl)methyl)acrylate (8b). Following the general procedure ACA1 for the first step, the bromoester **2** (929.1 mg, 4.8 mmol, 2.4 equiv) was then added. The mixture was removed from the cooling bath and stirred for 6 h at room temperature. The mixture was then quenched following the general procedure. The crude was purified by flash column chromatography (silica, pentane/Et_2O 9/1), to afford the desired compound **8b** as a colorless liquid (331.5 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.60 (s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.69 (dd, J = 14.4 Hz, J = 9.3 Hz, 1H), 2.43 (m, 3H), 2.25 (m, 1H), 1.95 (m, 2H), 1.59 (m, 4H), 1.35 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 167.1, 138.9, 126.4, 60.6, 54.5, 45.0, 41.2, 29.8, 28.4, 26.1, 25.2, 14.1, 10.7. IR ($CDCl_3$) ν (cm^{-1}) 3022, 2963, 1708, 1210. LRMS (EI, 70 eV, *m*/*z*) 238 $M^{+\bullet}$, 209 $(M - Et)^{+\bullet}$, 163 (base peak). HRMS *m*/*z* $M^{+\bullet}$ calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1557. $[\alpha]^{20}_D = +15.1$ (*c* 1.04, $CHCl_3$). ee of 98.7% was estimated by two chiral GC: one with a CHIRALSIL-DEX CB column (program: 90°-0′-1°/′-170°-10′, speed 30 cm/s). For major dia t_R: 58.78. For minor dia t_R: 5.95 and 10.362. The other with a CHIRAL-DEX G-TA column (program: 100°-60′-1°/′-170°-5′, speed 47 cm/s). For major dia t_R: 89.26 and 91.38 + for minor dia t_R: 91.38.

3-Ethyl-2-[8-toluene-10-sulfonyl)allyl]-cyclohexanone (8c). Following the general procedure ACA1 for the first step, the sulfone **3** (1.34 g, 4.8 mmol, 2.4 equiv) was then added. The mixture was removed from the cooling bath and stirred for 7 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, cyclohexane/ethyl acetate 8/2), to afford the desired compound **8c** as a colorless oil (383.8 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.34 (s, 1H), 5.77 (s, 1H), 2.64 (dd, J = 15.7 Hz, J = 9.1 Hz, 1H), 2.52 (dt, broad, J = 9.1 Hz, J = 2.3 Hz, 1H), 2.43 (s, 3H), 2.31 (m, 2H), 2.23 (dt, J = 12.1 Hz, J = 5.8 Hz, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.54 (m, 2H), 1.41 (m, 2H), 1.27 (dt, J = 7.3 Hz, J = 6.8 Hz, 1H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 148.6, 144.4, 135.9, 129.7, 128.2, 125.3, 53.6, 45.4, 41.6, 29.3, 26.6 (d, J = 30.5 Hz), 26.1, 25.9, 21.6, 10.4. IR ($CDCl_3$) ν (cm^{-1}) 2962, 2927, 2863, 1708, 1596, 1447, 1311, 1301, 1290, 1167, 1134, 1081, 951, 814, 731. LRMS (EI, 70 eV, *m*/*z*) 321 $(M + H)^{+\bullet}$, 166 $(M - SO_2p\text{-tol})^{+\bullet}$, 165 (base peak) 123, 91. Elemental analysis for $C_{18}H_{24}O_3S$: calcd C 66.50, H 7.53. Found: C 67.47, H 7.55. $[\alpha]^{20}_D = +29.3$ (*c* 1.00, $CHCl_3$). ee of 98.7% for major dia and ee of 99.1% for minor dia were measured by chiral SFC with a CHIRALPAK AS column (program: 3% MeOH-10′-1-25%, 200 bar, 2 mL/min, 30 °C). For major dia t_R: 6.37 and 7.16. For minor dia t_R: 7.97 and 11.61.

(3)-Methyl-(2)-[(8-nitro)-allyl]-cyclohexanone (12a). Following the general procedure ACA2 for the first step, the nitroolefin **1** (562.5 mg, 3.0 mmol, 1.5 equiv) was then added. The mixture was removed from the cooling bath and stirred for 3 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, pentane/Et_2O 8/2) to afford the desired compound **12a** as a slightly yellow liquid (316.8 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.74 (s, 1H), 2.96 (dd, J = 15.2 Hz, J = 9.8 Hz, 1H), 2.77 (d, J = 15.0 Hz, 1H), 2.33 (m, 1H), 2.06 (m, 1H), 1.89 (m, 1H), 1.67 (m, 2H), 1.52 (m, 1H), 1.18 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 156.7, 119.9, 55.6, 42.0, 40.1, 34.3, 27.1, 26.4, 20.5. IR ($CDCl_3$) ν (cm^{-1}) 2964, 2935, 1709, 1526, 1343. LRMS (EI, 70 eV, *m*/*z*) 152 $(M - NO_2)^{+\bullet}$, 109, 57 (base peak). HRMS *m*/*z* $(M - H)^{+\bullet}$ calcd for $C_{10}H_{14}O_3N$ 196.0974, found 196.0949, $(M - NO_2)^{+\bullet}$ calcd for $C_{10}H_{15}O$ 151.1123, found 151.1120. $[\alpha]^{20}_D = +14.7$ (*c* 1.00, $CHCl_3$). ee of 98.5% was measured by chiral SFC with a chiracel AD column (program: 3% MeOH-5′-1-10%, 200 bar, 2 mL/min, 30 °C). t_R: 2.95 and 3.47.

Ethyl 2-((2-Methyl-6-oxocyclohexyl)methyl)acrylate (12b). Following the general procedure ACA2 for the first step, the bromoester **2** (925.1 mg, 4.8 mmol, 2.4 equiv) was then added. The mixture was removed from the cooling bath and stirred for 3 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, pentane/Et_2O 9/1) to afford the desired compound 12b as a colorless liquid (331.3 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.62 (s, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.71 (dd, J = 14.5 Hz, J = 9.4 Hz, 1H), 2.44 (d, J = 14.7 Hz, 1H), 2.31 (m, 3H), 2.01 (m, 1H), 1.87 (m, 1H), 1.96 (m, 2H), 1.49 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 167.2, 139.1, 126.3, 60.5, 56.6, 41.7, 39.7, 33.5, 29.0, 25.9, 20.5, 14.1. IR ($CDCl_3$) ν (cm^{-1}) 2934, 1709, 1194, 1151 cm^{-1}. LRMS (EI, 70 eV, *m*/*z*) 224 $M^{+\bullet}$, 209 $(M - Me)^{+\bullet}$, 111 (base peak). HRMS *m*/*z* $M^{+\bullet}$ calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1405. $[\alpha]^{20}_D = +3.9$ (*c* 1.17, $CHCl_3$). ee of 98.9% was measured by chiral GC with a CHIRALSIL-DEX CB column (program: 90°-0′-1°/′-170°-10′, speed 30 cm/s). t_R: 51.29 and 51.68.

3-Methyl-2-[8-toluene-10-sulfonyl)allyl]-cyclohexanone (12c). Following the general procedure ACA2 for the first step, the sulfone **3** (1.32 g, 4.8 mmol, 2.4 equiv) was then added. The mixture was removed from the cooling bath and stirred for 6 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, cyclohexane/ethyl acetate 8/2) to afford the desired compound **12c** as a colorless oil (446.9 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 6.35 (s, 1H), 5.81 (s, 1H), 2.68 (dd, J = 15.4 Hz, J = 9.4 Hz, 1H), 2.49 (dt, broad, J = 9.1 Hz, J = 1.0 Hz, 1H), 2.43 (s, 3H), 2.26 (m, 3H), 2.23 (dt, J = 12.1 Hz, J = 5.8 Hz, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.56 (m, 2H), 1.46 (dt, J = 12.5 Hz, J = 3.4 Hz, 1H), 1.03 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 148.6, 144.4, 135.9, 129.7, 128.2, 125.5, 55.9, 41.8, 39.9, 34.1, 26.33, 26.30, 21.6, 20.5. IR ($CDCl_3$) ν (cm^{-1}) 2956, 2923, 2863, 1704, 1597, 1457, 1429, 1399, 1383, 1309, 1298, 1286, 1163, 1155, 1133, 1078, 944, 916, 812, 727. LRMS (EI, 70 eV, *m*/*z*) 307 $(M + H)^{+\bullet}$ 152 $(M - SO_2p\text{-tol})^{+\bullet}$, 151 (base peak), 91, 79. HRMS *m*/*z* $[M + H]^+$ calculated for $C_{17}H_{22}O_3S$ 307.1362, found 307.1375. $[\alpha]^{20}_D = -18.7$ (*c* 0.99, $CHCl_3$). ee of 99.1% was measured by chiral SFC with a chiracel OB−H column (program: 3% MeOH-7′-3-25%, 200 bar, 2 mL/min, 55 °C). For major dia t_R: 4.45 and 5.53 + for minor dia t_R: 5.99 and 10.362.

(3)-Ethyl-(2)-[(9-nitro)-allyl]-cycloheptanone (15a). Following the general procedure ACA1 for the first step, the nitroolefin **1** (562.3 mg, 3 mmol, 1.5 equiv) was then added. The mixture was removed from the cooling bath and stirred 6 h at room temperature. The mixture was then quenched following the general procedure. The product was purified by flash column chromatography (silica, pentane/Et_2O 8/2), to afford the desired compound **15a** as a slightly yellow liquid (305.6 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, J = 1.8 Hz, 1H), 5.61 (s, 1H), 2.88 (m, 2H), 2.67 (dt, J = 8.1 Hz, J = 3.3 Hz, 1H), 2.48 (m, 1H), 2.31 (td, J = 13.5 Hz, J = 5.7 Hz, 1H), 1.77−1.58 (m, 5H), 1.52−1.39 (m, 3H), 1.31 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3, 155.8, 119.9, 54.8, 42.1, 41.8, 31.0, 29.7, 26.0, 25.1, 24.3, 11.3. IR ($CDCl_3$) ν (cm^{-1}) 2936, 2867, 1701, 1527, 1462, 1344, 1213, 1113 (broad), 949, 863. LRMS (EI, 70 eV, *m*/*z*) 180 $(M - NO_2)^{+\bullet}$, 179, 139, 121, 95, 79, 57, 55 (base peak). HRMS *m*/*z* $[M + H]^+$ calculated for $C_{12}H_{19}O_3N$ 226.1437, found 226.1463. $[\alpha]^{20}_D = -5.1$ (*c* 1.02, $CHCl_3$). ee of 91% was measured by chiral SFC with a chiracel AD column (program: 2% MeOH-5′-1-10%, 200 bar, 2 mL/min, 30 °C). t_R: 3.48 and 3.94.

Ethyl 2-((2-Ethyl-7-oxocycloheptyl)methyl)acrylate (15b). Following the general procedure ACA1 for the first step, the bromoester **2** (928.0 mg, 4.8 mmol, 2.4 equiv) was then added. The mixture was removed from the cooling bath and stirred for 6 h at room temperature. The mixture was then quenched following the general

procedure. The product was purified by flash column chromatography (silica, pentane/Et_2O 8/2), to afford the desired compound **15b** as a colorless liquid (361.7 mg, 72% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, $J = 1.3$ Hz, 1H), 5.48 (d, $J = 1$ Hz, 1H), 4.16 (m, 2H), 2.53 (m, 4H), 2.23 (m, 1H), 1.77 (m, 2H), 1.62 (m, 3H), 1.39 (m, 1H), 1.27 (t, $J = 7.2$ Hz, 6H), 0.90 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 166.7, 138.3, 126.7, 60.6, 57.1, 41.9, 41.4, 33.4, 30.6, 26.9, 26.3, 25.6, 14.1, 11.2. IR ($CDCl_3$) ν (cm^{-1}) 2931, 2863, 1706, 1630, 1446, 1410, 1369, 1297, 1192, 1175, 1156, 1116, 1026, 946, 818. LRMS (EI) *m*/*z*: 252 $M^{+\bullet}$, 223 $(M - Et)^{+\bullet}$, 177, 139, 126, 69, 55 (base peak). HRMS *m*/*z* $[M + H]^+$ calculated for $C_{15}H_{24}O_3$ 253.1798, found 253.1781. Elemental analysis for $C_{15}H_{24}O_3$: calcd C 71.39, H 9.59. Found: C 69.99, H 9.24. $[\alpha]^{20}_D = -15.3$ (*c* 1.03, $CHCl_3$). ee of 95% was measured by chiral GC with a chirasil-DEX CB column (program: 100°-0′-1°/′-170°-10′, speed 31 cm/s), t_R: 55.73 and 56.29.

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Supporting Information Available: All NMR spectroscopic data and chiral GC or SFC of described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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