Multicomponent Reactions

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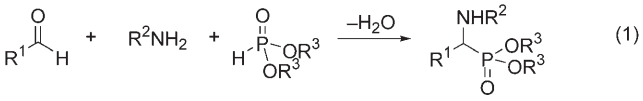
Direct Catalytic Asymmetric Three-Component Kabachnik–Fields Reaction**

*Xu Cheng, Richard Goddard, Gernot Buth, and Benjamin List**

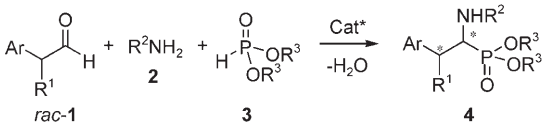
The reaction of a carbonyl compound, an amine, and a phosphite by in situ imine hydrophosphonylation [Eq. (1)], often called the Kabachnik–Fields reaction, is an attractive approach to α-amino phosphonates.



(1)

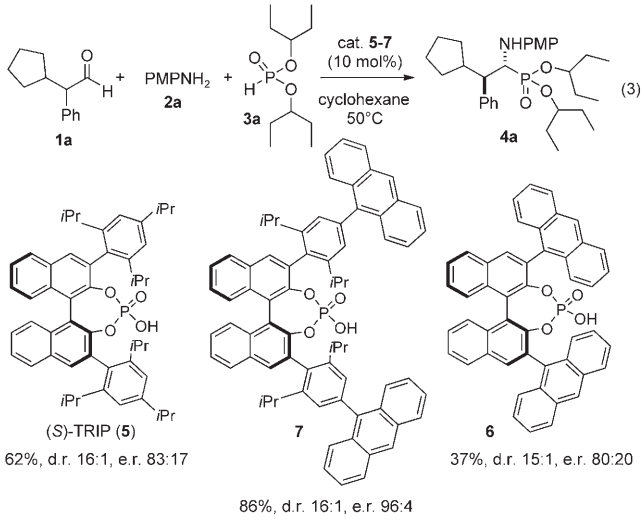
As mimics of α-amino acids,[1] α-amino phosphonates have great promise as antibacterial[2] and anti-HIV[3] agents as well as protease inhibitors.[4,5] Consequently, their enantioselective synthesis, in particular by catalytic enantioselective hydrophosphonylation of preformed imines, has attracted considerable interest.[6,7] Both chiral metal complexes[8] as well as organic catalysts such as Jacobsen's chiral thiourea derivatives,[9] chiral phosphoric acid derivatives,[10] and quinine have been used with success.[11] Despite these achievements however, a direct catalytic asymmetric Kabachnik–Fields reaction, has to our knowledge not been described before.[12] Here we show that racemic α-branched aldehydes, in the presence a new chiral phosphoric acid catalyst,[13] directly react with *p*-anisidine and a phosphite to furnish β-branched α-amino phosphonates highly diastereoselectively and enantioselectively by a dynamic kinetic resolution.

Akiyama et al.[10] recently developed an enantioselective hydrophosphonylation of preformed aromatic and unsaturated imines that is catalyzed by chiral binol-derived phosphoric acids pioneered in their laboratories as well as by Terada et al.[13b] Our group reported a highly enantioselective reductive amination of α-branched aldehydes by dynamic kinetic resolution (DKR) that is catalyzed by TRIP, a chiral phosphoric acid we have developed previously.[13c,14,15] We envisioned that an extension of these strategies to the Kabachnik–Fields reaction may be possible, leading directly to β-branched α-amino phosphonates **4** [Eq. (2)]. The analogous β-branched α-amino carboxylic acids have attracted attention in peptidomimetic chemistry as they uniquely restrict the conformational flexibility within a peptide.[16] Our design, however, seemed to be particularly challenging as it combines a dynamic kinetic resolution with the parallel creation of an additional stereogenic center.



(2)

Indeed, the direct asymmetric three-component Kabachnik–Fields reaction of one equivalent each of aldehyde **1a**, *p*-anisidine (**2a**), and di(3-pentyl)phosphite (**3a**),[17] catalyzed by TRIP (**5**, 10 mol%) furnished the desired product **4a** highly diastereoselectively (d.r. 16:1) and with moderate enantioselectivity (e.r. 83:17; 66% *ee*) [Eq. (3)]. We also tested the anthrancenyl-substituted catalyst **6**, which has previously been used with success in imine activation reactions.[18] However, no improvement in enantioselectivity was obtained. We then started investigating new phosphoric acids and found that the *p*-anthracenyl-substituted TRIP analogue **7**[19] was indeed both highly effective and stereose-



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[*] Dr. X. Cheng, Dr. R. Goddard, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2999
E-mail: list@mpi-muelheim.mpg.de
Dr. G. Buth
ISS, Forschungszentrum Karlsruhe
Postfach 3640, 76021 Karlsruhe (Germany)

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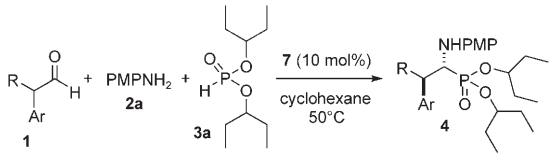
lective in this reaction. Phosphonate **4a** was obtained in 86% yield and both diastereoselectivity (d.r. 16:1) and enantioselectivity (e.r. 96:4) were excellent.

During optimization studies, we found the dosage of phosphite **3a** to be critical. Excess phosphite **3a** had a detrimental effect on the enantioselectivity with only little effect on the reactivity. However, only 0.9 equivalent of phosphite did not improve the enantiomeric ratio further. Also, it turned out to be important to degas the reaction mixture and run the reaction under an argon atmosphere to protect the phosphite from being oxidized to the corresponding phosphoric acid, which catalyzes the non-enantioselective reaction.

With the new highly selective catalyst **7** and optimized conditions in hand, we next investigated the substrate scope (Table 1). First we systematically investigated the effect of different aryl groups on aldehyde **1** (R = cyclopentyl (*c*Pent)). While yields and diastereoselectivities maintained a high level independent of the electronic nature or substitution of the aryl group, the enantioselectivity is slightly lower with substituents in the *o*- or *m*-position (Table 1, entries 1–11). Next we investigated the effect of the alkyl group (R) on aldehyde **1** (Ar = Ph). It quickly became apparent that rather bulky alkyl groups significantly increase both the diastereoselectivity and the enatioselectivity. While both methyl and ethyl substituents gave only moderate stereoselectivties, branched isopropyl and cyclohexyl groups gave excellent diastereoselectivities and enantioselectivities (Table 1, entries 12–15).

To determine the absolute and relative configuration of our products, suitable crystals of product **4g** were generated and analyzed by X-ray and synchrotron radiation.[20] The structure **4g** is given in Figure 1. The absolute configuration of the molecule was determined by anomalous dispersion on two crystals of the sample and established that the chiral centers at C1 and C2 both have *R* configurations. In the solid the molecules form centrosymmetric dimers held together by two short P=O···H–N hydrogen bonds (O···N 2.895 Å).

Table 1: Scope of the direct catalytic asymmetric Kabachnik–Fields reaction.



Entry	R	Ar	Product	Yield [%]	d.r.[a]	e.r.[a]
1	*c*Pent	Ph	**4a**	86	16:1	96:4
2	*c*Pent	4-MeC_6H_4	**4b**	85	22:1	96:4
3	*c*Pent	3-MeC_6H_4	**4c**	77	14:1	93:7
4	*c*Pent	4-MeOC_6H_4	**4d**	89	19:1	96:4
5	*c*Pent	3-MeOC_6H_4	**4e**	74	16:1	92:8
6	*c*Pent	2-MeOC_6H_4	**4f**	72	6.5:1	88:12
7	*c*Pent	4-ClC_6H_4	**4g**	83	20:1	94:6
8	*c*Pent	3-ClC_6H_4	**4h**	80	28:1	94:6
9	*c*Pent	4-BrC_6H_4	**4i**	81	17:1	92:8
10	*c*Pent	2-naphthyl	**4j**	64	17:1	92:8
11	*c*Pent	2-thienyl	**4k**	61	20:1	97:3
12	Me	Ph	**4l**	63	3:2	51:49 79:21
13	Et	Ph	**4m**	84	3:1	86:14 92:8
14	*i*Pr	Ph	**4n**	85	17:1	95:5
15	Cy	Ph	**4o**	86	16:1	95:5

[a] d.r. and e.r. values were determined by (chiral) HPLC.

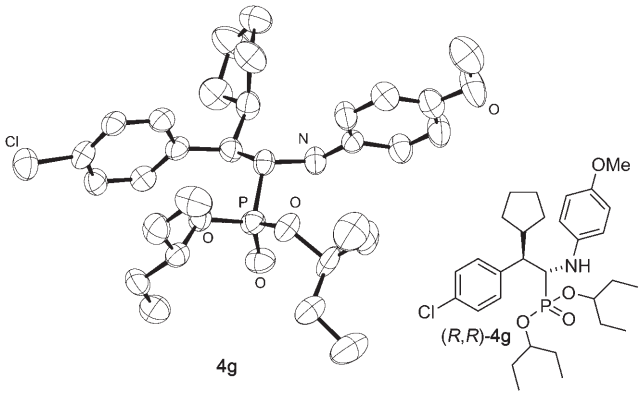
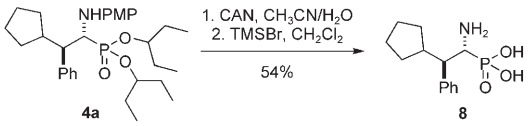


Figure 1. Absolute and relative configuration of the Kabachnik–Fields product **4g**.

Finally, the product **4a** can be readily converted into the corresponding amino phosphonic acid **8**. The PMP and ester groups were removed with CAN and TMSBr, respectively, to give the desired product in 54% overall yield [Eq. (4)].



(4)

Experimental Section

Typical procedure of the organocatalytic Kabachnik–Fields reaction: To a reaction vial charged with **7** (10.2 mg, 0.01 mmol), **2a** (12.3 mg, 0.1 mmol), and 5 Å MS (30 mg) under argon was added degassed cyclohexane (1 mL), **1a** (0.02 mL, 0.1 mmol), and phosphite **3a** (0.023 mL, 0.1 mmol). The mixture was stirred at 50 °C for 168 h. Then the mixture was concentrated and purified by silica gel chromatography (silica gel 60 hexane/ethyl acetate 3:1) to give **4a** as a slightly yellow oil (44.3 mg, 86%).

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[17] Alternative nitrogen sources that have been investigated include $BocNH_2$, $CbzNH_2$, benzamide, benzylamine, dibenzylamine, morpholine, and diphenylamine, which all gave no reaction. Among the anilines tested, *p*-anisidine gave higher enantioselectivities than *p*-hydroxylaniline, *p*-ethoxyaniline, *p*-phenoxyaniline, and *o*-methoxyaniline. We have also investigated other phospites, including diethyl-, diisopropyl-, and di(*o*-nitrobenzyl)phosphite and found di(3-pentyl)phosphite gave the highest enantioselectivities.

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[19] For synthetic details, see the Supporting Information.

[20] CCDC-679478 ($\lambda = 1.54178$ Å) and CCDC-679479 ($\lambda = 1.77121$ Å) (**4g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

