

Nickel-Catalyzed Hydrogenolysis and Conjugate Addition of 2-(Hydroxymethyl)pyridines via Organozinc Intermediates

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S Supporting Information

ABSTRACT: 2-Hydroxymethylpyridines undergo nickel-catalyzed hydrogenolysis upon activation with a chlorophosphate. Reactions employ diethylzinc and are proposed to proceed through secondary benzylzinc reagents. Quenching with deuteromethanol provides straightforward incorporation of a deuterium label in the benzylic position. Intramolecular conjugate additions with $\alpha_{j}\beta$ -unsaturated esters are also demonstrated and support the intermediacy of a benzylzinc complex.

ickel catalysts have been employed to activate $C(sp^3)$ -O bonds for many transf bonds for many transformations, including crosscoupling, cross-electrophile coupling, and metalation reactions.^{1,2} Nickel-catalyzed hydrogenolysis of benzylic ethers has also been reported^{3,4} with recent advances employing hydrogen gas (Scheme 1a).^{5,6} We hypothesized that a reaction that

Scheme 1. Nickel-Catalyzed Hydrogenolysis Reactions



effected net hydrogenolysis of a benzylic alcohol, via stoichiometric formation of an intermediate organozinc complex, would provide a mild, functional group tolerant method for deoxygenation.⁷ We based our hypothesis in part on related hydrogenolysis reactions of primary benzylic alcohols that proceed through organomagnesium intermediates (Scheme 1b).⁸ By employing nickel catalysis to generate organozinc reagents in situ, this reaction also provides access to secondary heterobenzylzinc reagents, which can be challenging intermediates to generate by traditional methods.^{9,10} We reasoned that using C-O electrophiles and a nickel catalyst would result in a polar oxidative addition, thereby suppressing competitive Wurtz-type coupling resulting from benzylic radicals. In situ activation of the alcohol is achieved using diethyl chlorophosphate;¹¹ subsequent oxidative addition generates a benzylnickel intermediate. Transmetalation with diethylzinc generates the desired benzylzinc reagent, which

upon quenching with methanol provides the product of net hydrogenolysis (Scheme 1c).

EtO₂C

OH

R

NiCl₂(dppe), ZnEt₂

In this paper, we report nickel-catalyzed formation of secondary benzylzinc reagents from readily accessible 2pyridylcarbinols (Scheme 1c). We propose that the pyridyl substituent serves as a directing group and stabilizes the benzylzinc reagent, slowing possible side reactions, including β hydride elimination and Negishi-type cross-coupling.^{12,13} This method provides reduction of (hydroxymethyl)pyridines with incorporation of deuterium in the benzylic position, which can be useful in elucidation of metabolic pathways and improve metabolic stability.¹⁴ The intramolecular capture of the organozinc intermediate, via conjugate addition, to provide disubstituted cyclopentanes and cyclohexanes is also reported.

We examined hydroxymethylpyridine 1 as our model substrate for the hydrogenolysis reaction. Reactions were performed employing diethylchlorophosphate to activate the alcohol, a series of nickel catalysts, and diethylzinc as a transmetalating agent. We found that at room temperature $Ni(dppe)Cl_2$ furnishes the desired deoxygenated product 2 in high yield (Table 1, entry 1). The data in Table 1 illustrate how changes in the reaction parameters affect the transformation. When the nickel catalyst or diethyl chlorophosphate is omitted, the reaction does not afford the desired product (entries 2-4). These results are consistent with a mechanism of benzylic alcohol activation prior to reaction with a nickel catalyst. Employing toluene as solvent or ZnMe₂ instead of ZnEt₂ does not significantly affect the efficiency of the reaction (entries 5 and 6). A decreased yield of 2 was observed when catalysts ligated by other bidendate or monodentate phosphine ligands were used in the reaction (entries 7-10). Under optimized conditions, the reaction provides the desired product in high yield, even on a 1-g scale (entry 11).

Having developed robust conditions for the deoxygenation of 1, we turned our attention to investigating the source of "H"

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10

11

1		
N	1) P(O)(OEt) ₂ Cl (1.2 equiv) OH NiCl ₂ (dppe) (10 mol %) H ZnEt ₂ (2.5 equiv) THF, rt, 18 h 1 2) MeOH	H Ph 2
	"standard conditions"	
entry	change from standard conditions	yield ^{a} (%)
1	none	77
2	dppe instead of NiCl ₂ (dppe)	<5
3	no NiCl ₂ (dppe)	<5
4	no P(O)(OEt) ₂ Cl	<5
5	PhMe instead of THF	72
6	ZnMe ₂ instead of ZnEt ₂	74
7	NiCl ₂ ·DME/DPEphos instead of NiCl ₂ (dppe)	42
8	NiCl ₂ ·DME/dppf instead of NiCl ₂ (dppe)	55
9	NiCl ₂ ·DME/PCy ₃ instead of NiCl ₂ (dppe)	21

 Table 1. Effect of Reaction Parameters on Hydrogenolysis of

"Yield determined by ¹H NMR based on comparison with PhSiMe₃ as internal standard. ^bIsolated yield after column chromatography.

50 72⁶

NiCl₂·DME/PPh₃ instead of NiCl₂(dppe)

found in the product. We proposed that 2 is formed from the methanol quench of the benzylzinc reagent generated in situ. To test our hypothesis, we performed an isotopic labeling study with methanol-OD. Upon quenching the deoxygenation reaction of 3 with CH₃OD, we observed high yield and high deuterium incorporation of the corresponding product 5 (Scheme 2). The result of the isotopic labeling experiment provides strong support for our proposed hypothesis that the reaction proceeds by formation of a benzylzinc reagent (4).

Scheme 2. Deuterium Incorporation

1.0 g scale of 1



Next, we examined the hydrogenolysis of a range of heterobenzylic alcohols (Scheme 3). Secondary benzylic alcohols bearing alkyl chains were well tolerated under the reaction conditions (2, 6, and 7). Substrates containing acetal and olefin functional groups provided deoxygenated products in good yield (8–10). The high yield of 9 demonstrates tolerance of olefins and highlights the reaction's orthogonality to hydroboration-transmetalation procedures that are often used to prepare secondary benzylzinc reagents.¹⁵

Modification of the pyridine moiety was also tolerated in the reaction. When the arene was changed from 2-pyridyl to a 1-isoquinoline derivative, a modest yield of the deoxygenated product was obtained (10). Substitution of the pyridine ring was also tolerated, affording deoxygenated pyridines in high yield (11). Diarylmethanols were converted to diarylmethanes under the reaction conditions, providing access to products that bear electron-donating and electron-withdrawing substituents (12-14).

Scheme 3. Reaction Scope^a



^{*a*}All yields are isolated yields after column chromatography.

We reasoned that a pendant pyridine could direct the reaction, which would expand the scope of the reaction beyond 2-hydroxymethylpyridines.¹⁶ We synthesized benzylic alcohol **15**, with a pyridine disposed for formation of a six-membered metallocycle (**16**, Scheme 4). We were pleased to see that upon subjecting **15** to the reaction conditions the expected hydrogenolysis product **17** was formed in high yield.

Scheme 4. Formation of a Six-Membered Metallocycle



A plausible mechanism for the hydrogenolysis reaction that proceeds through a benzylzinc reagent is outlined in Figure 1. The active catalyst is formed by reduction of Ni(dppe)Cl₂ with ZnEt₂ to give a Ni(0)(dppe) complex. Oxidative addition with the phosphorylated alcohol **18** forms the benzylnickel(II) intermediate **19**. Transmetalation results in formation of benzylzinc reagent **4** and ethylnickel complex **20**. β -Hydride elimination followed by loss of ethylene gas yields nickel hydride species **22**. A second transmetalation from an ethylzinc species allows formation of **23**, whereupon extrusion of ethane by reductive elimination regenerates the Ni(0) catalyst.¹⁷



Figure 1. Proposed mechanism.

To demonstrate the utility of this method further, we coupled the formation of a benzylzinc reagent to an intramolecular conjugate addition (Scheme 5).^{18–20} 2-Pyridyl

Scheme 5. Intramolecular 1,4-Addition



carbinol **24** bearing a pendant $\alpha_{,\beta}$ -unsaturated ester underwent smooth cyclization to produce the desired cyclopentane **25** in excellent yield and 2.5:1 dr. Similarly, cyclization of **26** afforded cyclohexane **27** in 2.5:1 dr. Efforts to produce 3- or 7membered rings were unsuccessful and resulted predominantly in hydrogenolysis.

In summary, we have developed nickel-catalyzed hydrogenolysis of a range of 2-(hydroxymethyl)pyridines. The reaction proceeds in high yield and with straightforward incorporation of deuterium from deuteromethanol. The proposed mechanism involves formation of a benzylzinc reagent. The reaction has been applied to an intramolecular 1,4-addition for formation of pyridyl-substituted cyclopentanes and cyclohexanes. Further development of the reactivity of the putative organozinc intermediates and elucidation of mechanistic details are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03049.

Experimental procedures and spectroscopic and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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