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Ti-mediated addition of diethylzinc to benzaldehyde. The effect of chiral additives

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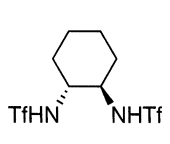
Abstract—In the presence of a chiral tridentate bissulfonamide, the titanium-mediated addition of diethylzinc to benzaldehyde gave alkylated products ranging from the (*R*)-enantiomer, formed with an e.e. of 26%, to the (*S*)-enantiomer, formed in 72% e.e. The enantioselectivity was also affected by the presence of additional chiral mono- and bidentate ligands, with the reactions proceeding via complexes containing the chiral sulfonamide and the additive. The addition of (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine and (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine gave the (*S*)-product with e.e. of 49% and the (*R*)-product with 16% e.e., respectively, whereas without additives the (*R*)-product was obtained in 26% e.e. In the presence of (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine only (i.e. without the chiral sulfonamide), the (*S*)-product formed with a 3% e.e.

1. Introduction

The enantioselective titanium-mediated addition of diethylzinc to aldehydes has emerged as a versatile synthetic method for the preparation of enantiopure chiral secondary alcohols.[1] High stereoselectivity has been observed in the presence of chiral ligands such as *trans*-1,2-diaminocyclohexane bistrifluoromethanesulfonate **1**,[2] TADDOL **2**[3] and BINOL **3**.[4] Bissulfonamide **1** has proved particularly useful and has found a number of synthetic applications including reactions with a wide range of aldehydes and dialkylzinc compounds.[5]

A variety of optimisation studies have been completed, most including the variation of ligand structure. Thus, ligands incorporating chiral sulfonyl moieties[6] or bearing additional coordinating groups[7] have been prepared and some were found to have advantageous properties in the catalytic reaction. Bispeptidosulfonamide structures based on *trans*-1,2-diaminocyclopentane were optimised using a solid-phase library,[8] and a solution library was prepared employing solid-phase extraction methodology.[9]

The mechanism of the process is not known in detail, but some features have emerged. A pentacoordinated titanium intermediate has been suggested,[3] although a hexacoordinate species comprising coordinating sulfonyl oxygen atoms seems more probable according to recent structural investigations.[10] The structure of a titanium complex prepared from $Ti(NMe_2)_4$ and a bisarylsulfonate of *trans*-1,2-diaminocyclohexane was determined and showed Ti to be five- or six-coordinated, with the sulfonyl oxygen atoms taking part in coordination. The intermediate responsible for the enantioselectivity of the catalytic reaction has been suggested to be either an ethyltitanium species, formed by transfer of an ethyl group from Zn to Ti, or a bimetallic complex containing a bridging alkoxy group. The latter assumption is favoured, as mixing $Ti(O\text{-}i\text{-}Pr)_4$ and Et_2Zn results in a concentration-dependent equilibrium mixture of bimetallic complexes and an



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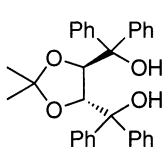

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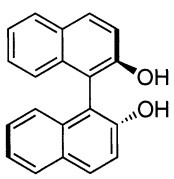

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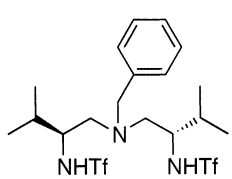

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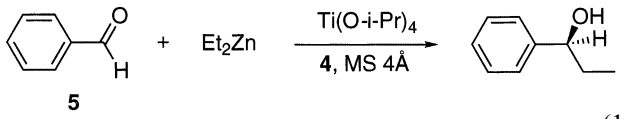
ethyltitanium compound.[2a] The absence of non-linear effects was suggested to indicate a monomeric catalytically active species.[11] However, regardless of the structure of the catalytic intermediate, a dianionic ligand requires coordination of at least one *iso*-propoxy group to yield a neutral complex. Exchange of the *iso*-propoxide for a *tert*-butoxide group resulted in a drastic increase in the enantioselectivity when zinc compounds with low steric hindrance were used.[12] However, the sterically more demanding titanium reagent resulted in slower reactions in some systems.[6b,12] Exchange of the alkoxide for a chiral moiety offers an alternative way to optimise the catalytic system. This was accomplished in one study, where *iso*-propoxide was exchanged for (*R*)-1-phenylpropoxide, resulting in high enantioselectivities even when sulfonamides derived from *meso*-1,2-diaminocyclohexane were employed.[13]

Using our previously designed tridentate bissulfonamide **4**,[14] we now report a study of the effects of adding a variety of monodentate and bidentate coordinating compounds under various reaction conditions.[15]

2. Results and discussion

2.1. Composition of the catalyst

Initially, the influence of the amount of $Ti(O\text{-}i\text{-}Pr)_4$ and Et_2Zn and the effect of molecular sieves on the enantioselectivity in the addition of diethylzinc to benzaldehyde in the presence of ligand **4** (Eq. (1)) were studied.



5 (1)

In order to achieve acceptable reaction rates, an excess of titanium *iso*-propoxide is commonly employed in the Ti-mediated additions of Et_2Zn to aldehydes, standard conditions with sulfonamide **1** being aldehyde:R_2Zn:ligand:$Ti(O\text{-}i\text{-}Pr)_4$ 1:1.2:0.02:1.2.[2a] It has been suggested that the increase in reaction rate is a result of removal of the product alkoxide by excess $Ti(O\text{-}i\text{-}Pr)_4$, thus reconstituting the catalyst.[3] In our standard conditions, an aldehyde:Et_2Zn:ligand ratio of 1:1.2:0.125 and a temperature of −35°C were used. Activated 4 Å molecular sieves were added to the reaction mixture as it was believed that this would enhance complex formation.[16] When the amount of $Ti(O\text{-}i\text{-}Pr)_4$ was successively increased, from 0.12 to 1.68 equiv., drastic changes in the enantioselectivity as well as increased reaction rates were observed (entries 1–6, Table 1 and Fig. 1). With 0.12 equiv. the product with (*R*)-absolute configuration was obtained with moderate selectivity (26% e.e.), whereas with higher amounts of Ti alkoxide the (*S*)-enantiomer dominated, reaching a maximum at about 1.48 equiv. (affording the (*S*)-configured product in 59% e.e.), after which the ratio of isomers remained approximately constant.

Table 1. Ti-mediated addition of Et_2Zn to benzaldehyde

Entry	Ligand **4** (equiv.)	$Ti(O\text{-}i\text{-}Pr)_4$ (equiv.)	Et_2Zn (equiv.)	4 Å MS (mg/mmol **5**)	Time (h)	Conv.[a] (%)	E.e., % (abs. config.)
1	0.125	0.12	1.2	250	94	100	26 (*R*)
2	0.125	0.34	1.2	250	1	69	24 (*S*)
					4	87	22 (*S*)
3	0.125	0.68	1.2	250	0.05	77	40 (*S*)
					0.25	100	45 (*S*)
4	0.125	1.02	1.2	250	1	100	47 (*S*)
5	0.125	1.48	1.2	250	0.05	93	56 (*S*)
					0.25	100	59 (*S*)
6	0.125	1.68	1.2	250	1	100	56 (*S*)
7	0.125	0.68	1.2	250[b]	26	30	53 (*S*)
8	0.125	1.48	1.2	–	0.25	100	59 (*S*)
9	–	0.68	1.2	250	0.25	7	–
					4	58	–
10	–	1.35	1.2	250	2	64	–
					4	87	–
					16	100	–
11	–	1.35	1.2	–	2	64	–
					4	87	–
					16	100	–
12	0.125	–	1.2	250	50	24	15 (*S*)
					96	58	21 (*S*)
13[c]	0.125	1.48	1.2	250	0.25	97	72 (*S*)
14[c]	0.125	1.48	3.0	250	1.2	96	16 (*S*)
15[c]	0.125	0.68	3.0	250	1.2	94	10 (*S*)

[a] Determined by GC.
[b] Unactivated 4 Å MS.
[c] The reaction mixture was kept at rt before addition of the aldehyde.

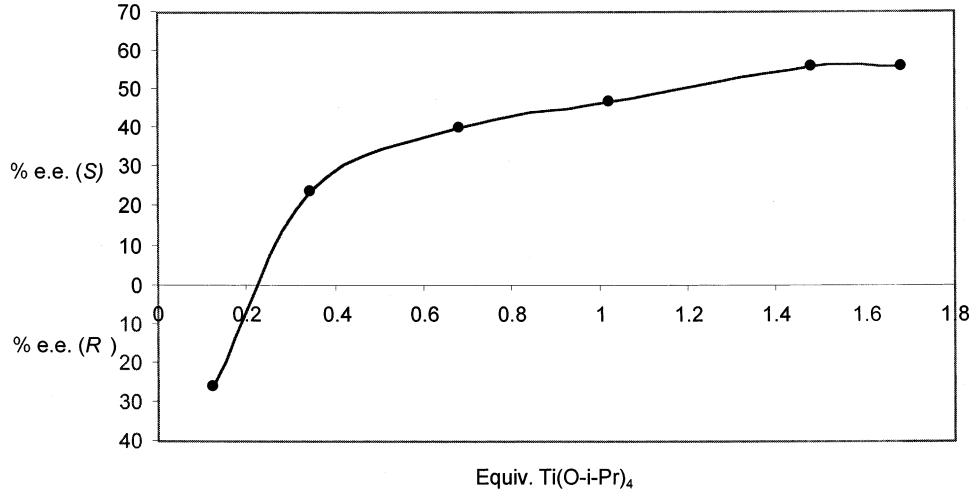


Figure 1. The enantioselectivity of the catalytic reaction as a function of the amount of Ti(O-*i*-Pr)$_4$.

With 0.34 equiv. of Ti(O-*i*-Pr)$_4$ 87% conversion required 4 hours, whereas full conversion was achieved within 15 minutes with 0.68 equiv. Use of unactivated in place of activated 4 Å molecular sieves resulted in somewhat increased selectivity (53% e.e., entry 7, compared to 45%, entry 3),[17] but the reaction was considerably slower, with only 30% conversion after 26 hours. In the absence of molecular sieves (entry 8), results identical to those obtained with sieves present (entry 5) were achieved.

In contrast to what was observed with ligand **4**, enhanced enantioselelctivity is commonly observed upon decreasing the amount of Ti(O-*i*-Pr)$_4$.[2b] The same behaviour as that observed for **4** was, however, found in a few previous investigations where decreasing the levels of Ti present resulted in decreased enantioselectivity. For example, with a tetradentate sulfonamide comprising phenolic groups, the use of 1.4 equiv. of the Ti compound resulted in 99% e.e., whereas 0.2 equiv. gave merely 4% e.e.[18] Even more drastic variation of the e.e. with the amount of Ti was observed when a spirotitanate was used.[19]

Some reactions were also performed without chiral ligand. With conditions otherwise identical to those in entry 3, a mere 7% conversion was achieved within 15 min (entry 9). The reaction is thus ligand-accelerated, the background reaction being at least 55 times slower than that involving the ligand. As expected, the ligand-free process was also faster with an excess of Ti(O-*i*-Pr)$_4$ (entry 10). Without molecular sieves the reaction was also slow in the absence of ligand (entry 11). Thus, 4 Å molecular sieves have no influence on either the catalytic reaction or the background reaction.

In the absence of Ti(O-*i*-Pr)$_4$, a slow unselective reaction, probably catalysed by a zinc–ligand complex, occurred (entry 12). Analogous results were also obtained with the previously investigated ligand **1**.[2c]

2.2. Complex formation

Mixing the sulfonamide ligand **4** with Ti(O-*i*-Pr)$_4$ does not, according to NMR spectroscopy, yield a metal–ligand complex. This is in accordance with previous observations involving other nitrogen-containing ligands.[11] Instead, complex formation takes place upon addition of the dialkylzinc species, which serves to deprotonate the ligand.[20] In reactions with sulfonamides of *trans*-1,2-diaminocyclohexane use of preformed complexes has been shown to yield results identical to those observed using a mixture of Ti(O-*i*-Pr)$_4$ and ligand, demonstrating that a ligand–Ti complex is a likely intermediate in the catalytic reaction.[11]

In order to achieve metal complex formation prior to the catalytic reaction, Ti(O-*i*-Pr)$_4$, ligand and Et_2Zn were mixed at −78°C and warmed to room temperature over 75 minutes and kept for 140 minutes prior to the addition of the aldehyde. Under these conditions, an improved e.e., 72% (entry 13, Table 1), was observed. The enantioselectivity was not improved when the reaction was kept for an extended time of 11 hours at room temperature. Increasing the amount of Et_2Zn (entry 14) and decreasing the amount of Ti(O-*i*-Pr)$_4$ (entry 15) resulted in reduced enantioselectivity.

Employing these more favourable conditions, the effect of decreasing the amount of chiral ligand was also studied. Use of down to 4 mol% of ligand **4** (entries 1 and 2, Table 2) did not affect the conversion or the enantioselectivity, whereas a further decrease resulted in a somewhat slower reaction and decreased selectivity (entry 3), probably due to competition from the background reaction. It is interesting to note that, at least in reactions with a low amount of chiral ligand, the enantioselectivity increases with conversion.

Some reactions were performed employing cyclohexanecarboxaldehyde in place of benzaldehyde. Low

Table 2. Ti-mediated addition of Et_2Zn to benzaldehyde[a]

Entry	Ligand **4** (equiv.)	Ti(O-*i*-Pr)$_4$ (equiv.)	Et_2Zn (equiv.)	Time (h)	Conv.[b] (%)	E.e., % (abs. config.)
1	0.06	1.48	1.2	0.25	86	67 (*S*)
				1	97	71 (*S*)
2	0.04	1.48	1.2	0.25	81	66 (*S*)
				1	96	70 (*S*)
3	0.02	1.48	1.2	0.25	53	57 (*S*)
				1	95	66 (*S*)
				3	96	67 (*S*)

[a] No 4 Å MS were used and the reaction mixture was kept at rt before addition of the aldehyde.
[b] Determined by GC.

enantioselectivity (25% e.e.) and a slow reaction (90% conversion after 36 hours) were observed.

2.3. The effect of additives

To study the effect of additives on the enantioselectivity and rate of the reaction, 12.5% catalyst, consisting of equimolar amounts of Ti(O-*i*-Pr)$_4$, ligand **4** and additive, were used. These conditions were selected as it was assumed that a Ti:ligand ratio of 1:1 would favour the formation of complexes comprising both ligand and additive. Reaction without any additive afforded under these conditions the (*R*)-product with 26% e.e. (1, Fig. 2). The results obtained from the addition of 21 monodentate and bidentate chiral amines and alcohols and of 2 amino alcohols are shown graphically in Fig. 2.[21] With a few exceptions, the conversions were 85–100%.

In contrast to the reaction without additive, those where either of the *trans*-1,2-diaminocyclohexanes were added (4 and 5) gave an excess of the (*S*)-product. The latter product was also obtained in a small excess using *meso*-1,2-diaminocyclohexane as an additive (6, Fig. 2). These results as well as those involving other pairs of enantiomers indicate that diastereomeric complexes are involved in the reactions. With complexes comprising only one chiral ligand, reaction in the presence of (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine **8**, for example, would have resulted in a product with opposite configuration to that obtained using (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine **7**, and with at least as high a

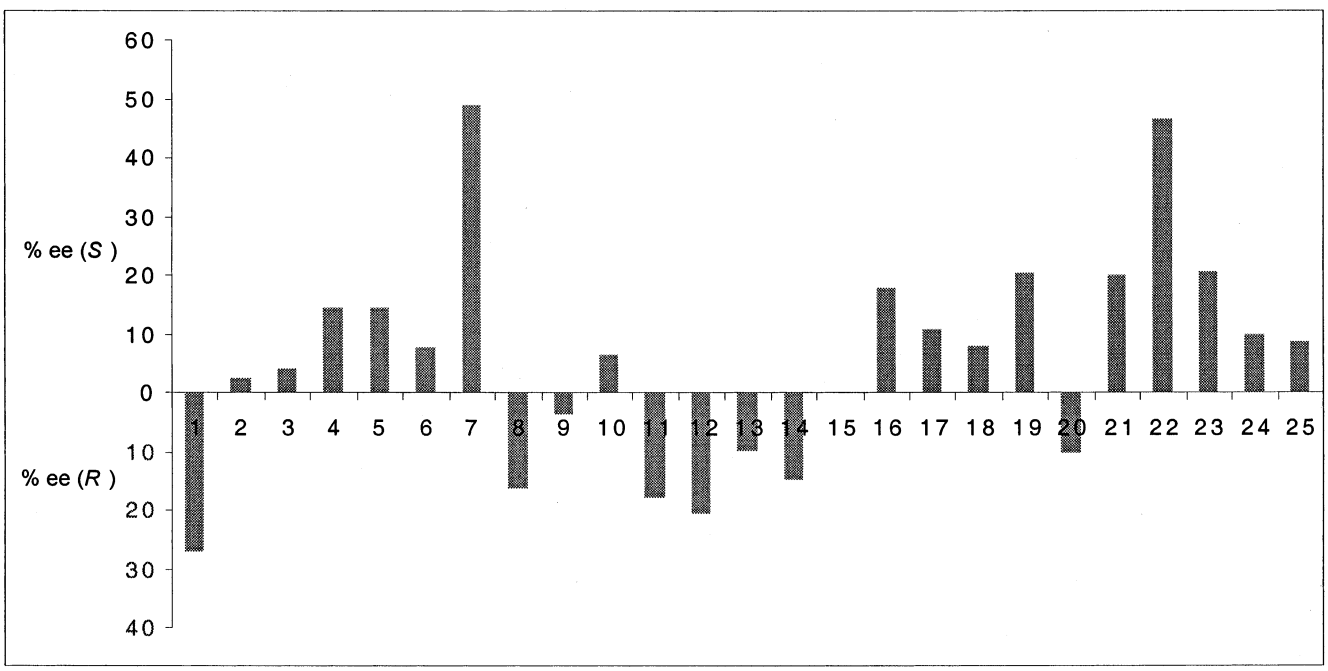


Figure 2. The effect of additives on the enantioselectivity of the catalytic reaction (1 equiv. added unless otherwise noted). 1: No additive; 2: (*R*)-(+)-1-phenylethylamine; 3: (*S*)-(+)-1-phenylethylamine; 4: (1*R*,2*R*)-(−)-1,2-diaminocyclohexane; 5: (1*S*,2*S*)-(+)-1,2-diaminocyclohexane; 6: *cis*-1,2-diaminocyclohexane; 7: (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine; 8: (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-ethanediamine; 9: (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine; 10: (−)-sparteine; 11: D-menthol; 12: L-menthol; 13: L-menthol (2 equiv.); 14: (1*S*,2*S*,5*S*)-(−)-myrtanol; 15: methyl (*S*)-(+)-mandelate; 16: (2*S*,5*S*)-2,5-hexanediol; 17: (2*R*,5*R*)-2,5-hexanediol; 18: *cis*-1,2-cyclohexanediol; 19: (1*S*,2*S*)-1,2-di-*o*-tolylethane-1,2-diol; 20: (*R*)-(+)-BINOL; 21: (*S*)-(−)-BINOL; 22: (−)-TADDOL; 23: dimethyl L-tartrate; 24: (*R*)-(−)-2-phenylglycinol; 25: L-phenylalaninol.

stereoselectivity. Best results under the conditions employed were obtained using (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (7, Fig. 2, 48% e.e. (*S*)) and (−)-TADDOL (22, Fig. 2, 46% e.e. (*S*)). Increasing the amount of added L-menthol from 1 to 2 equiv. caused a decrease in enantioselectivity (12 and 13, from e.e. of 21 to 10%).

When the reaction with (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine as an additive was performed under the conditions employed for the reaction in entry 14, Table 1 (i.e. keeping the reaction mixture at ambient temperature prior to addition of the aldehyde, but with no excess of Ti), the enantioselectivity was improved from 49 to 53%. An excess of diethylzinc (3.0 equiv.) resulted in a somewhat lower e.e. of 45% for the (*S*)-enantiomer, and the addition of an excess of Ti(O-*i*-Pr)$_4$ (1.35 equiv.), after complex formation, in a drastically lower e.e. of 3% (*S*)-product. It is interesting to note that a catalytic reaction performed with (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine as a ligand and in the absence of **4** resulted in an e.e. of 3% (of the (*S*)-isomer).

3. Conclusion

It has been shown that the enantioselectivity of the addition of diethylzinc to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$ and bissulfonamide ligand **4** is highly dependent on the reaction conditions. Furthermore, the selectivity is affected by the presence of chiral additives, which probably yield intermediate complexes containing both the additive and the chiral ligand.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in flame-dried glassware. Toluene was freshly distilled over sodium/benzophenone under a nitrogen atmosphere. Benzaldehyde and Ti(O-*i*-Pr)$_4$ were distilled prior to use. Et_2Zn (1.1 M) in toluene (Aldrich) was used. Powdered 4 Å molecular sieves (Lancaster) were activated by heating at around 250°C/0.1 mm Hg for at least 16 h. E.e.s were determined by GLC using chiral columns, either Supelco Gamma-DEX 120 30 m (115°C; 18 psi; (*R*)-enantiomer $t_R = 18.0$ min; (*S*)-enantiomer $t_R = 18.3$ min) or Chrompack CP-cyclodextrin β-2,3,6-M-19 50 m (110–140°C; 2°C/min; 5 min at 140°C; 20 psi, (*R*)-enantiomer $t_R = 18.4$ min; (*S*)-enantiomer $t_R = 18.6$ min). The assignment of the absolute configuration of (*R*)- and (*S*)-1-phenylpropanol was made according to our earlier work.[14]

4.2. General procedures for the catalytic reactions

4.2.1. With additive. A stock solution of the ligand–titanium mixture was prepared by adding ligand **4** (1.625 g, 3.00 mmol) and 4 Å MS to a 100 mL flask. Toluene (30 mL) was added followed by Ti(O-*i*-Pr)$_4$ (0.89 mL, 3.00 mmol). The mixture was heated for 11 h at 40°C and for 4 h at 60°C. The mixture was then allowed to cool and the sieves were removed by filtration. The sieves were washed with toluene and the solvent was removed in vacuo. Toluene (23 mL) was added and the solution was used for 24 catalytic reactions.

The appropriate additive (0.125 mmol) and 4 Å MS (250 mg) were placed in a 7 mL vial. The stock solution of the complex (1.00 mL, 0.125 mmol) was added and the mixture was heated at 60°C for 90–160 min. The vial was cooled to −78°C and Et_2Zn (1.09 mL, 1.2 mmol) was added. Benzaldehyde (102 μL, 1.00 mmol) was added dropwise after 15 min and stirring was continued for another 15 min, at which time the temperature was raised to −35°C. The reaction was quenched after about 90 h by the dropwise addition of 0.2 M HCl. The aqueous phase was extracted with diethyl ether. The combined organic phases were filtered through a small pad of silica.

4.2.2. Without additive. The ligand (67.7 mg, 0.125 mmol) and 4 Å MS (250 mg) were added to a 10 mL flask. Toluene (1.00 mL) was added followed by Ti(O-*i*-Pr)$_4$ (0.44 mL, 1.48 mmol). The mixture was cooled to −78°C and stirred for 15 min before Et_2Zn (1.09 mL, 1.2 mmol) was added and the stirring was continued for another 15 min. Benzaldehyde (102 μL, 1.00 mmol) was added dropwise and the mixture was stirred for 20 min at −78°C before it was placed at −35°C and stirred for the times noted in Table 1. The work-up was performed as described above. (Alternatively, the temperature was slowly increased from −78 to −20°C over 1 h after the addition of the Et_2Zn. The flask was then placed at 0°C for 15 min, after which it was held at room temperature for 140 min. The colour of the mixture changed from yellow to dark green. The flask was cooled to −78°C and the aldehyde was added after 15 min.) The procedure was completed as above in Section 4.2.1.

Acknowledgements

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