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#### 1. Introduction

The most important analogs of  $\alpha$ -amino acids are  $\alpha$ -aminophosphonic acids and examples include both natural and synthetic derivatives.1 Among their biological activities many are related to their ability to inhibit enzymes that are involved in cleavage of peptide bonds since they can serve as transitionstate analogs of a tetrahedral intermediate formed from an amide carbonyl during hydrolysis.<sup>1,2</sup> Examples of biologically active a-aminophosphonic acids and esters are shown in Scheme 1 and include glyphosate 1 (Roundup),<sup>3</sup> the antibacterial alafosfalin 2 (the other three isomers are less active)<sup>4</sup> and phospholeucine 3 which is a leucine aminopeptidase inhibitor (the (S)-enantiomer is  $10^3$  times less active than the (R)-enantiomer).<sup>5</sup> The phospholeucine 3 is a key component of, and plays an important role in, the activity of the pepsin and penicillopepsin inhibitor 4.6 The naturally occurring phosphotyrosine tripeptide K-26 5 is an ACE inhibitor with comparable activity to captopril,<sup>1b,7a</sup> although analogs of 5 were found to be more active.7b,c Dufulin 6 has been widely used to treat viral diseases in agricultural crops in China.8

The most common methods for the synthesis of  $\alpha$ -aminophosphonic acids involve the two component reaction of an

# Zirconium-catalyzed asymmetric Kabachnik–Fields reactions of aromatic and aliphatic aldehydes†

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An effective catalyst has been developed for the three-component reaction of aldehydes, anilines and phosphites in an asymmetric catalytic Kabachnik–Fields reaction to give  $\alpha$ -aminophosphonates. A catalyst was sought that would give high asymmetric inductions for aromatic and, and more particularly, for aliphatic aldehydes since there has not previously been an effective catalyst developed for this class of aldehydes. The optimal catalyst is prepared from three equivalents of the 7,7'-di-t-butylVANOL ligand, one equivalent of *N*-methylimidazole and one equivalent of zirconium tetraisopropoxide. This catalyst was most efficient in the presence of 10 mol% benzoic acid. Optimal conditions for aryl aldehydes required the use of 3,5-diisopropyl-2-hydroxyaniline and gave the aryl  $\alpha$ -aminophosphonates in up to 96% yield and 98% ee over 11 different aryl aldehydes. The best aniline for aliphatic aldehydes was found to be 3-*t*-butyl-2-hydroxyaniline and gave the corresponding phosphonates in up to 83% yield and 97% ee over 18 examples. The asymmetric inductions for aliphatic aldehydes were comparable with those for aromatic aldehydes with a mean induction of 90% ee for the former and 91% ee for the latter. The best method for the liberation of the free amine from the aniline substituted  $\alpha$ -aminophosphonates involved oxidation with *N*-iodosuccinimide.

imine and a phosphite (Pudovik reaction<sup>9</sup>) and the three component reaction of an aldehyde, an amine and a phosphite (Kabachnik-Fields reaction<sup>10,11</sup>). Given the level of difficulty it is not surprising that the three component Kabachnik-Fields reaction has been the more difficult of the two to develop asymmetric catalytic versions.11 The first catalytic asymmetric Kabachnik-Fields reaction was reported by List and coworkers in 2008 (Fig. 1).12 They developed the BINOL hydrogen phosphate catalyst 10 for the three component reaction to give  $\alpha$ aminophosphonic esters 11 with high enantioselectivity. Interestingly, this reaction also involved a dynamic kinetic resolution of the aldehyde, yielding product 11 with high diastereoselectivity. The transformation was limited to aryl acetaldehydes and the reaction times were quite long. Feng and coworkers reported that a scandium catalyst with the bis-amine oxide ligand 14 gives good asymmetric inductions with aryl aldehydes and aniline 13a with the diphenyl phosphite 15.13 However, this was not actually a Kabachnik-Fields reaction since the imine was generated first at 30 °C and then the phosphite was added at -20 °C. A second example involving a BINOL hydrogen phosphate catalyst was published by Ma and coworkers in 2010 and gave the  $\alpha$ -aminophosphonate 19 in low to high asymmetric induction with 16 different aromatic aldehydes.14 In 2011 Nakamura and Shibata and coworkers reported the success of a zinc-bis-imidazolidine catalyst in the reaction of 16 different aldehydes with the aniline 8 and the bis-o-tolylphosphite 21.15 The α-aminophosphonate diester 23 was obtained in 68-93% ee with aryl aldehydes but the two alkyl

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<sup>†</sup> Electronic supplementary information (ESI) available: Procedures for the preparation of new compounds and characterization data for all new compounds. See DOI: 10.1039/d1sc03222d



Scheme 1 Examples of biologically active  $\alpha$ -aminophosphonic acids.

aldehydes that were examined gave low to moderate induction (31-61% ee). The organocatalyst **26** has been reported by Bhusare and coworkers to give good to excellent asymmetric inductions in the Kabachnik–Fields reaction for a variety of aryl aldehydes.<sup>16</sup> This reaction is unusual in that, instead of a phosphite diester, a phosphite triester was employed in this Kabachnik–Fields reaction where one of the ethyl groups was cleaved during the reaction to give the phophonate diester **27**. Finally, Reddy and coworkers reported the use of the bisthiourea catalyst **29** to give the *α*-aminophosphonate **30** from the aldehyde **28** in low enantioselectivity.<sup>17</sup>

To summarize, the existing methods for the asymmetric catalytic Kabachnik-Fields reaction work well only for aromatic aldehydes. The only two examples with aliphatic aldehydes come from the work of Nakamura and Shibata who were able to prepare the α-aminophosphonate 23 from cvclohexanecarboxaldehyde and isovaleraldehyde in 61% and 31% ee, respectively.<sup>15</sup> Given that  $\alpha$ -aminophosphonates are largely of interest as analogs of  $\alpha$ -amino acids, and that most  $\alpha$ -amino acids do not contain aromatic groups, it is clear that improved methods for the catalytic asymmetric Kabachnik-Fields reaction are needed.

#### 2. Results and discussion

We decided to begin the search for new catalysts for the Kabachnik–Field reaction by examining aromatic aldehydes since it was the expectation that reaction optimization would not be as challenging. We had previously reported a three-component reaction for the catalytic asymmetric synthesis of aziridines from an aldehyde, amine and an  $\alpha$ -diazoacetate (Scheme 2).<sup>18</sup> The catalyst was a boroxinate (BOROX) derived from either the VAPOL or VANOL ligands and both gave the aziridines **34** in 98% ee. The reaction gives low conversion in the absence of molecular sieves. This was not surprising given that an imine is generated *in situ*. Later it was found that the BOROX catalyst **39** generated from the *t*-Bu<sub>2</sub>VANOL ligand **37** gives the

highest yields and asymmetric inductions.<sup>19</sup> Unfortunately, the success with the BOROX catalysts did not transfer from the three component aziridination reaction to the three component Kabachnik–Fields reaction since the VANOL-BOROX catalyst **38** only gave the  $\alpha$ -aminophosphonate **42** in 29% ee.

Although not three-component reactions, we have had success with zirconium catalysts in the asymmetric catalytic transformation of imines in Mannich reactions<sup>20</sup> and α-imino rearrangements<sup>21</sup> (Scheme 3). In each case the catalyst is generated by combining zirconium tetraisopropoxide, a vaulted biaryl ligand and N-methylimidazole. This catalyst type was initially screened in the reaction of benzaldehyde, 2-hydroxyaniline 13a and diethyl phosphite 41 with three different vaulted biaryl ligands (Scheme 3). In the absence of molecular sieves, only a low 20% yield of the α-aminophosphonate 48 was obtained with the VANOL ligand 36 in 35% ee (entry 1). The yield was greatly increased in the presence of molecular sieves, but the product was nearly racemic (entry 2). The yield was excellent with a catalyst generated from the VAPOL ligand 35 but the asymmetric induction was low (22% ee) (entry 3). The best result was achieved with the 7,7'-di-t-butylVANOL ligand 37 giving 48 in 82% yield and 37% ee (entry 4).

In the Mannich reaction with the zirconium catalyst indicated in Scheme 3, we had observed that higher asymmetric inductions and yields were obtained with the 3,5-dimethyl-2hydroxyaniline **13b**.<sup>20</sup> This was also the case in the present study where the asymmetric induction of the  $\alpha$ -aminophosphonate increased from 37 to 67% ee (Table 1, entries 1 and 2). Further studies revealed that if the amount of molecular sieves was increased from 100 to 200 wt% relative to the aniline, the asymmetric induction with aniline **13b** could be increased from 67 to 82% ee (entries 2 *vs.* 3). Additional amounts of molecular sieves were not beneficial (see the ESI†). Further optimization was possible by screening other 3,5-disubstituted-2-hydroxyanilines in this reaction. The  $\alpha$ -aminophosphonate **51** could be obtained in 90% ee with the 3,5-diisopropyl-2hydroxyaniline **13c** (entry 5). We had also observed that if



Fig. 1 Reported examples of the asymmetric catalytic Kabachnik–Fields reaction.

benzaldehyde **31a** was not freshly distilled, the yield improved. Assuming that the difference here was due to benzoic acid, this prompted a study into the effect of added benzoic acid. Here the yield increased by 10% upon the addition of 5 mol% benzoic acid (entries 5 vs. 6), and the induction was slightly higher with 10 mol% benzoic acid but dropped with 100 mol% benzoic acid (entries 5 to 8). This effect of benzoic acid was not noted for the 3,5-dimethyl-2-hydroxyaniline **13b** (entries 3 and 4). The di-*n*butylaniline **13d** did not give as high an asymmetric induction as the di-i-propylaniline **13c** (82% *vs.* 90%, entries 5 *vs.* 9) and the highest induction was observed with the di-*t*-butylaniline **13e** (95%, entry 10). Unfortunately in the latter case, the reaction was very slow and in the same time period, only a 12% yield of **53** was isolated. The yield could only be slightly recovered



Scheme 2 Previous three-component aziridination with BOROX catalysts.

upon the addition of benzoic acid (entries 10  $\nu s$ . 13). The yield could be increased to 52% with a reaction temperature of 60 °C, but the induction fell to 89%. The absolute configuration of the phosphonate **51** from the (*S*)-catalyst was determined to be (*S*)-**51** after deprotection to the free amine as indicated in Scheme 6.

The structure(s) of the zirconium catalysts shown in Scheme 3 are not known with great certainty. We had assumed that the structure of the catalyst for the Mannich reaction in Scheme 3 (ref. 20) had two molecules of ligand per zirconium as this had been reported for the BINOL analog.<sup>22</sup> However, in studies on the  $\alpha$ -imino rearrangements<sup>21</sup> we were able to grow crystals of the zirconium complex 54 (Scheme 4) which revealed that the zirconium has three VANOL ligands around the zirconium with two protonated *N*-methylimidazoles to balance the charge. A homoleptic zirconium complex with three bis-phenol ligands has not been reported before, but Shibasaki has reported that

rare earth catalysts with three BINOL ligands are effective for a number of reactions.23 However, later, Schelter and Walsh have shown that Shibasaki's catalysts are in equilibrium with species that only have two BINOL ligands and may be the actual active catalyst species.24 Although we have examined the structure of the zirconium catalyst in the present work by NMR the results were not conclusive. Thus, presently it is not known whether the complex 54 is the actual catalyst or if it loses a VANOL ligand in solution to give the active catalyst with only two molecules of VANOL per zirconium. It was found that if the catalyst was prepared from a 1:1:3 mixture of Zr(O-i-Pr)<sub>4</sub>, Nmethylimidazole and VANOL the rearrangement of 46 to 47 occurred with essentially the same result as from a 1:1:2 mixture (Scheme 4). If the catalyst was prepared from a 1:2:3 mixture the reaction was a little slower and with a 1 : 20 : 2 ratio the yield drops to 8% in the same time (Scheme 4). This may suggest that one of the imidazoles needs to dissociate to initiate

(%)

97

28

10 <sup>a</sup>

97

OEt

OEt



Scheme 3 Initial success with zirconium catalysts.

**Table 1** The effect of substituents on aniline **13** on the Kabachnik–Fields reaction<sup>a</sup>



Entry	R	Aniline	Temp (°C)	Benzoic acid (mol%)	Product	% Yield <sup>b</sup>	% ee
1	$H^{c}$	13a	rt	0	49	82	37
2	$Me^{c}$	13b	rt	0	50	55	67
3	Ме	13b	rt	0	50	87	82
4	Me	13b	rt	10	50	87	80
5	i-Pr	13c	rt	0	51	76	90
6	i-Pr	13c	rt	5	51	86	92
7	i-Pr	13c	rt	10	51	80	94
8	i-Pr	13c	rt	100	51	59	77
9	<i>n</i> -Bu	13d	rt	0	52	73	$-82^{d}$
10	<i>t</i> -Bu	13e	rt	0	53	12	95
11	<i>t</i> -Bu	13e	40	0	53	41	92
12	<i>t</i> -Bu	13e	60	0	53	52	$-89^{d}$
13	<i>t</i> -Bu	13e	rt	10	53	17	95

<sup>a</sup> Unless otherwise specified, the reactions were carried out on 0.1 mmol of aldehyde with 1.0 equiv. of aniline and 1.0 equiv. of phosphite and with 200 wt% of 4 Å MS relative to the aniline. <sup>b</sup> Isolated yield. <sup>c</sup> 100 wt% MS relative to the aniline. <sup>d</sup> (R)-t-Bu<sub>2</sub> VANOL ligand was used and *ent*-52/53 was obtained.





the reaction. Additionally, crystals were grown from both the 1:1:2 and the 1:1:3 mixtures, their structures were solved, and both were found to be zirconium complex 54.

Based on the above discussion, the final optimization of the Kabachnik–Field reaction of aryl aldehydes involved examining the effect of the ratio of the components in catalyst formation (Table 2). Unlike the case with  $\alpha$ -imino rearrangements (Scheme 4) the use of a large amount of *N*-methylimidazole (10 equiv.) relative to zirconium was not noticeably detrimental to the reaction (entry 1). The yield was slightly higher with three equivalents of VANOL per zirconium than with two but the asymmetric induction was the same (entries 3 *vs.* 5). The yield dropped a bit with a 1 : 2 : 3 ratio of zirconium to NMI to ligand (entry 7 *vs.* entries 3 and 5). The outcomes of the reactions with all variations of the ratio of catalyst components were greatly dependent on the presence of benzoic acid with a decrease in

yields of 30 to 69% in the absence of benzoic acid although the asymmetric inductions only decreased by 5 to 10% (entries 1 vs. 2, 3 vs. 4 and 5 vs. 6). The decrease in yields was smaller for a larger ratio of NMI to zirconium (entries 1 vs. 2).

The scope of the Kabachnik–Fields reaction with aromatic aldehydes is summarized in Table 3 and the optimal conditions identified in entry 5 of Table 2 are employed. Both electron rich and electron poor substituted benzaldehydes are tolerated by this catalyst and all but one give  $\alpha$ -amino phosphonates **51** with 90 to 98% ee and in 70 to 96% yield. The exception is 4-meth-ylbenzaldehyde **31e**. This aldehyde gives the  $\alpha$ -amino-phosphonate **51e** in 70% yield and 75% ee under the standard conditions indicated in Table 3. However, if the amount of benzoic acid is lowered from 10 mol% to 5 mol% the % ee increases to 81% with 96% yield. This stands out from most of the other benzaldehydes that were investigated with both 5 and



<sup>*a*</sup> Unless otherwise specified, the reactions were carried out on 0.1 mmol of aldehyde with 1.0 equiv. of aniline and 1.0 equiv. of phosphite and with 200 wt% of 4 Å MS relative to the aniline.

 Table 3
 Substrate scope for aromatic aldehydes in the Kabachnik–Fields reaction<sup>a</sup>



<sup>*a*</sup> Zirconium catalysts were prepared by stirring a mixture of 5 mol% Zr(O-i-Pr)<sub>4</sub>(HO-i-Pr), 5 mol% *N*-methylimidazole (NMI) and 15 mol% (*S*)-*t*-Bu<sub>2</sub>VANOL ligand in dry toluene for 30 min at rt under air. Unless otherwise specified, all reactions were carrired out under nitrogen on 0.1 mmol of aldehyde **31** with 1 equiv. of aniline **13c** and 1 equiv. of diethylphosphite **41** in toluene at rt for 16 h in the presence of 4 Å molecular sieves (200 wt% relative to **13c**) and 10 mol% of benzoic acid. All yields are isolated yields. The % ee was determined by HPLC. <sup>*b*</sup> Reaction with 5 mol% benzoic acid. <sup>*c*</sup> With a reaction time of 40 h the yield was 80% with 96% ee. <sup>*d*</sup> With a reaction time of 40 h the yield was 92% with 96% ee.

10 mol% benzoic acid that are indicated in Table 3 where the higher asymmetric induction is observed with 10 mol% benzoic acid. The reaction with pyrrole-2-carboxaldehyde immediately turns very dark and led to the consumption of the starting material with no detectable product formation. However, the reaction with Boc protected pyrrole-2-carboxaldehyde proceeds to give a 92% yield of the  $\alpha$ -aminophosphonate **51j** in 77% ee. Pyridine-4-carboxaldehyde **31k** was not a suitable substrate giving the  $\alpha$ -aminophosphonate **51k** in 35% yield with 17% ee. The absolute configuration of the  $\alpha$ -aminophosphonate **51a** from the (*S*)-catalyst was determined to be (*S*)-**51a** after deprotection to the free amine as shown in Scheme 6. The products from the other aromatic aldehydes were assumed to be homochiral.

Next, attention was turned to aliphatic aldehydes. The cyclohexanecarboxaldehyde 550 served as a prototypical aliphatic aldehyde and the initial results from its reaction with aniline 13c and phosphite 41 are presented in Table 4. It was

quite interesting to observe that there is a vast difference between the reaction carried out with the catalyst prepared from a 1:1:2 mixture of zirconium/NMI/ligand and that with a 1:1:3 mixture (Table 4, entry 1 vs. 3). The a-aminophosphonate 56 was isolated in 45% yield with 11% ee with the former and 80% yield and 82% ee with the latter. This is in sharp contrast to the observation with benzaldehyde, where no real significant difference was observed between a 1:1:2 and 1:1:3 catalyst ratio (Table 2, entries 3 vs. entry 5). However, as with benzaldehyde (Table 2), there is a significant difference between the effect of benzoic acid on the reaction of cyclohexanecarboxaldehyde 550. With the 1:1:2 catalyst, the yield dropped from 45% to 9% without benzoic acid although the % ee was slightly enhanced (Table 4, entries 1 and 2). This strong dependence was also observed with the 1:1:3 catalyst where the yield dropped from 80% to 14% without benzoic acid but in this case the % ee also dropped significantly (entries 3 vs. 4). Such a strong dependence on benzoic acid was not seen for Table 4 Optimization of the reaction of cyclohexanecarboxaldehyde 550 with aniline  $13c^a$ 



<sup>a</sup> Unless otherwise specified, the reactions were carried out on 0.1 mmol of aldehyde with 1.0 equiv. of aniline and 1.0 equiv. of phosphite and with 200 wt% of 4 Å MS relative to the aniline.

a 1:10:3 catalyst preparation (entries 5 vs. 6). The optimal conditions for the reaction of cyclohexanecarboxaldehyde gave phosphonate 56 in 80% yield with 82% ee (Table 4, entry 3). This is to be compared to the same reaction of benzaldehyde under the same conditions which gave phosphonate 51a in 90% yield and 93% ee (Table 2, entry 5). This is a less than desirable outcome for the reaction of this aliphatic aldehyde, and thus further optimization was needed.

It was decided to probe the effect of substituents on all four of the aryl positions of the aniline 13 and determine the

consequence of their resulting interactions with the catalyst in a systematic way. All four methyl derivatives 13f to 13i were prepared and their reactions with cyclohexanecarboxaldehyde 550 were examined under the optimal conditions given in Table 4 (entry 3), with the results outlined in Scheme 5. The greatest asymmetric induction (56%) was observed with a methyl group in the 3-position. A further increase to 67% ee was observed when the larger *n*-propyl group was introduced into the 3position (13j) but this was found to decrease to 55% ee when replaced with an iso-propyl (13k). Surprisingly, the induction



Scheme 5 Optimization of aniline 13 for cyclohexanecarboxaldehyde.

1

2

3

4

5

6

#### Table 5 Evaluation of the reaction of *n*-butanal with anilines 13c and $13l^a$



<sup>a</sup> Unless otherwise specified, the reactions were carried out on 0.1 mmol of aldehyde with 1.0 equiv. of aniline and 1.0 equiv. of phosphite and with 200 wt% of 4 Å MS relative to the aniline and 10 mol% benzoic acid.

was found to increase again to 90% when the even larger t-butyl group was introduced into the 3-position (131), leading to the isolation of the phosphonate 63 in 43% yield. The introduction of t-butyl groups into both the 3- and 5-positions leads to a slow reaction and the isolation of phosphonate 64 in only 13% yield. As a result of the screening of the various anilines shown in Scheme 5, the highest asymmetric induction (90% ee) was realized with the 3-t-butyl-2-hydroxyaniline 13l and this was identified as the aniline of choice for screening additional aliphatic aldehydes. The set of anilines shown in Scheme 5 was also employed in the screening of the reaction of benzaldehyde but none gave higher asymmetric inductions than 3,5diisopropyl-2-hydroxyaniline 13c used in Table 3 for aromatic aldehydes, although the 3-t-butyl-2-hydroxyaniline 13l gave an identical induction of 93% ee (see the ESI<sup>†</sup>).

Before committing to a broad investigation of the scope of the reactions of aliphatic aldehydes, we probed the use of 3-t-butyl substituted aniline 13l instead of 3,5-diisopropyl substituted aniline 13c. The data for the reactions of butanal 55a are presented in Table 5. The t-Bu<sub>2</sub>VANOL ligand 37 was superior to the VANOL ligand 36, giving the  $\alpha$ -aminophosphonate 65 in 81% ee vs. 39% ee with aniline 13c (Table 5, entries 1 vs. 2). A slight increase in induction to 85% was observed with the catalyst prepared from a 1:1:3 mixture of zirconium/NMI/ligand and the yield was increased slightly when the catalyst loading was increased to 10 mol% (entries 3 and 4). Finally, the reaction of butanal was compared under the same conditions with both anilines 13c and 13l with the result that the *t*-butyl substituted aniline 13l gave both higher yield and higher asymmetric induction than aniline 13c (entries 4 vs. 5).

With the identification of the aniline 13l as the optimal third component for the Kabachnik-Fields reaction of aliphatic aldehydes, a general study of the scope was undertaken with a set of 18 aliphatic aldehydes (Table 6). The yields for these reactions varied from 20 to 83% and the asymmetric inductions

ranged from 71-97%. The asymmetric inductions for the aliphatic aldehydes compared favorably with those for the aromatic aldehydes with the mean asymmetric induction of 90% ee for the aliphatic aldehydes and 91% ee for the aromatic aldehydes shown in Table 3. The best yields were observed in general for  $\alpha$ -unbranched aldehydes while  $\alpha, \alpha$ -dibranched aldehydes generally gave less product. 2,2-Dimethylpropanal 55q gave the highest asymmetric induction of 97% but the yield of a-aminophosphonate 66q was only 28%. Extension of the reaction time from 16 to 48 h did not improve the yield. The reaction is tolerant of a number of functional groups including alkyne (66e), a primary bromide (66f), silyl ethers (66g and 66h), protected amines (66i and 66j), azides (66k and 66l) and an ester (66m). Interestingly, for reasons that we do not understand at this point, the terminal olefin in 5-hexenal 55d only reacted to give the  $\alpha$ -aminophosphonate **66d** in 20% yield. Increasing the reaction time with aldehyde 55d from 16 to 48 h did not improve the yield of 66d. This was true of many of the aldehydes in Table 6, however, an increase in the reaction time with the phthalimide protected y-amino butanal 55j from 16 to 72 h increased the yield of 66j from 24% to 53%. The α-branched aldehydes 55n, 55o and 55p gave the corresponding  $\alpha$ -aminophosphonates in moderate yields and good to excellent asymmetric inductions. The β-branched aldehyde isovaleraldehyde 55r gave the phosphonoleucine diethyl ester 66r in 83% yield and 91% ee. The absolute configuration of the a-aminophosphonate 66r from the (S)-catalyst was determined to be (S)-66r after deprotection to the free amine as shown in Scheme 6. The products from the other aliphatic aldehydes in Table 6 were assumed to be homo-chiral.

The liberation of the  $\alpha$ -aminophosphonates requires a slightly different protocol for the aryl and aliphatic aldehydes. For the phosphonate (R)-51a from benzaldehyde it is first necessary to methylate the phenol function to give the methyl ether (R)-68. The free amine can then be obtained by oxidative

1

2

3

4

5

#### Table 6 Substrate scope for aliphatic aldehydes in the Kabachnik–Fields reaction<sup>a</sup>



<sup>*a*</sup> Zirconium catalysts were prepared by stirring a mixture of 10 mol%  $Zr(O-i-Pr)_4(HO-i-Pr)$ , 10 mol% *N*-methylimidazole (NMI) and 30 mol% (*S*)-*t*-Bu<sub>2</sub>VANOL ligand in dry toluene for 30 min at rt under air. Unless otherwise specified, all reactions were carried out under nitrogen on 0.1 mmol of aldehyde 55 with 1 equiv. of aniline 13I and 1 equiv. of diethylphosphite 41 in toluene at rt for 16 h in the presence of 4 Å molecular sieves (200 wt% relative to 13I) and 10 mol% of benzoic acid. All yields are isolated yields. The % ee was determined by HPLC. <sup>*b*</sup> Reaction time was 24 h. <sup>*c*</sup> Reaction time was 72 h. <sup>*d*</sup> Reaction time was 48 h. <sup>*e*</sup> This reaction was repeated and both times 71% ee was obtained.

deprotection of (*R*)-**68** with *N*-iodosuccinimide to give the  $\alpha$ aminophosphonate (*R*)-**67** in 78% yield in two steps. The absolute configuration of **67** was determined by comparison of its optical rotation with that previously reported for this compound<sup>25</sup> and by the ECCD method<sup>26</sup> (see the ESI†). Direct oxidation of the unprotected phenol unit in (*R*)-**51a** with *N*iodosuccinimide gave the desired deprotected product (*R*)-**67** but in only 10% yield along with several other products. Direct oxidation of (*R*)-**51a** with ceric ammonium nitrate gave a benzoxazole (see the ESI†). As a consequence of this failure, the Kabachnick–Fields reaction of benzaldehyde **31a** was performed with the *O*-methylated aniline derivative **69** according to the optimized procedure in Table 3 but only gave a 9% yield of **68** as a racemic compound. Thus, the phenol function in the aniline **13c** must play an important role in the reaction by either H-bonding to the catalyst center or by forming a covalent bond with the zirconium. The deprotection of the  $\alpha$ -amino phosphonates derived from 3-*t*-butyl-2-hydroxyaniline **13l** and



Scheme 6 Liberation of  $\alpha$ -aminophosphonates.

aliphatic aldehydes is much more straightforward. Treatment of the  $\alpha$ -amino phosphonate (*R*)-**66r** directly with three equivalents of *N*-iodosuccinimide and 1 equivalent of sulfuric acid in a mixture of water and acetonitrile gave phospholeucine diethyl ester (*R*)-**70** in 84% yield. The absolute configuration of **70** was determined by comparison of its optical rotation with that previously reported for this compound<sup>27</sup> and by the ECCD method developed previously<sup>26</sup> (see the ESI†).

#### 3. Conclusion

An effective asymmetric catalyst has been developed for the Kabachnik-Fields three component reaction of aldehydes, amines and phosphites to give  $\alpha$ -aminophosphonates. This catalyst was first optimized for aromatic aldehydes and later was extensively re-optimized to find a suitable catalyst for aliphatic aldehydes. The catalyst is generated in situ from zirconium tetraisopropoxide, N-methylimidazole (NMI) and a vaulted biaryl ligand with the optimal ratio of 1:1:3. Several different vaulted biaryl ligands were examined including VAPOL, VANOL and several 7,7'-disubstituted VANOL ligands with 7,7'-di-t-butylVANOL found to be the most effective. It was found that the yields and to some extent the asymmetric inductions could be increased in the presence of 10 mol% benzoic acid. For aromatic aldehydes the optimal amine was found to be a substituted 2-hydroxyaniline and of the several anilines screened 3,5-diisopropyl-2-hydroxyaniline was identified as superior and the optimal phosphite was diethyl phosphite. To achieve the desired level of asymmetric induction with aliphatic aldehydes an additional set of eight substituted 2hydroxyanilines was prepared and screened and the most effective was found to be 3-t-butyl-2-hydroxyaniline. The asymmetric inductions for aliphatic aldehydes were comparable with

those for aromatic aldehydes with a mean induction of 90% ee for the former and 91% ee for the latter. The best method for the liberation of the free amine from the aniline substituted  $\alpha$ -aminophosphonates involved oxidation with *N*-iodosuccinimide and in the case of aromatic substrates, this first required the *O*-methylated phosphonate.

### Data availability

The data is in the ESI.†

#### Author contributions

YD conceived the project and carried out the large majority of the reactions. WW wrote the manuscript and the other authors were minor contributors in the laboratory. All authors contributed to discussions.

## Conflicts of interest

There are no conflicts to declare.

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