Cooperative Catalysis Utilizing the Hydrogen Borrowing Principle in Conjunction with Organocatalysis

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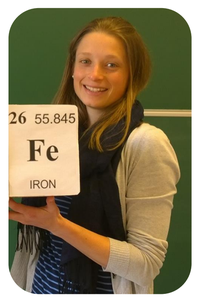


Introduction

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, we are investigating the possibility to couple hydrogen borrowing catalytic systems (Knölker's complex[3]) with (chiral) organocatalysts (e.g. phosphoric acids, amino acids), which should promote an additional transformation step. The combination of multiple catalytic processes within a one-pot synthesis should not only provide access to more complex products, but it may do so in a stereoselective manner as well.[4]

Herein, we present the synthesis of α-amino phosphonates *via* one-pot three component condensation of alcohols, amines and phosphites by combining an iron promoted *N*-alkylation with an organocatalytic hydrophosphonylation.

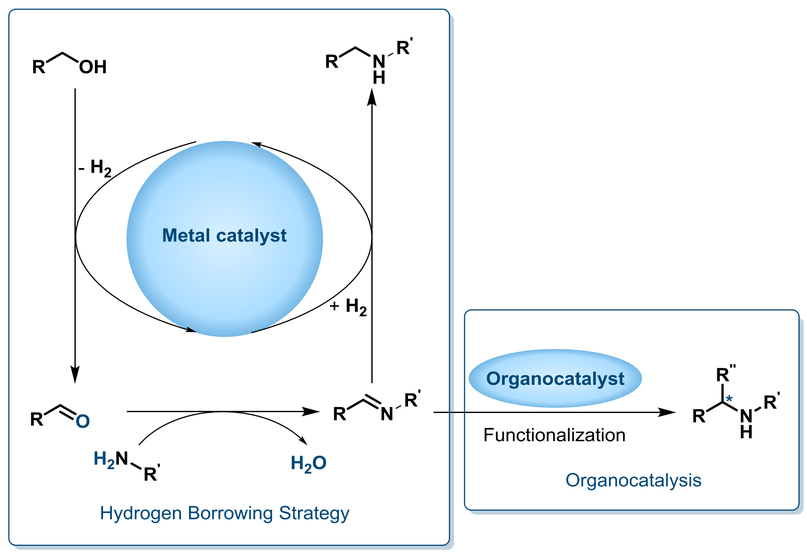
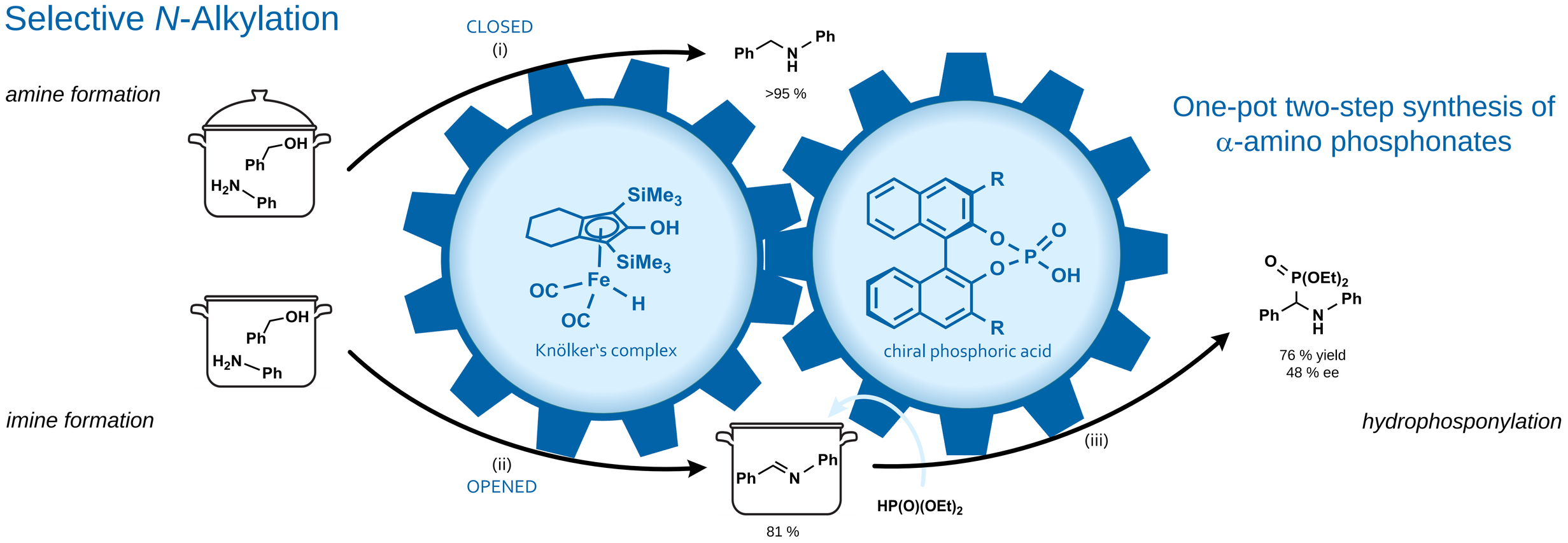


Figure 1: Illustration of a cooperative catalysis utilizing the hydrogen borrowing principle in combination with organocatalysis

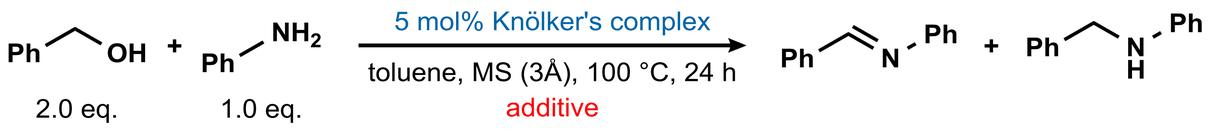
Selective *N*-Alkylation



reaction conditions: (i) 2.5 eq. benzyl alcohol, 1.0 eq. aniline, 5 mol% Knölker's complex, toluene, MS (3 Å), 0.8 *M*, 100 °C, 24 h, argon, closed vessel; (ii) 2.0 eq. benzyl alcohol, 1.0 eq. aniline, 7.5 mol% Knölker's complex, toluene, MS (3 Å), 0.8 *M*, 100 °C, 24 h, argon, opened vessel; (iii) 1.1 eq. $HP(O)(OEt)_2$, 10 mol% chiral phosphoric acic (*R* = 3,5-$(CF_3)_2C_6H_3$), 25 °C, 24 h.

Compatibility Studies

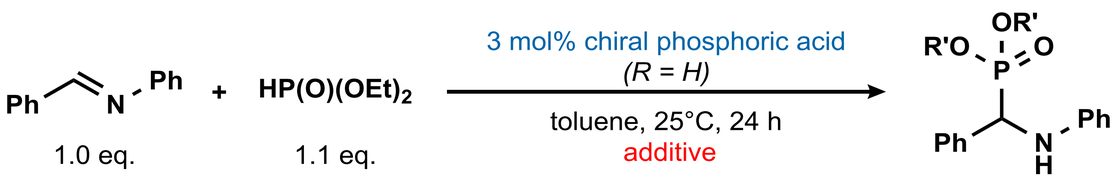
N-Alkylation



#	Additive		Conversion[1] *[%]*		
	Type	Amount *[eq.]*	Imine	Amine	Overall
1	---	---	6	88	94[2]
2	$HP(O)(OEt)_2$	1.1	<5	64	64[3]
3	phosphoric acid (*R* = H)	0.1	5	19	24[3]
4	$HP(O)(OEt)_2$ phosphoric acid (*R* = H)	1.1 0.1	<5	68	68[2]

[1] Conversion was determined *via* GC/MS analysis.
[2] Selected examples were worked up and the obtained yields confirmed the results obtained *via* GC/MS analysis.
[3] Various by-products were observed: *N*-methyl-1-phenylmethanamine, *N*-benzyl-*N*-ethylaniline, *N*,*N*-dibenzylaniline (10-15 %).

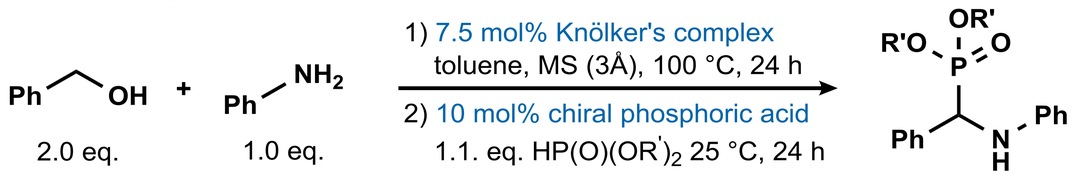
Hydrophosphonylation



#	Additive		Yield[1] *[%]*
	Type	Amount *[mol%]*	
1	---	---	91
2	aniline	30	18
3	benzyl alcohol	30	95
4	Knölker's complex	10	90

[1] Isolated Yield.

Selectivity Studies



#	Phosohoric acid *R* =	Phosphite *R'* =	Yield[1] *[%]*	ee[2] *[%]*
1	---	Et	---	---
2	H	Et	74	<5
3	2,4,6-(^{i}Pr)$_3C_6H_2$	Et	73	21
4	$SiPh_3$	Et	68[3]	40
5	3,5-$(CF_3)_3C_6H_3$	Me	75	48
6	3,5-$(CF_3)_3C_6H_3$	Et	76	48
7	3,5-$(CF_3)_3C_6H_3$	*i*Pr	76	11
8	3,5-$(CF_3)_3C_6H_3$	Ph	80	<5

[1] Isolated Yield.
[2] Determined *via* chiral HPLC analysis.
[3] Reaction time: 48h.

Conclusion & Outlook

In brief, we report the *N*-alkylation of anilines with benzylic alcohols by applying the highly reactive hydride species of the Knölker's complex without requiring any additional base for further activation. Besides, we have explored reaction conditions for the selective imine formation by varying the applied reaction conditions. The highly reactive C=N-bond can be used in an additional functionalization step, for instance the synthesis of α-amino phosphonates by a one-pot three-component condensation of alcohols, amines and phosphites.

As enantiopure α-amino phosphonates are in particular high demand, other possibilities (e.g. sterically more demanding phosphites and phosphoric acids) to further improve the outcome of the reaction will be investigated.

References:

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[2] A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410-1459.
[3] H.-J. Knölker, J. Heber, C. H. Mahler, *Synlett* **1992**, 1002–1004.
[4] A. Quintard, T. Constantieux, J. Rodriguez, *Angew. Chem. Int. Ed.* **2013**, *52*, 12883–12887.