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Authors: Natalie Hofmann and Kai Hultzsch

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Switching the *N*-Alkylation of Arylamines with Benzyl Alcohols to Imine Formation Enables the One-Pot Synthesis of Enantioenriched α-*N*-Alkylamino Phosphonates

Natalie Hofmann,[a] and Kai C. Hultzsch*[a]

Dedication ((optional))

Abstract: The selective *N*-alkylation of anilines with benzylic alcohols can be switched in favor of the dehydrogenative condensation process using the nitrile-ligated Knölker's complex by conducting the reaction either in a closed system under inert conditions, or in an open system in air. The selective formation of imines, containing reactive C=N bonds, provides an opportunity towards further functionalization. Indeed, a one-pot three-component condensation of alcohols, amines and phosphites, promoted by an iron-based Knölker-type complex in combination with a chiral BINOL-based phosphoric acid, provides access to enantioenriched α-*N*-alkylamino phosphonates.

Introduction

The development of atom-efficient transformations that lead to valuable compounds bearing carbon-heteroatom bonds starting from innocuous and cheap starting materials is in the focus of modern synthetic chemistry.[1] Therefore, hydrogen borrowing catalysis is an important contemporary research topic as it provides a green method for a variety of transformations of alcohols, in particular the formation of new carbon-carbon or carbon-nitrogen bonds.[2] In order to gain access to higher functionalized products the combination of metal-based hydrogen borrowing catalysis with organocatalysis provides promising possibilities.[3–5] Our interest is primarily focused on different derivatives of the well-known iron-based Knölker's complex **1a**–**1c** (Figure 1).[6]

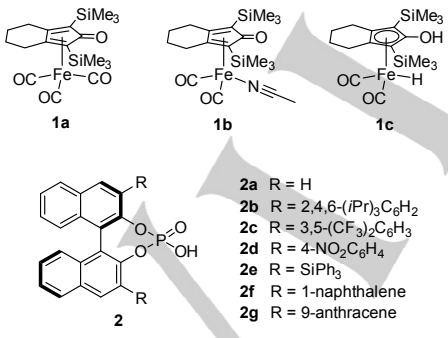

Figure 1. Applied metal and organocatalysts.

[a] N. Hofmann, MSc., Univ.-Prof. Dr. K. C. Hultzsch
Universität Wien, Fakultät für Chemie,
Institut für Chemische Katalyse
Währinger Straße 38, 1090 Wien (Austria)
E-mail: kai.hultzsch@univie.ac.at
https://chemcat.univie.ac.at/

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Iron is particularly attractive as it is one of the most abundant metals in the earth crust. Besides, iron species are ubiquitous in biological systems and metabolic processes making them interesting for applications in the food and pharmaceutical industry.[7] The low toxicity of iron is often used in the discussion on iron-based catalysts as well; however, the toxicity level of iron has to be viewed critically.[8] Knölker's complex itself has been applied in combination with different organocatalysts. Rodriguez *et al.* established the enantioselective functionalization of allylic alcohols by applying, among others, a triple iron/copper/iminium activation,[3] whereas Beller *et al.* reported enantioselective hydrogenations of imines and quinoxalines by combining iron catalysis with chiral phosphoric acids **2**.[4] In this work we focus on the synthesis of enantioenriched α-*N*-alkylamino phosphonates by combining a hydrogen-borrowing based *N*-alkylation with the Kabachnik-Fields reaction.[9] As α-amino phosphonates are valuable replacements of α-amino carboxylic acids, which are building blocks of proteins and peptides and therefore play an important role in many physiological processes, their easy and waste-free synthesis is of particular interest.[10] To the best of our knowledge there are only two heterogeneous systems for the one-pot condensation of anilines, alcohols and phosphites, but no homogeneous system at all. On one hand Hosseini *et al.* reported $CuO@Fe_3O_4$ nanoparticles to be suitable catalysts,[11] on the other hand Fan and coworkers conducted the reaction with gold supported on hydroxyapatite.[12] With this in mind we decided to develop a homogeneous system to synthesize enantioenriched α-amino phosphonates. As Beller and coworkers could combine the iron-based Knölker's complex **1c** with chiral phosphoric acids **2** for hydrogenations[4] and phosphoric acids are common organocatalysts for hydrophosphonylations,[9b,13] we chose to combine similar systems for the exploration of the enantioselective one-pot condensation of anilines, alcohols and phosphites. In the course of our investigations we found that it is possible to control the selectivity of the *N*-alkylation of aniline promoted by Knölker's complex **1b** and **1c** by varying the reaction conditions (Scheme 1).[14] So far, under base-free conditions iron is known to favor the formation of the respective amine, whereas manganese is prone to stop at the imine-intermediate.[15] In this study we will show that a selective formation of the *N*-alkylated amine can be achieved by conducting the reaction under argon, whereas a selective imine formation is observed when the reaction is performed under atmospheric conditions. The reactive imine can subsequently undergo a hydrophosphonylation reaction leading to α-*N*-alkylamino phosphonates. Therefore, three different products are accessible starting from anilines and benzylic alcohols simply by varying the reaction conditions and by combining metal catalysis with organocatalysis.

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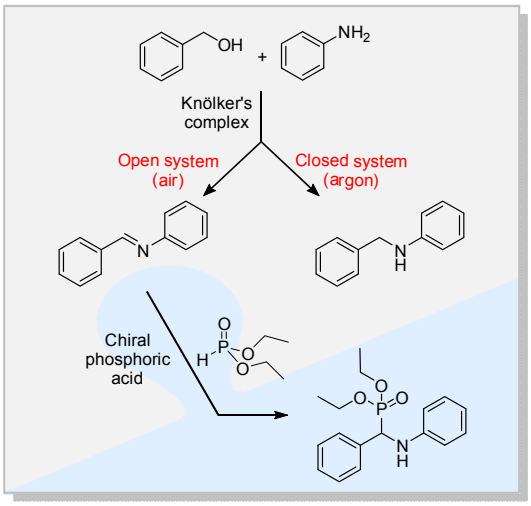


Scheme 1. Selective synthesis of *N*-alkylated amines, imines and α-*N*-alkylamino phosphonates.

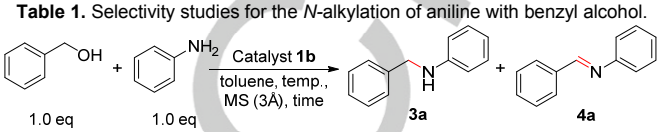
Results and Discussion

Selective *N*-alkylation. Initially, we started our investigations on this topic using Knölker's complex **1a** (Figure 1),[6] which was already successfully applied for the direct alkylation of amines with alcohols.[14] However, applying this type of catalyst required additional base or activation reagents to achieve any reactivity in the *N*-alkylation of aniline. As our goal was to combine the *N*-alkylation with a subsequent hydrophosphonylation step promoted by chiral phosphoric acids **2**, we were searching for a way to avoid the application of base. Thus, we decided to utilize Knölker's complex **1b**,[6b] in which one CO ligand is replaced by acetonitrile. This variant of Knölker's complex is a known catalyst for transfer hydrogenations of aldehydes, ketones and alkynes using isopropanol as hydrogen source.[16] Feringa and coworkers used this air-stable nitrile-ligated complex for the *N*-alkylation of amino acids.[14f] Darcel *et al.* observed moderate activity in the α-alkylation of ketones with alcohols.[17] Fortunately, this catalyst turned out to be highly active in our base-free benchmark reaction with aniline and benzyl alcohol as well. Besides, we synthesized the hydride derivative **1c** of the Knölker's complex,[6c, 18] which proved to be active as well.

To our delight we could control the selectivity of this reaction simply by switching between a closed system under argon atmosphere and an open system under atmospheric conditions with both catalysts (**1b** and **1c**, see Table S1 in supporting information). Realization under inert conditions resulted in the quantitative formation of *N*-benzylaniline (**3a**), whereas execution in an open system in air led to the selective formation of *N*-benzylideneaniline (**4a**). In general, the nitrile-ligated complex **1b** exhibits a higher reactivity and is easier to handle than **1c** thanks to its bench stability.[6b] Therefore, this catalyst was used for the following screening and optimization reactions (Table 1).

We found that the application of 5 mol% of **1b** at 110 °C in a closed system under argon leads to a quantitative formation of **3a**. Higher catalyst loadings (7.5 mol%) and temperatures (140 °C) as well as longer reaction times (55 h) are required in an open system in order to achieve good conversions to **4a**. By changing the solvent from toluene to the higher boiling *p*-xylene the outcome was improved further. Despite these harsh conditions, a practical feature is that the selective formation of the imine can be conducted under atmospheric conditions, significantly simplifying the reaction's feasibility. Further investigations showed that the application of molecular sieves (3 Å) is crucial for the success of both reactions.

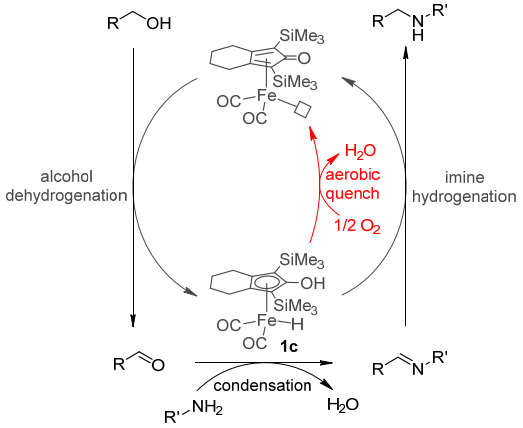
Table 1. Selectivity studies for the *N*-alkylation of aniline with benzyl alcohol.



#	Cat. **1b** *[mol%]*	Open/ closed	Temp. *[°C]*	Time *[h]*	Conversion *[%]*[a] Overall	Amine **3a**	Imine **4a**
1	5.0	closed	100	24	93	92	<1
2	**5.0**	**closed**	**110**	**24**	**quant.**	**>99**	**<1**
3	5.0	open	110	48	47	7	40
4	7.5	open	110	48	63	9	54
5	7.5	open	140	48	87	14	73
6	7.5	open	140	55	94	16	78
7	**7.5**	**open**[b]	**140**	**55**	**quant.**	**17**	**83**

Reaction conditions: 150 mg molecular sieves (3Å), 0.250 mmol benzyl alcohol, 0.250 mmol aniline, 0.3 mL toluene. Closed = reaction in closed vial under an argon atmosphere. Open = reaction in opened vial in air at 60 °C for 15 min, then the vial was loosely capped in order for hydrogen to be able to escape and heated to 140 °C for 55 h.
[a] Conversion was determined *via* GC/FID and GC/MS using mesitylene as internal standard. [b] *p*-xylene was applied as solvent.

The change in product selectivity upon switching from a closed system under argon to an open system in air can be attributed to an oxidative quenching of the reduced Knölker's complex by oxygen, which bypasses the imine hydrogenation pathway (Scheme 2).[19, 20]



Scheme 2. Proposed mechanism for the aerobic quench of **1c** short-circuiting the hydrogen borrowing *N*-alkylation.

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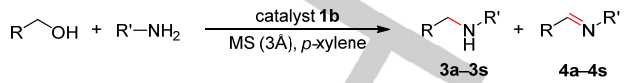
After optimization of the reaction conditions we explored the functional group tolerance and the selectivity of the catalyst. We applied benzylic alcohols and anilines with several electron-donating and electron-withdrawing groups. (Table 2). Methyl and methoxy substituents proved to be well tolerated leading to the corresponding secondary amines (**3b**, **3c**, **3f**, **3g**, **3i**, **3j**), respectively imines (**4b**, **4c**, **4f**, **4g**, **4i**, **4j**) in good to excellent yields. The reaction of *ortho*-hydroxybenzyl alcohol with aniline, preferentially led to the amine **3e** under both reaction conditions, while the respective imine **4e** was only formed in small amounts. Similar observations were made in the reaction of 2- and 3-aminopyridine with benzyl alcohol to preferentially form amines **3k** and **3l**, but here the overall conversion was also diminished. The converse was noticed in the reaction of *ortho*-chlorobenzyl alcohol with aniline (**3d, 4d**). The reaction of aniline with linear aliphatic alcohols *n*-butanol, *n*-pentanol, and *n*-hexanol led to the corresponding amines **3m**–**o** in good yields, similar to observations made by Kirchner *et al.* using an iron PNP pincer catalyst;[14a] however, even under atmospheric conditions the amines **3m**–**o** remained the prevailing products and only trace amounts of imines **4m**–**o** were formed. Piperidine was completely converted into the corresponding tertiary amine (**3p**) after increasing the reaction temperature, which confirms the observation by Feringa *et al.* that the catalyst is capable of converting secondary amines as well.[14f] The exploration of an intramolecular reaction with 2-aminophenethyl alcohol showed a complete consumption of the starting material; however, only 36% of *1H*-indoline (**3q**) were formed and *1H*-indole (**4q**) was detected as the major product, independent of the reaction conditions. Obviously, tautomerization of the imine intermediate is more facile than reduction to **3q**, driven by the rearomatization of **4q**. The reaction of benzyl alcohol with hexylamine produced amine **3r** in good yield under the closed system conditions, while under atmospheric conditions a 1:1 mixture of amine **3r** and imine **4r** was observed. The analogous reaction with benzylamine gave the amine **3s** preferentially under both sets of conditions.

With the knowledge that allylic alcohols have been successfully applied in iron-catalyzed borrowing hydrogen *N*-alkylation[14e] and cascade processes[3] and that imines derived from cinnamaldehyde are well-suited for the enantioselective hydrophosphonlyation with chiral phosphoric acids,[13] we decided to subject allylic alcohols to our *N*-alkylation and imine formation conditions (Table 3). The reaction of cinnamyl alcohol and crotyl alcohol with either aniline or *p*-anisidine gave mixtures of 4 possible amine and imine products with or without α,β-unsaturation. Interestingly, the application of crotyl alcohol in a closed system provided the fully saturated amines **3't** and **3'u** as major product, whereas cinnamyl alcohol led predominantly to the α,β-unsaturated amines **3v** and **3w**. Under atmospheric conditions the amount of α,β-unsaturated imine **4t**–**w** significantly increased for all substrates, although the selectivity remained moderate.

Table 2. Synthesis of amines and imines through coupling of various alcohols with amines.



(A) select. formation of amines **3**		(B) select. formation of imines **4**	
R = H	**3a** >99%	R = H	**4a** 83%
R = CH_3	**3b** 75%	R = CH_3	**4b** 90%
R = OCH_3	**3c** >99%	R = OCH_3	**4c** 69%
R = Cl	**3d** 24%	R = Cl	**4d** 70%[d]
R = OH	**3e** 94%[a]	R = OH	**4e** 11%[a]
	3f 96%		**4f** 86%
R' = CH_3	**3g** 91%	R' = CH_3	**4g** 72%
R' = F	**3h** 71%	R' = F	**4h** 67%[d]
	3i >99		**4i** 75%
	3j 97%		**4j** 77%
	3k 67%		**4k** 6%
	3l 47%		**4l** 13%
n=1	**3m** 91%[b]	*n*=1	**4m** 9%[b]
n=2	**3n** >99%	*n*=2	**4n** 5%
n=3	**3o** 95%	*n*=3	**4o** <1%
	3p 99%[b]		**4p** none
	3q 36%[c]		**4q** 75%[c,d]
	3r 85%		**4r** 49%
	3s 86%		**4s** 23%

Reaction conditions:
A) selective formation of amine: 5 mol% **1b**, 150 mg molecular sieves (3Å), 0.250 mmol alcohol, 0.250 mmol aniline, 0.3 mL *p*-xylene, 110 °C, 24 h, closed system, argon.
B) selective formation of imine: 7.5 mol% **1b**, 150 mg molecular sieves (3Å), 0.300 mmol alcohol, 0.250 mmol aniline, 0.3 mL *p*-xylene, 140 °C, 55 h, open system, air.
Conversions and product ratios were determined *via* GC/FID and GC/MS using mesitylene as internal standard. Amine/imine-ratios for all reactions are listed in the supporting information in Tables S3A and S3B.
[a] NMR-yield. [b] Reaction temperature: 130 °C. [c] The identity of the products was verified by ^{1}H-NMR spectroscopy. [d] Reaction time: 92 h.

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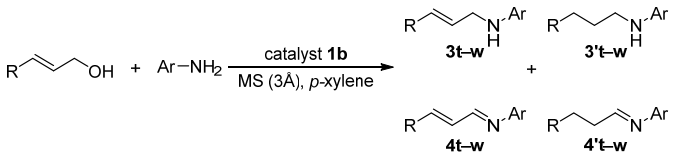
Table 3. Investigation of allylic alcohols in the *N*-alkylation and imine formation.



t: R = CH_3, Ar = Ph **v:** R = Ph, Ar = Ph
u: R = CH_3, Ar = PMB **w:** R = Ph, Ar = PMB

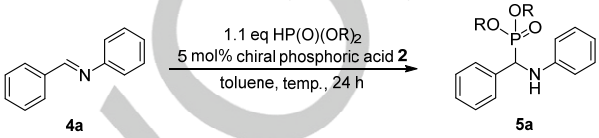
#	R	Ar	Conversion [%][a] Overall	3	3'	4	4'
(A) closed system under argon							
1	CH_3	Ph	>99	2	83	2	13
2	CH_3	PMB	>99	3	48	33	16
3	Ph	Ph	>99	61	30	9	<1
4	Ph	PMB	>99	68	17	15	<1
(B) open system in air							
5	CH_3	Ph	>99	2	43	50	5
6	CH_3	PMB	94	3	31	53	8
7	Ph	Ph	90	46	5	39	<1
8	Ph	PMB	95	47	10	38	<1

Reaction conditions:
A) selective formation of amine: 5 mol% **1b**, 150 mg molecular sieves (3Å), 0.250 mmol alcohol, 0.250 mmol aniline, 0.3 mL *p*-xylene, 110 °C, 24 h, closed system, argon.
B) selective formation of imine: 7.5 mol% **1b**, 150 mg molecular sieves (3Å), 0.300 mmol alcohol, 0.250 mmol aniline, 0.3 mL *p*-xylene, 140 °C, 24 h, open system, air.
[a] Conversions and product ratios were determined *via* GC/FID and GC/MS using mesitylene as internal standard.

Enantioselective hydrophosphonylation. In order to promote the enantioselective hydrophosphonylation, we focused on chiral phosphoric acids, which are known to be efficient organocatalysts for various selective additions to imines,[21] including the hydrophosphonlyation.[9b, 13] Akiyama[13a, 13b] and Ma[13c] studied the enantioselective hydrophosphonlyation of *N*-benzylidene *p*-anisidine and aldimines derived from cinnamaldehyde derivatives using the BINOL-based phosphoric acids **2a**–**g**. As a test reaction, we therefore decided to investigate the addition of various phosphites to *N*-benzylideneaniline (**4a**) (Table 4).

In general, decent yields were obtained for all phosphoric acids and phosphites, while enantioselectivities remained moderate. In agreement to results obtained for *N*-benzylidene *p*-anisidine,[13] the sterically hindered 3,5-bis(trifluoromethyl)phenyl-substituted acid **2c** gave the highest selectivity (52% ee). Despite its bulkiness, the anthracene-substituted phosphoric acid **2g** was significantly less enantioselective (35% ee). Interestingly, the sterically more demanding diisopropyl and diphenyl phosphite led to a diminished enantioselectivity as well. In particular, diphenyl phosphite gave essentially a racemic product. This observation can be explained by a fast uncatalyzed background reaction for this substrate. The reaction is complete within 15 min even in the absence of an acid catalyst. In order to rule out a radical process, the reaction of diphenyl phosphite with **4a** was repeated in the presence of 1 equiv hydroquinone with and without added phosphoric acid **2a**, leading also to complete conversion within 15 min in both cases.

Table 4. Influence of the acid catalyst, structure of phosphite and reaction temperature on the enantioselective hydrophosphonylation of imine **4a**.



#	Product	2	$HP(O)(OR)_2$	Temp. [°C]	Yield [%][a]	ee [%][b]
Different phosphoric acids **2**						
1	**5a**	---	$HP(O)(OEt)_2$	25	21	---[c]
2	**5a**	**2a**	$HP(O)(OEt)_2$	25	94	<5
3	**5a**	**2b**	$HP(O)(OEt)_2$	25	91	23
4	**5a**	**2c**	$HP(O)(OEt)_2$	**25**	**93**	**52**
5	**5a**	**2d**	$HP(O)(OEt)_2$	25	89	9
6	**5a**	**2e**	$HP(O)(OEt)_2$	25	84[d]	45
7	**5a**	**2f**	$HP(O)(OEt)_2$	25	90	8
8	**5a**	**2g**	$HP(O)(OEt)_2$	25	91	35
Different phosphites						
9	**5aa**	**2c**	$HP(O)(OMe)_2$	25	91	47
10	**5ab**	**2c**	$HP(O)(O^iPr)_2$	25	95	39
11	**5ac**	**2c**	$HP(O)(OPh)_2$	25	98[e]	<5
Varying temperatures						
12	**5a**	**2c**	$HP(O)(OEt)_2$	0	91[f]	51
13	**5a**	**2c**	$HP(O)(OEt)_2$	60	95[g]	47
14	**5a**	---	$HP(O)(OEt)_2$	100	94	<5

Reaction conditions: 5 mol% **2**, 0.250 mmol *N*-benzylideneamine, 0.275 mmol phosphite, 0.3 mL toluene.
[a] Isolated yield. [b] Determined *via* chiral HPLC. [c] Not applicable. [d] Reaction time: 48 h. [e] The reaction proceeded to completion within 15 min also in the absence of an acid catalyst or when 1 equiv hydroquinone (relative to **4a**) was added. [f] Reaction time: 90 h; [g] Reaction time: 5 h.

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Varying the reaction temperature solely influenced the rate of the reaction, but hardly showed any impact on the enantioselectivity (Table 4, entries 4, 12, 13). Lower reaction temperatures required longer reaction times, whereas higher temperatures led to a faster completion of the reaction. In general, the addition of diethyl phosphite to the imine proceeded also in the absence of catalyst when the reactions were conducted at 100 °C.

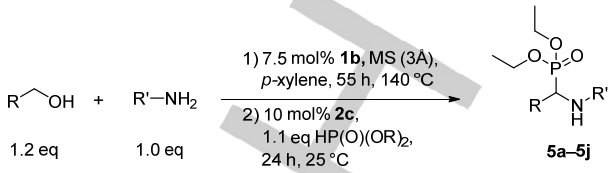
Attempts to extend the substrate scope of the enantioselective hydrophosphonlyation of imines to the aliphatic imine *N*-phenylhexanimine were frustrated by its instability in the presence of either diethyl phosphite ($pK_A \approx 13.0$)[22a] or chiral phosphoric acid ($pK_A \approx 3.0$),[22b] leading to facile cleavage of the imine.

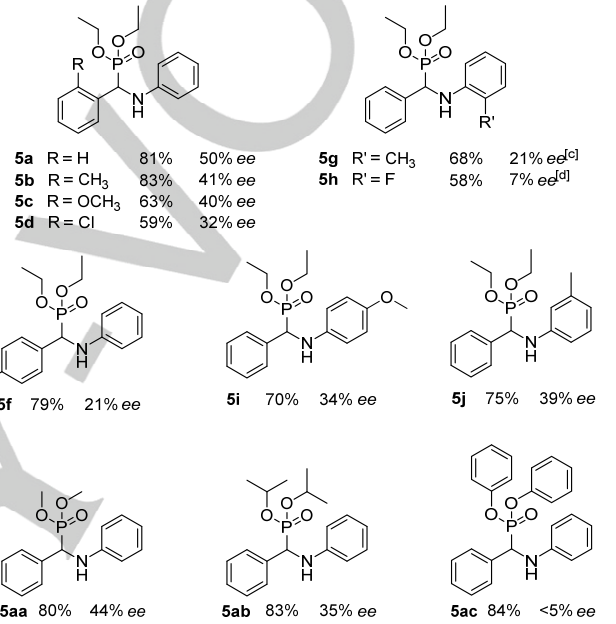
One-pot synthesis of *α*-*N*-alkylamino phosphonates. Since we wanted to couple the *N*-alkylation with the hydrophosphonylation, we performed compatibility studies as well. We found that aniline hampers the addition of diethyl phosphite to *N*-benzylideneaniline, whereas phosphoric acids **2** suppress the *N*-alkylation. This led us to the conclusion that a one-pot cascade reaction is not feasible, but the synthesis of α-*N*-alkylamino phosphonates can be achieved in a sequential one-pot procedure (for detailed experimental data see supplementary information, Tables S4 and S5). With the optimized reaction conditions for each reaction step, we were able to carry out the synthesis of diethyl (phenyl(phenylamino)methyl)phosphonate (**5a**) in 80% isolated yield with 50% *ee* *via* one-pot condensation of aniline, benzyl alcohol and diethyl phosphite (Table 5). Fractional crystallization of *rac*-**5a** was observed during recrystallization from heptane, leaving the enantioenriched form in the supernatant and increasing the enantiomeric excess up to 81%. However, none of the other products showed a similar fractionation.

After showing the proof of principle with the benchmark reaction, we chose suitable substrates to investigate the influence of steric and electronic changes on the hydrophosphonylation. We found that steric hindrance in the *ortho*-position, either in the alcohols or the amines, did not improve the selectivity of the reaction and the enantiomeric excess remained in the 30–40% range in most cases. However, the addition of diethylphosphite to the imines derived from *ortho*-methyl- and *ortho*-fluoro-aniline were hampered and no reaction was observed at ambient temperature. Only heating to 60 °C, respectively 100 °C, produced the desired products **5g** and **5h** in decent yields.

During purification of products **5a**–**5j** we managed to recover the valuable chiral phosphoric acid catalysts **2** from the last fraction of the column chromatography.

Table 5. One-pot two step synthesis of α-amino phosphonates **5**





Reaction conditions: 1) 7.5 mol% **1b**, 150 mg molecular sieves (3Å), 0.300 mmol alcohol, 0.250 mmol aniline, 0.3 mL *p*-xylene, open system, air; 2) 10 mol% **2c**, 0.275 mmol phosphite; Isolated yields.
[b] Determined *via* chiral HPLC. [c] Reaction temperature: 60 °C. [d] Reaction temperature: 100°C.

Conclusions

In brief, the *N*-alkylation of anilines with benzylic alcohols catalyzed by the highly reactive acetonitrile-ligated Knölker complex **1b** can be switched in favor of imine formation. While the borrowing hydrogen process is achieved in a closed system under argon, the dehydrogenative condensation occurs at a higher temperature in an open system in air. Both reactions do not require activation by a base additive. The highly reactive C=N-bond of the *in situ* formed imine can be used for the atom-efficient synthesis of *α*-*N*-alkylamino phosphonates by a one-pot three-component condensation of alcohols, amines and phosphites. Notably, this tandem reaction can be performed under atmospheric conditions, forming water as the only by-product and the applied chiral phosphoric acid can be recovered. However, this protocol appears to be only amenable to aniline and benzyl alcohol derivatives, as aliphatic alcohols and amines either lead to predominant amine formation under both sets of reaction

conditions or the resulting aliphatic imines are unstable under the conditions of hydrophosphonylation.

Experimental Section

General considerations. Toluene and *p*-xylene were distilled from sodium benzophenone ketyl. Alcohols and phosphites used as substrates for catalysis were distilled from Na_2SO_4. Amines used as substrates for catalysis were distilled from CaH_2. If not mentioned differently all commercially available starting materials were used without further purification. All ^1H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded on a Bruker UltrashieldTM 400 or 600 Plus instrument, whereby the ^1H NMR spectra were measured at 400.3 MHz or 600.2 MHz, the ^{13}C NMR spectra at 100.6 or 150.9 MHz, and the ^{31}P NMR spectra at 162.0 MHz. All chemical shifts are noted in ppm. ^1H and ^{31}C chemical shifts are indicated relative to TMS and were referenced to residual signals of the solvent (^1H NMR ($CDCl_3$): 7.27 ppm, ^{13}C NMR ($CDCl_3$): 77.0 ppm). ^{31}P chemical shifts were referenced to H_3PO_4 (0.00 ppm). Column chromatography was performed by using Biotage® SP4 and Isolera flash systems and the applied columns were packed with silica gel 60 Å or aluminium oxide 90 standardised (activity II-III). TLC was performed with commercial Kieselgel 60 F254 or ALOX N/UV254 and visualized via UV lamp. GC/MS measurements were conducted on an Agilent Technologies with 5977B MSD High Efficiency Source and 7820A GC-system. GC/FID measurements were conducted on a Shimadzu GC-2010 system. HPLC measurements were conducted on an Agilent Technologies Series 1200 system with 61379B Degasser, 61311A QuatPump, 61329A LLS, 61316A TCC, G1315D DAD. The Knölker's complexes **1a**,[14d] **1b**,[6b,16a,16b] and **1c**[6c, 18] were synthesized according to the literature, as well as the chiral BINOL-based phosphoric acids **2a**,[23] **2b**,[23] **2c**,[23] **2d**,[24] **2e**,[25] **2f**,[26] and **2g**.[27]

Synthesis of *N*-benzylaniline (3a). In an argon filled glovebox, a PTFE-lined screw-cap vial (1.5 mL), equipped with a magnetic stirring bar and molecular sieves (3 Å, 150 mg), Knölker's complex **1b** (5.3 mg, 0.013 mmol, 0.05 equiv) was dissolved in *p*-xylene (0.3 mL). Benzyl alcohol (26 µL, 1.04 g/mL, 0.250 mmol, 1.0 equiv) and aniline (23 µL, 1.03 g/ml, 0.250 mmol, 1.0 equiv) were added and the vial was closed tightly and sealed with Teflon tape. The vial was placed in an aluminum block, covered with aluminum foil, and the resulting reaction mixture was heated to 110°C with magnetic stirring for 24 h. After cooling to room temperature the reaction was quenched by addition of H_2O (0.5 mL) and the water layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. Purification *via* column chromatography (silica, hept:CH_2Cl_2:Et_3N = 9:1:0.1) led to 42 mg (93%) of *N*-benzylaniline as a slightly yellow oil.

Synthesis of *N*-benzylideneaniline (4a). In a PTFE-lined screw-cap vial (1.5 mL), equipped with a magnetic stirring bar and molecular sieves (3 Å, 150 mg), Knölker's complex **1b** (8.1 mg, 0.019 mmol, 0.075 equiv) was dissolved in *p*-xylene (0.3 mL). Benzyl alcohol (31 µL, 1.04 g/mL, 0.300 mmol, 1.2 equiv) and aniline (23 µL, 1.03 g/ml, 0.250 mmol, 1.0 equiv) were added. The vial was placed in an aluminum block, and the resulting reaction mixture was heated in the vial opened to air to 60°C with magnetic stirring for 15 min, then the vial was loosely capped in order for hydrogen to be able to escape, covered with aluminum foil, and heated to 140°C for 55 h. After cooling to room temperature the reaction was quenched by addition of H_2O (0.5 mL) and the water layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. Purification *via* pipette chromatography (silica, hept:CH_2Cl_2:Et_3N = 9:1:0.1) led to 37 mg (82%) of *N*-benzylideneaniline as a slightly yellow solid.

Synthesis of diethyl (phenyl(phenylamino)methyl) phosphonate (5a). In a PTFE-lined screw-cap vial (1.5 mL), equipped with a magnetic stirring bar and molecular sieves (3 Å, 150 mg), Knölker's complex **1b** (8.1 mg, 0.019 mmol, 0.075 equiv) was dissolved in *p*-xylene (0.3 mL). Then benzyl alcohol (31 µL, 1.04 g/mL, 0.300 mmol, 1.2 equiv) and aniline (23 µL, 1.03 g/ml, 0.250 mmol, 1.0 equiv) were added. The vial was placed in an aluminum block and the resulting reaction mixture was heated in the vial opened to air to 60 °C with magnetic stirring for 15 min, then the vial was loosely capped in order for hydrogen to be able to escape, covered with aluminum foil, and heated to 140°C for 55 h. After cooling to room temperature, chiral phosphoric acid **2c** (19.3 mg, 0.025 mmol, 0.10 equiv) was added, followed by the addition of $HP(O)(OEt)_2$ (35 µL, 1.07 g/mL, 0.275 mmol, 1.1 equiv). The mixture was stirred for additional 24 h at ambient temperature. The reaction was quenched by addition of sat. $NaHCO_3$-solution (0.5 mL) and the water layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. Purification *via* column chromatography (silica, 20–50% EtOAc in heptane, 0.5% Et_3N) led to 64 mg (81%) of diethyl (phenyl(phenylamino)-methyl)phosphonate as white solid.

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Keywords: hydrogen borrowing catalysis • organocatalysis • tandem catalysis • α-amino phosphonates • chiral phosphoric acids

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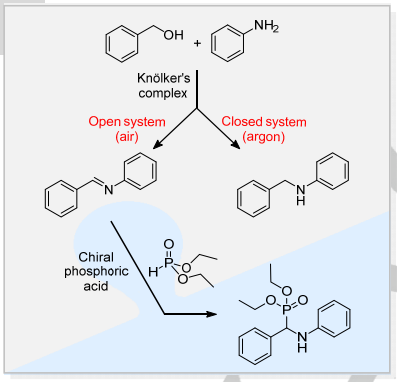
Layout 1:

FULL PAPER

The base-free *N*-alkylation of anilines with benzylic alcohols can be switched in favor of imine formation simply by switching between a closed and an open reaction system. Further functionalization of the in situ synthesized imine leads to α-*N*-alyklamino phosphonates *via* a one-pot procedure in an atom-economic fashion.



Key Topic*

Hydrogen Borrowing Catalysis, Organocatalysis

*Natalie Hofmann, Kai C. Hultzsch**

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Switching the *N*-Alkylation of Arylamines with Benzyl Alcohols to Imine Formation Enables the One-Pot Synthesis of Enantioenriched α-*N*-Alkylamino Phosphonates

*one or two words that highlight the emphasis of the paper or the field of the study