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One-pot multi-substrate enantioselective conjugate addition of diethylzinc to nitroalkenes

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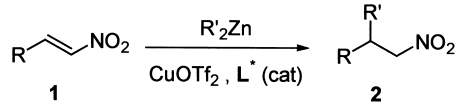
Abstract—A multi-substrate approach is used in the copper-phosphoramidite catalyzed enantioselective conjugate addition of diethylzinc to nitroalkenes, using up to nine different nitroalkenes in a one pot procedure. The 18 products (9 times 2 enantiomers of nine different nitroalkanes) can be analyzed by chiral CG in a single run since on overlap in the peaks is observed. The obtained enantioselectivities are amongst the highest reported so far for the catalytic 1,4-addition of dialkylzinc reagents to nitroalkenes.

1. Introduction

Conjugate addition reactions of dialkylzinc reagents to Michael acceptors (e.g. enones) have reached a very high level of enantioselectivity with copper catalysts based on phosphoramidites, and more recently employing phosphites, phosphonates and phosphines as chiral ligands.[1–5] The selectivities which can be obtained for acyclic substrates with these catalysts is usually lower than for the cyclic ones, though very recently Hoveyda et al. showed that a copper-dipeptide phosphine catalyst gives high enantioselectivities for both types of enones.[6,7] For acyclic substrates chalcone is often used as the model enone but nitroalkenes **1** are a more interesting class of substrates. Nitroalkenes are suitable Michael acceptors due to the strong electron-withdrawing nitro group.[8] They can be easily synthesized via the Henry condensation and many substituted nitrostyrenes are commercially available.[9] Enantioselective addition of dialkylzinc reagents to nitroalkenes leads to chiral nitroalkanes **2** and through functional group transformations, such as reduction and the Nef reaction, chiral amines and aldehydes can be obtained.[10] Nitroalkanes can also be used in a sequence involving the Henry reaction with aldehydes followed by reduction, leading to amino alcohols.[11]

Enantioselective routes to chiral nitroalkanes have been developed using stoichiometric amounts of chiral auxiliaries or Ti-TADDOLates.[12,13] Catalytic methods however, have the advantage of low amounts of chiral auxiliaries and a higher atom economy,[14] and using copper-phosphoramidite catalysts in the 1,4-addition of diethylzinc to nitroalkenes moderate to high enantioselectivities have been obtained by Sewald and Wendisch,[15] Feringa and Versleijen et al.[16] and Alexakis and Benhaim[17] (Scheme 1). Gennari and co-workers have shown that a parallel library of sulfonamide ligands is able to generate moderate enantioselectivities in the copper catalyzed conjugate addition of diethylzinc to nitroalkenes.[18] Hayashi et al. have recently shown that the rhodium catalyzed addition of arylboronic acids to cyclic nitroalkenes gives high enantioselectivities. The use of alkenylboronic acids leads to a lower selectivity however and only one example employing an acyclic nitroalkene has been reported.[19] Despite the progress in enantioselective 1,4-addition to nitroalkenes the methodology is still limited and cannot be considered of general use so far to prepare the valuable enantiomerically pure nitroalkane building blocks. Since there is no unique catalyst for all members of a substrate class, e.g. nitroalkenes, rapid fine tuning of catalyst for a particular substrate is necessary leading to tailor made catalysts. Several combinatorial methods have been developed for this purpose over the last decade,[20] most of them employing a set of parallel reactions followed by a high throughput screening technique in which all reactions are analyzed individually.[21] A one-pot procedure employing a mixture of catalysts for an enantioselective reaction is not feasible since the opposite selectivities and different reaction rates of the catalysts



Scheme 1. Copper catalyzed 1,4 addition of dialkylzinc to nitroalkenes.

Keywords: combinatorial chemistry; asymmetric catalysis; phosphoramidities; copper; conjugate addition.

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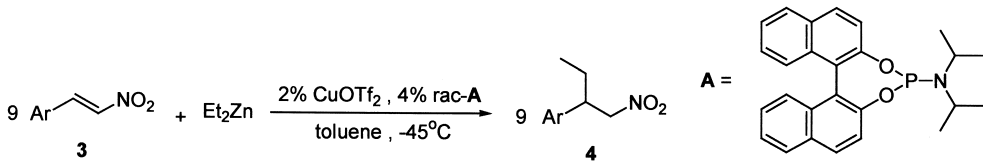
Table 1. Retention times of aromatic nitroalkenes and nitroalkanes on chiral GC

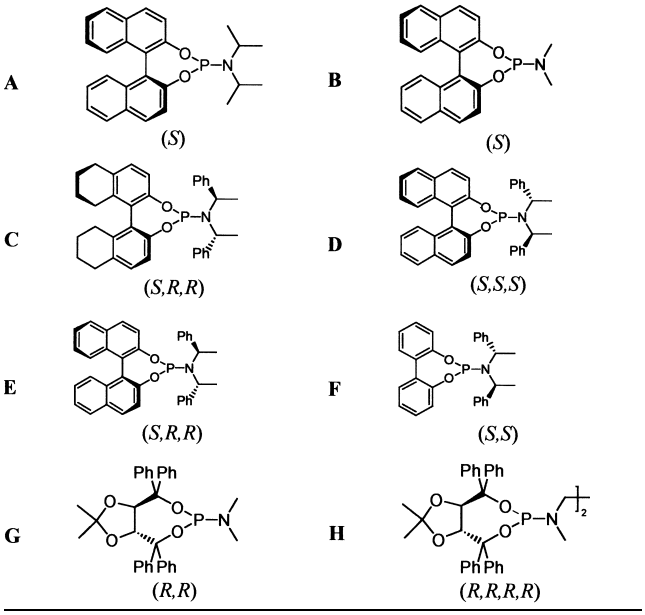


Entry	Ar	GC retention time of **3** (min)[a]	Conversion of **3** (%)	Product **4**	GC retention time of **4** (min)[a]
1	**3a**: furyl	29	100	**4a**: furyl	10.7/11.0
2	**3b**: thienyl	50	100	**4b**: thienyl	22.8/23.4
3	**3c**: C_6H_5	52	100	**4c**: C_6H_5	24.4/25.2
4	**3d**: 4-CH_3–C_6H_4	64	100	**4d**: 4-CH3–C_6H_4	36.2/37.5
5	**3e**: 4-F–C_6H_4	69	100	**4e**: 4-F–C_6H_4	39.9/40.7
6	**3f**: 4-CF_3O–C_6H_4	77	100	**4f**: 4-CF_3O–C_6H_4	41.1/42.4
7	**3g**: 4-CF_3–C_6H_4	79	100	**4g**: 4-CF_3–C_6H_4	44.9/46.2
8	**3h**: 4-CH_3O–C_6H_4	94	100	**4h**: 4-CH_3O–C_6H_4	59.2/60.2
9	**3i**: 4-$B_FC_6H_4$	174	100	**4i**: 4-$B_FC_6H_4$	77.6/78.5

[a] Analysis on an A-TA column, see Section 4 for details.

will lead to unexplicable results. In 1998 Kagan introduced the 'one-pot multi-substrate' method by reducing mixtures of up to seven different ketones in one pot with the Corey oxazaborolidine (CBS) catalyst.[22] Liskamp et al. used the one-pot multi substrate method for the addition of diethylzinc to a mixture of four aldehydes.[23] With this method the enantioselectivity of a catalyst of multiple substrates can be screened without the need for (sophisticated) parallel equipment. The absence of competing catalytic pathways will allow an unambiguous interpretation of the results. The utility of this procedure can be even more enhanced when a single chiral GC or HPLC run can analyze the products. The two basic requirements of such a system are: (i) the product peaks in the chromatogram should not overlap, and the product peaks in their turn not with the peaks resulting from unconverted starting material, (ii) the different substrates and products should not interfere with each other during the reaction, for instance by autocatalysis.[24] A major advantage is that different catalysts can be evaluated with the same setup once such a multi-substrate procedure is established. In this manuscript we report the development of a one-pot multi-substrate procedure using up to nine different nitroalkenes followed by analysis in a single chiral GC run. Moderate to high ees for aromatic nitroalkanes using copper-phosphoramidite catalysts were obtained whereas with these catalysts high ees were found for aliphatic nitroalkanes.

Table 2. Phosphoramidite ligands (absolute configuration)



2. Results and discussion

In the initial experiments single aromatic nitroalkenes **3a–i** were reacted with diethylzinc in toluene at −45°C under the influence of 2 mol% of a racemic copper phosphoramidite catalyst to give complete conversion to racemic nitroalkanes **4a–i** in 3 h (Table 1). The enantiomer separation of the nine products with chiral GC showed that the retention times of the enantiomers of the nine nitroalkanes are sufficiently different to allow separation in a single GC run. Since these reactions are not known to show autocatalytic effects,[17] the above mentioned conditions for a one-pot multi-substrate procedure are met. A one-pot multi-substrate experiment with the nine nitroalkenes **3a–i** and racemic phosphoramidite **A** under the same conditions as the individual experiments revealed that that was indeed the case. Since not all catalysts might give complete conversion the retention times of the starting materials were also determined and to our delight the peaks did not overlap and only in one case overlap with a product peak was found (**3f** entry 6 and **4i** entry 9). The starting materials are however easily removed after the reaction by a quick filtration of the concentrated reaction mixture with an apolar solvent through a short path of silica.

With this established one-pot multi-substrate procedure, eight phosphoramidites (**A–H**, Table 2)[25] were tested as chiral ligands in the copper catalyzed enantioselective conjugate addition of diethylzinc to nitroalkenes **3a–i**. In a typical experiment, 2.25 mmol of a mixture of nine nitroalkenes (**3a–i**, 0.25 mmol each) was reacted with diethylzinc and 2 mol% of catalyst in toluene at −45°C. Lower temperatures led to a lower reaction rate whereas higher temperatures were detrimental to the ee. This also

Table 3. Ees (%) of aromatic nitroalkanes in the one-pot multi-substrate procedure

Ligand	A	B	C	D	E	F	G	H
Product:								
4a	42	5	4	46	56	57	16	60
4b	48	13	1	49	66	71	52	43
4c	33	13	35	32	59[a]	77	44	38
4d	44	15	35	34	55	62	52	35
4e	47	21	28	30	63	70	48	35
4f	45	19	23	26	61	64	38	41
4g	57	13	37	6	52	48	30	36
4h	42	34	27	38	69	75	56	27
4I	54	18	31	20	63	63	46	36

Absolute configurations were not determined
[a] 48% according to Ref. 15, 2% according to Ref. 17.

holds for the use of other solvents like THF, DCM and Et_2O. With all eight ligands complete conversion was obtained within three hours. After workup and filtration, the reaction mixture was analyzed by chiral GC (Fig. 2) and the ees obtained for the products **4a–i** are shown in Table 3. In order to prove that there was no influence of the different reactions upon each other, excluding autocatalysis, different reaction rates or concentration effects,[22] the reactions were also performed separately with ligand **E**, which resulted in no difference in ee or conversion in comparison to the combinatorial reaction. In the first experiment, with enantiopure phosphoramidite ligand **A**, moderate ees were obtained, ranging from 33% for **4c** to 57% for **4g**. Ligand **B**, an excellent ligand for enantioselective hydrogenations,[26] does not lead to a high selectivity in the present reaction. A more bulky amine moiety in the ligand seemed to be important in order to obtain higher enantioselectivities and therefore ligands **C–F**, derived from bis(1-phenylethyl)-amine, were tested. The amine part of the ligand is not only important for the level of enantioselectivity; its absolute configuration also dictates the direction of the enantioselectivity. Ligands **A**, **B**, and **E** give the same major enantiomers in the products whereas for ligand **D** it is reversed. The octahydro-BINOL[27] based ligand **C** raised the ee only slightly to 35 % for **4c**, but with ligands **E** and **F** moderate to high enantioselectivities were obtained. Like in the case of the conjugate addition to enones[28] the diastereomeric ligands **D** and **E** display a matched/mismatched combination where the latter is also the matched one for the conjugate addition reactions to nitroalkenes, e.g. 32 and 59% ee for **4c**, respectively. The ees obtained for **4a–i** are the highest reported so far with ligand **E**.[14,15] Phosphoramidite **F**, which contains the atropisomeric bisphenol moiety,[29] reported by Alexakis,[30] gives even higher enantioselectivities for almost all products, leading to 77% for **4c**. For **4b** 71% ee is obtained, whereas only moderate ees have been reported until now for this substrate.[18] The influence of a bidentate ligand was investigated by comparing TADDOL phosphoramidites **G** and **H**, but no improvement was observed going from a mono- to bidentate ligand.[31] As can be concluded from Table 3, there is no clear correlation between the electronic effect of a variety of substituents on the *para* position of the arene moiety of the substrate and the ee.

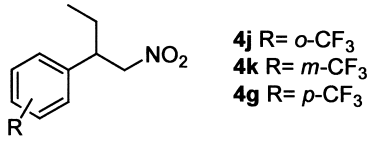
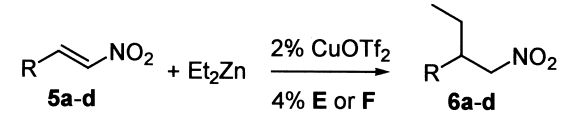
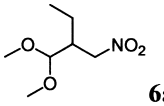
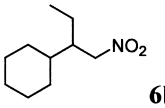
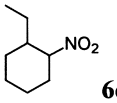
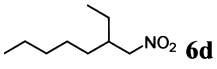


Figure 1. Trifluoromethyl-substituted aromatic nitroalkanes.

Table 4. Addition of diethylzinc to aliphatic nitroalkenes



Product **6**	Ee (%) **E**	Ee (%) **F**
 **6a**	90	87
 **6b**	82	72
 **6c**	90 (83:17)[a]	90 (84:16)[a]
 **6d**	54	–[b]

[a] *cis*:*trans* ratio.
[b] Not tested.

The position of the substituent on the aromatic ring was investigated using *ortho*-, *meta*- and *para*-trifluoromethyl-substituted nitrostyrene (**3j**, **k** and **g**) and the copper catalyst based on ligand **E**, resulting in 79, 53 and 52% ee for the corresponding nitroalkanes **4j**, **k** and **g**, respectively (Fig. 1). This result implies that steric factors might play a larger role than electronic ones in the enantiodetermining step.

Next to aromatic nitroalkenes also four aliphatic nitroalkenes were tested as substrates in the enantioselective conjugate addition (Table 4). Since ligands **E** and **F** showed the highest selectivities in the addition to aromatic nitroalkenes, these were selected for the reactions with **5a–d**. For products **6a–c** high ees and complete conversions were reached with both ligands, but ligand **E** gave slightly better results. Nitroalkane **6a**, obtained with 90% ee, is particularly interesting since it provides access to β-amino alcohols after deprotection and reduction. In our hands **6b** is obtained with 82% ee using ligand **E**, despite a reported result of 94% ee.[17,†] In the case of **6c** a *cis*/*trans* mixture of products is obtained in good yield with a high ee of 90% for both diastereomers. The 83/17 ratio of the *cis* and *trans* isomers can be converted to a 11/89 ratio in favor of the thermodynamically more stable *trans* form, by treatment with 1 equiv. of DBU at room temperature without loss of enantiomeric excess.[32]

[†] Several attempts to reproduce the literature results failed in our hands.

3. Conclusions

In conclusion we have shown that phosphoramidites are excellent ligands for the enantioselective conjugate addition of diethylzinc to nitroalkenes. In a one-pot multi-substrate procedure moderate to high ees have been obtained for a mixture of nine different aromatic nitroalkanes. The benefits of such a procedure are a considerable reduction of time in the screening and optimization of catalysts. Other catalytic systems that lead to these products, such as the enantioselective conjugate reduction of nitroalkenes,[33] can also be evaluated in this way. In the reaction with aliphatic nitroalkenes good yields and high ees can be obtained by using bis(1-phenylethyl)amine derived phosphoramidite ligands, and applications of these reactions are currently under investigation.

4. Experimental

4.1. General

Toluene was distilled from sodium. All reactions were carried out under nitrogen atmosphere using dried glassware. Chromatography: Merck silica gel Type 9385 230–400 mesh, TLC: Merck silica gel 60 F_{254}. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.25 for ^1H, $CDCl_3$: δ 77.0 for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and integration. Nitroalkenes were commercially available (**3a**–**k** and **5c**, Aldrich) or synthesized (**5a**, **b** and **d**). Phosphoramidite ligands were synthesized according to a literature procedure.[25] Enantiomer separation of compounds **4a**–**i** and **k** was performed on a HP 5890A gas chromatograph equipped with an Astec A-TA column (30 m×0.25 mm), helium as the carrier gas (1.0 mL/min) with an oven temperature of 120°C, heated to 130°C with 10°C/min after 10 min, then to 150°C with 10°C/min after 27 min and finally to 170°C with 10°C/min after 20 min. Retention times for **4a**–**i** are given in Table 1, for **4k** 39.2 and 40.5 min. Enantiomer separation of compounds **6b** and **6c** was performed on the same equipment with an oven temperature of 105°C for **6b**, retention times 57.7 and 59.7 min, and an oven temperature of 100°C for **6c**, retention times 18.3 and 19.0 min for the *cis* isomer and 20.4 and 22.8 min for the *trans* isomer. Enantiomer separation of compounds **4j**, **6a** and **6d** was performed on a HP 5890A gas chromatograph equipped with a Supelco β-dex 120 column (30 m×0.25 mm), helium as the carrier gas (1.0 mL/min). At an oven temperature of 130°C, retention times of 33.8 and 34.4 min for **4j**, and at an oven temperature of 100°C, retention times of of 34.9 and 36.0 min for **6a** and 48.4 and 49.4 min for **6d**.

4.2. General procedure A

Synthesis of racemic nitroalkanes **4a**–**i**, **6a**–**d**. In a Schlenk flask 7.2 mg (0.02 mmol) of $CuOTf_2$ was flame-dried, and together with 16.6 mg (0.04 mmol) of racemic phosphoramidite **A** dissolved in 3 mL of dry toluene. After stirring 30 min at room temperature 1.0 mmol of nitroalkene was added to the clear solution. The reaction mixture was cooled to −45°C and 1.5 mL of Et_2Zn (1.5 mmol, 1.0 M solution in hexanes) was added. The reaction mixture was stirred at −45°C for 3 h and then poured into 10 mL of saturated aqueous NH_4Cl and diluted with 10 mL of ethyl acetate. The aqueous layer was extracted twice with 10 mL of ethyl acetate and the combined organic layers were dried over Na_2SO_4, concentrated and purified with column chromatography.

4.2.1. 2-(1-Nitromethyl-propyl)-furan (4a). According to general procedure A, 139 mg (1.0 mmol) of **3a** gave 69 mg (0.4 mmol, 41% yield) of **4a** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[12,17]

4.2.2. 2-(1-Nitromethyl-propyl)-thiophene (4b). According to general procedure A, 155 mg (1.0 mmol) of **3b** gave 82 mg (0.4 mmol, 44% yield) of **4b** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[12]

4.2.3. (1-Nitromethyl-propyl)-benzene (4c). According to general procedure A, 149 mg (1.0 mmol) of **3c** gave 75 mg (0.4 mmol, 42% yield) of **4c** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[12,17]

4.2.4. 1-Methyl-4-(1-nitromethyl-propyl)-benzene (4d). According to general procedure A, 163 mg (1.0 mmol) of **3d** gave 106 mg (0.5 mmol, 55% yield) of **4d** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[12,17]

4.2.5. 1-Fluoro-4-(1-nitromethyl-propyl)-benzene (4e). According to general procedure A, 167 mg (1.0 mmol) of **3e** gave 105 mg (0.5 mmol, 53% yield) of **4e** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. ^1H NMR δ: 7.13 (m, 2H), 7.01 (m, 2H), 4.52 (m, 2H), 3.36 (m, 1H), 1.69 (m, 2H), 0.82 (t, J=7.5 Hz, 3H); ^{13}C NMR δ: 163.6 (s), 134.9 (s), 129.0 (d), 128.9 (d), 115.9 (d), 115.6 (d), 80.6 (t), 45.2 (d), 26.1 (t), 11.4 (q); HRMS Calcd for $C_{10}H_{12}NO_2F$ 197.0851. Found 197.0856.

4.2.6. 1-(1-Nitromethyl-propyl)-4-trifluoromethoxy-benzene (4f). According to general procedure A, 233 mg (1.0 mmol) of **3f** gave 110 mg (0.4 mmol, 42% yield) of **4f** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. ^1H NMR δ: 7.20 (m, 5H), 4.55 (m, 2H), 3.38 (m, 1H), 1.70 (m, 2H), 0.83 (t, J=7.5 Hz, 3H); ^{13}C NMR δ: 148.4 (s), 138.0 (s), 128.9 (d), 121.2 (d), 118.6 (s), 80.3 (t), 45.2 (d), 26.1 (t), 11.4 (q); HRMS Calcd for $C_{11}H_{12}NO_3F_3$ 263.0769. Found 263.0760.

4.2.7. 1-(1-Nitromethyl-propyl)-4-trifluoromethyl-benzene (4g). According to general procedure A, 217 mg (1.0 mmol) of **3g** gave 106 mg (0.4 mmol, 43% yield) of **4g** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. ^1H NMR δ: 7.60 (d,

J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 4.58 (m, 2H), 3.44 (m, 1H), 1.74 (m, 2H), 0.84 (t, J=7.5 Hz, 3H); ^{13}C NMR δ: 143.4 (s), 127.9 (d), 125.9 (d), 125.8 (s), 80.1 (t), 45.7 (d), 26.1 (t), 11.4 (q); HRMS Calcd for $C_{11}H_{12}NO_2F_3$ 247.0819. Found 247.0822.

4.2.8. 1-Methoxy-4-(1-nitromethyl-propyl)-benzene (4h). According to general procedure A, 179 mg (1.0 mmol) of **3h** gave 114 mg (0.5 mmol, 55% yield) of **4h** after column chromatography (pentane/diethyl ether 9:1 R_f 0.5) as a colorless oil. Spectral data were in accordance with literature.[12]

4.2.9. 1-Bromo-4-(1-nitromethyl-propyl)-benzene (4i). According to general procedure A, 228 mg (1.0 mmol) of **2i** gave 121 mg (0.5 mmol, 47% yield) of **4i** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. ^{1}H NMR δ: 7.46 (dd, J=8.6, 1.8 Hz, 2H), 7.07 (d, J=8.6 Hz, 2H), 4.53 (m, 2H), 3.32 (m, 1H), 1.68 (m, 2H), 0.82 (t, J=7.5 Hz, 3H); ^{13}C NMR δ: 138.2 (s), 131.9 (d), 129.2 (d), 121.3 (s), 80.3 (t), 45.4 (d), 26.0 (t), 11.4 (q); HRMS Calcd for $C_{10}H_{12}NO_2{}^{79}Br$ 257.0050. Found 257.0044.

4.2.10. 1-(1-Nitromethyl-propyl)-2-trifluoromethyl-benzene (4j). According to general procedure A, 217 mg (1.0 mmol) of 1-(2-nitro-vinyl)-3-trifluoromethyl-benzene 114 mg (0.4 mmol, 46% yield) of **4j** after column chromatography (pentane/diethyl ether 9:1 R_f 0.5) as a colorless oil. ^{1}H NMR δ: 7.70 (m, 1H), 7.57 (m, 1H), 7.37 (m, 2H), 4.56 (d, J=11.1 Hz, 2H), 3.87 (quint, J=11.1 Hz, 1H), 1.81 (m, 2H), 0.81 (t, J=10.8 Hz, 3H); ^{13}C NMR δ: 132.3 (s), 127.5 (d), 127.4 (d), 126.8 (d), 126.6 (d), 121.4 (s), 80.2 (t), 40.4 (d), 26.3 (t), 11.2 (q); HRMS Calcd for $C_{11}H_{12}NO_2F_3$ 247.0819. Found 247.0831.

4.2.11. 1-(1-Nitromethyl-propyl)-3-trifluoromethyl-benzene (4k). According to general procedure A, 217 mg (1.0 mmol) of 1-(2-nitro-vinyl)-2-trifluoromethyl-benzene gave 110 mg (0.4 mmol, 45% yield) of **4k** after column chromatography (pentane/diethyl ether 9:1 R_f 0.8) as a colorless oil. ^{1}H NMR δ: 7.45 (m, 4H), 4.58 (m, 2H), 3.41 (m, 1H), 1.72 (m, 2H), 0.84 (t, J=7.5 Hz, 3H); ^{13}C NMR δ: 140.4 (s), 131.0 (d), 129.4 (d), 125.8 (s), 80.1 (t), 45.7 (d), 26.1 (t), 11.4 (q); HRMS Calcd for $C_{11}H_{12}NO_2F_3$ 247.0819. Found 247.0834.

4.3. General procedure B

Synthesis of nitroalkenes **5a**, **b** and **d**. According to a slightly modified literature procedure,[34] potassium *tert*-butoxide (0.05 equiv.) was added to a stirred solution of aldehyde (1.0 equiv.), nitromethane (1.5 equiv.), THF (3.0 equiv.) and *tert*-butanol (2.8 equiv.) at 0°C. The stirred mixture was allowed to warm to room temperature over 2 h and stirred overnight. The mixture was poured into water and extracted with three portions of diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the crude β-nitro-alcohol, which was dehydrated without further purification. Trifluoroacetic anhydride (1.05 equiv.) was added to a solution of β-nitroalcohol (1.0 equiv.) in CH_2Cl_2 (18 equiv.) at −10°C. The resulting solution was stirred for exactly 2 min, and then triethylamine (2.0 equiv.) was added dropwise over 15 min and the reaction mixture was stirred for an additional 30 min at −10°C. The resulting mixture was poured into CH_2Cl_2 and washed with two portions of saturated aqueous NH_4Cl. The aqueous layers were extracted with two portions of CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography.

4.3.1. (*E*)-3,3-Dimethoxy-1-nitro-propene (5a). According to general procedure B, 3.12 g (30 mmol) of glyoxal dimethylacetal (5.12 g of a 60% aqueous solution) gave 2.94 g (20 mmol, 67% yield) of **5a** after column chromatography (pentane/ethyl acetate 10:1 R_f 0.4) as a light yellow oil. ^{1}H NMR δ: 7.17 (dd, J=13.5, 1.5 Hz, 1H), 7.00 (dd, J=13.5, 3.3 Hz, 1H), 5.08 (dd, J=3.3, 1.5 Hz, 1H) 3.31 (s, 6H); ^{13}C NMR δ: 142.4 (d), 136.3 (d), 97.9 (d), 52.9 (q); MS (CI+) 165 $[M+NH_4]^+$; Anal. Calcd for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52. Found C, 40.60; H, 6.04; N, 9.38.

4.3.2. (*E*)-(-2-Nitro-vinyl)-cyclohexane (5b). According to general procedure B, 3.00 g (26 mmol) of cyclohexane-carboxaldehyde gave 2.22 g (14 mmol, 55% yield) of **5b** after column chromatography (pentane/ethyl acetate 20:1 R_f 0.8) as a light yellow oil. Spectral data were in accordance with literature.[34]

4.3.3. (*E*)-1-Nitro-hept-1-ene (5d). According to general procedure B, 3.00 g (30 mmol) of hexanal gave 3.43 g (12 mmol, 40% yield) of **5d** after column chromatography (pentane/ethyl acetate 20:1 R_f 0.8) as a light yellow oil. Spectral data were in accordance with literature.[34]

4.3.4. 1,1-Dimethoxy-2-nitromethyl-butane (6a). According to general procedure A, 147 mg (1.0 mmol) of **5a** gave 114 mg (0.6 mmol, 64% yield) of **6a** after column chromatography (pentane/ethyl acetate 3:1 R_f 0.6) as a colorless oil. Spectral data were in accordance with literature.[17]

4.3.5. (1-Nitromethyl-propyl)-cyclohexane (6b). According to general procedure A, 155 mg (1.0 mmol) of **5b** gave 112 mg (0.6 mmol, 61% yield) of **6b** after column chromatography (ethyl acetate/dichloromethane 1:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[17]

4.3.6. 1-Ethyl-2-nitro-cyclohexane (6c). According to general procedure A, 127 mg (1.0 mmol) of **5c** gave 107 mg (0.7 mmol, 68% yield) of **6c** after column chromatography (pentane/diethyl ether 20:1 R_f 0.8) as a colorless oil. Spectral data were in accordance with literature.[17]

4.3.7. 3-Nitromethyl-octane (6d). According to general procedure A, 143 mg (1.0 mmol) of **5d** gave 82 mg (0.5 mmol, 47% yield) of **6d** after column chromatography (pentane/ethyl acetate 3:1 R_f 0.8) as a colorless oil. ^{1}H NMR δ: 4.30 (d, J=7.2 Hz, 2H), 2.14 (m, 1H), 1.35 (m, 10H), 0.88 (m, 6H); ^{13}C NMR δ: 79.2 (t), 38.7 (d), 31.7 (t), 30.6 (t), 25.8 (t), 23.8 (t), 22.4 (t), 13.9 (q), 10.3 (q); HRMS Calcd for $C_9H_{19}NO_2$ 173.1416. Found 173.1426.

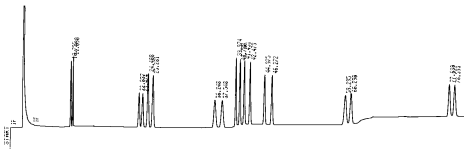


Figure 2. One-pot multi-substrate chiral GC chromatogram for **4a**–**i**.

4.4. General procedure C

One-pot multi-substrate reactions. In a Schlenk flask 16.2 mg (0.045 mmol) of $CuOTf_2$ was flame-dried and together with 0.09 mmol of phosphoramidite dissolved in 3 mL of dry toluene. After 30 min of stirring at room temperature 0.25 mmol of each nitroalkene (**3a**–**i**) was added to the clear solution. The reaction mixture was cooled to −45°C and 3.4 mL of Et_2Zn (3.4 mmol, 1.0 M solution in hexanes) was added. The reaction mixture was stirred at 0°C for 3 h and then poured into 10 mL of saturated aqueous NH_4Cl and diluted with 10 mL of ethyl acetate. The aqueous layer was extracted twice with 10 mL of ethyl acetate and the combined organic layers were dried over Na_2SO_4, concentrated and filtered through a short path of silica with pentane/diethyl ether 9:1 to give the mixture of nine nitroalkanes (**4a**–**i**) as a clear colorless oil, which was analyzed by chiral GC (Fig. 2).

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References

1. Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
2. Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841–5842.
3. Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 927–930.
4. Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196.
5. Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*, Krause, N., Ed.; Wiley-VCH: Weinhiem, 2002; pp 224–258.
6. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755–756.
7. Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779–781.
8. Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751–762.
9. Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017–1018.
10. Brown, B. R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Oxford University: Oxford, 1994; pp 443–469.
11. Blicke, F. F.; Faust, J. A.; Warzynski, R. J.; Gearien, J. E. *J. Am. Chem. Soc.* **1945**, *67*, 205–207.
12. Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305–2324.
13. Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M. *Synthesis* **1996**, 48–52.
14. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
15. Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341–1344.
16. Versleijen, J. P. G.; Van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803–5806.
17. Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581.
18. Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C.; Eur *J. Org. Chem.* **2001**, 803–807.
19. Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717.
20. Reetz, M. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310.
21. Porte, A. M.; Riebenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180–9187.
22. Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120–124.
23. Brouwer, A. J.; Van der Linden, H. J.; Liskamp, R. M. B. *J. Org. Chem.* **2000**, *65*, 1750–1757.
24. Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265–7266.
25. Arnold, L. A.; Imbos, R.; Mandoli, A.; De Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878.
26. Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540.
27. Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930–1946.
28. Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 2620–2623.
29. Reetz, M.; Neugebauer, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 179–181.
30. Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375–1378.
31. Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184–185.
32. Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5939–5944.
33. Ohta, H.; Kobayashi, N.; Ozaki, K. *J. Org. Chem.* **1989**, *54*, 1802–1804.
34. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850–3856.