Hydrogen Transfer

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Nickel-Catalyzed N-Alkylation of Acylhydrazines and Arylamines Using Alcohols and Enantioselective Examples

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Abstract: *A borrowing-hydrogen reaction between amines and alcohols is an atom-economic way to prepare alkylamines, ideally with water as the sole byproduct. Herein, nickel catalysts are used for direct N-alkylation of hydrazides and arylamines using racemic alcohols. Moreover, a nickel catalyst of (S)-binapine was used for an asymmetric N-alkylation of benzohydrazide with racemic benzylic alcohols.*

Chiral benzylamines are key motifs in pharmaceuticals and they are present in about 15% of blockbuster drugs. Such examples include solifenacin, plavix, ezetimibe, and rivastigmine (Figure 1).[1] Therefore, efficient synthetic methods

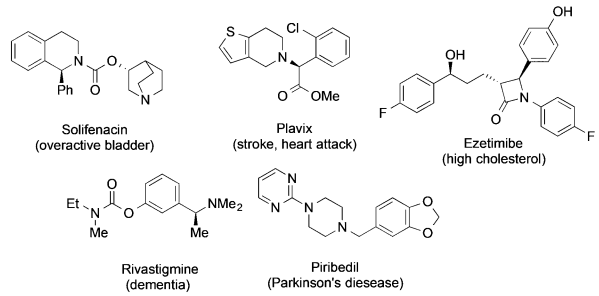
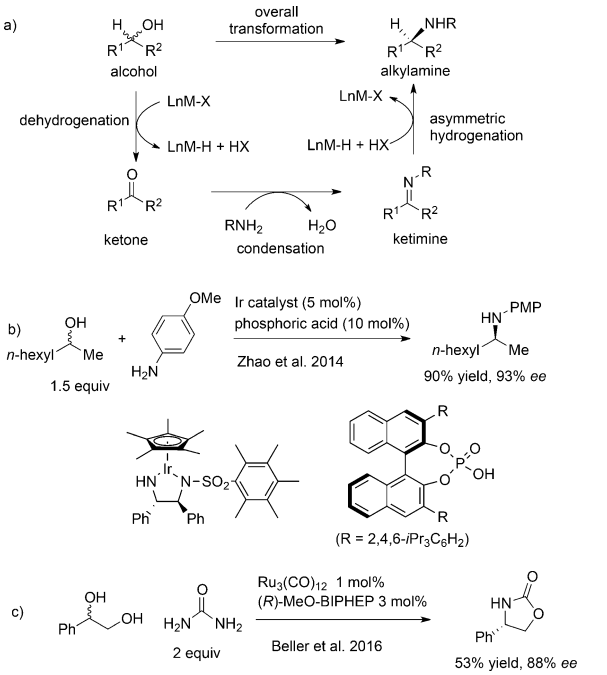


Figure 1. Examples of drugs containing benzylamines.

towards these chiral amines have been actively pursued.[2] Among the extensively developed methods are asymmetric hydrogenation,[3] reductive amination,[4] and resolution of racemic alkylamines.[5] In recent years, biocatalytic amination using ketones[6] and even alcohols[7] have emerged as promising alternatives to supply optically pure alkylamines, provided that enzyme mutants can be optimized in a cost- and time-efficient way.

The most straightforward synthesis of chiral alkylamines is arguably direct N-alkylation of amines using cheap, readily available alcohols by the so-called "borrowing hydrogen reaction" or hydrogen autotransfer reaction (Scheme 1a).[8]



Scheme 1. Asymmetric N-alkylation of amines using racemic alcohols by hydrogen borrowing. a) A possible pathway. Examples using anilines (b) and urea (c).

A typical process involves dehydrogenation of an alcohol to form a ketone by a metal catalyst, in situ condensation to a ketimine, and subsequent addition of the metal hydride catalyst.[9–12] No prior chemical activation of alcohols is needed and ideally water is the only byproduct. Furthermore, only a catalytic amount of a metal hydride complex is present at anytime, and allows better compatibility of polar groups.

In previous studies on amination of alcohols, achiral catalysts based on expensive rare metals were developed extensively, in particular ruthenium[13] and iridium.[14] In recent years, much attention has been paid to catalytic applications of earth-abundant, cheap 3d metals for this reaction, for example, homogeneous catalysts of manganese,[15] iron,[16] cobalt,[17] and copper.[18] Additionally, Raney nickel and nickel nanoparticles were also effective in simple N-alkylation of ammonia and amines with alcohols.[19] Nickel

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is produced in millions of tons yearly, but as a word of caution, nickel(II) salts are considerably toxic in animal models.[20]

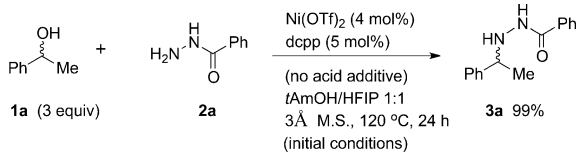
Today, there are only few examples of delivering enantioenriched alkylamines by the borrowing hydrogen pathway.[21] For example, Zhao et al. made a seminal discovery of N-alkylation of anilines, under a dual catalysis system comprising a chiral iridium catalyst and a large phosphoric acid (Scheme 1b).[22] Later, his group extended this iridium catalysis to dynamic kinetic amination of α-branched alcohols,[23] cyclization to form chiral tetrahydroquinolines,[24] and asymmetric amination of racemic 1,2-diols using a ruthenium catalyst.[25] Recently, Beller et al. disclosed the asymmetric synthesis of oxazolidin-2-ones from racemic vicinal diols and urea, using a ruthenium catalyst (Scheme 1c).[26] However, all of these reactions relied on expensive and rare metals (iridium and ruthenium) in the catalysts.

During our previous study of nickel-catalyzed asymmetric reductive amination of arylamines,[27] *N*-isopropylaniline was isolated in moderate yield, and was derived from the N-alkylation of isopropanol, the reaction solvent. Herein, we report nickel-catalyzed N-alkylation of both acylhydrazines and arylamines using alcohols, and additionally, an asymmetric process of acylhydrazines to produce chiral benzylamines.

In the beginning, we investigated the N-alkylation of benzohydrazide (**2a**) with racemic 1-phenylethanol (**1a**) in the presence of 4 mol% of $Ni(OTf)_2$ and dcpp (Table 1). The desired product **3a** was not observed under strongly basic or acidic conditions (entries 1 and 2). When acetic acid was used as an additive in *t*-amyl alcohol, good yields of **3a** were obtained (entry 3). Without acetic acid, no product was produced in this solvent (entry 4). In slightly acidic 1,1,1,3,3,3-hexafluoroisopropanol (HFIP; pK_a value of 9.3 in water) or in a 1:1 mixture of the two solvents, however, no acetic acid was needed to form **3a** (entries 5,6). A small amount of the hydrazone was detected as the byproduct in these reactions, along with a trace amount of acetophenone. Neither aldol condensation of acetophenone nor its reductive byproduct of the aldol condensation was seen. Thus, both acids or acidic solvents and molecular sieves (100 mg per 0.4 mmol of **2a**) are crucial for condensation of acetophenone to form the hydrazine in situ. When 2 mol% of the nickel catalyst and 2 equivalents of **1a** were used, the yield was almost quantitative (entry 7). However, the use of 1 equivalent of **1a** in the presence of 2 mol% and 1 mol% of the nickel catalyst led to 72 and 50% yields, respectively, of **3a** (entries 8 and 9). Another bulky and electron-rich diphosphine, dcpe, also formed an active nickel catalyst (entry 10). Notably, in the absence of the strongly donating dcpp (entries 3 and 7), **3a** was not formed. In comparison, dmpp was not electronically donating enough to form an active nickel catalyst and formed a catalytically inactive $(P\text{-}P)_2Ni^{2+}$ species[34] (entry 11).

The *N*-benzoylhydrazines were N′-alkylated selectively by a wide range of benzylic alcohols in good yields (Scheme 2a). Both electron-donating and electron-withdrawing groups on aryl rings were well tolerated. Furthermore, secondary aliphatic alcohols also afforded the desired hydrazides in high yields. On the hydrazides, N-acyl groups can contain a free phenol group (**3t**), pyridine, and thiophene rings (**3u** and **3v**). Notably, Cbz-protected hydrazine also delivered **3x** in 89% yield.

Table 1: Optimization of N-alkylation of **2a** with **1a**.

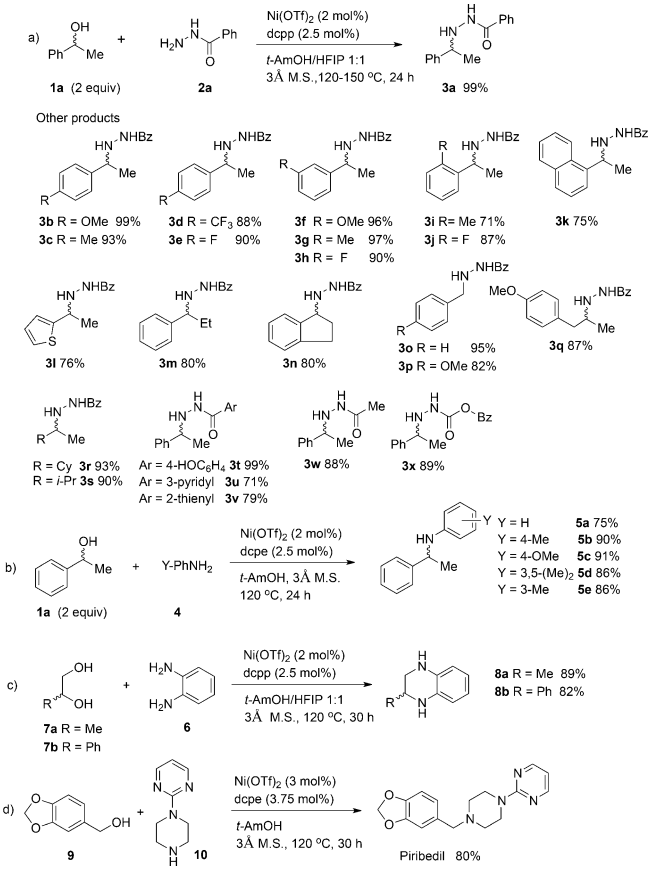


1a (3 equiv) **2a** **3a** 99%

Entry	Changes from initial conditions	Yield [%][a]
1	*t*BuOK (0.2 equiv) as additive in *t*AmOH	0
2	*p*-TsOH (0.2 equiv) in *t*AmOH	< 5
3	AcOH (2 equiv) in *t*AmOH	88
4	no acid in *t*AmOH	6
5	no additive in HFIP	95
6	no additive in *t*AmOH/HFIP 1:1 (initial conditions)	99
7	2% Ni and 2.5% dcpp; 2 equiv **1a** (optimized conditions)	99
8	2% Ni and 2.5% dcpp; 1 equiv **1a**	72
9	1% Ni and 1.2% dcpp; 1 equiv **1a**	50
10	dcpe (5%) as ligand	83
11	dmpp (5%) as ligand	0

where dcpp =  dcpe =  dmpp = 

[a] Yield is that of the isolated product. M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.



Scheme 2. Examples *of* N-alkylation of a) hydrazides and b) arylamines. c) Double alkylation of *o*-phenylenediamine with vicinal diols. d) Synthesis of piribedil.

The catalytic process of nickel/dcpe in *t*AmOH can be applied to arylamines of different electronic properties (Scheme 2b). In comparison, the use of the nickel/dcpp catalyst led to only 60% yield of **5b**. Furthermore, double alkylation of *o*-phenylenediamine (**6**) with diols (**7**) successfully produced 2-substituted tetrahydroquinoxalines (**8**) in high yields (Scheme 2c).

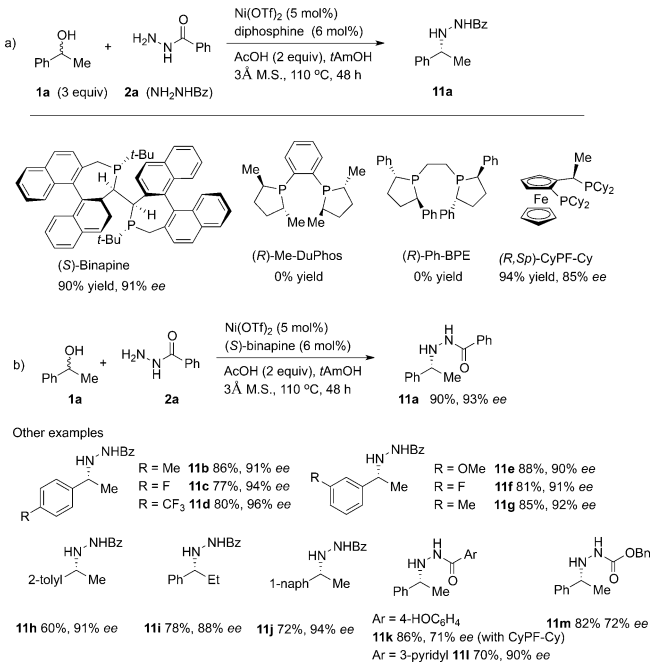
We found that the elaborated piperidine **10** was also selectively alkylated by the benzylic alcohol **9** to provide piribedil in one step (Scheme 2d). Piribedil is a pharmaceutical used for the treatment of Alzheimer's disease. No background reaction occurred in the absence of the nickel catalyst. The use of the $Ni(OTf)_2$/dcpp catalyst, in comparison, led to 50% yield of piribedil.

Next, we explored a selected sample of chiral diphosphines in search for an asymmetric amination. Unfortunately, the reaction of 3 equivalents of **1a** and *p*-anisylamine using a combination of 5% $Ni(OTf)_2$ and 6% (*R*)-Ph-BPE only provided **5c** in about 50% yield and 27% *ee*, under reaction conditions similar to those in Scheme 2b. Later, we were gratified to find that the reaction of **1a** and **2a**, using $Ni(OTf)_2$ and (*S*)-binapine,[28] enabled the formation of **11a** in 90% yield and 93% *ee* in *t*AmOH (Scheme 3a). A nickel catalyst of CyPF-Cy, also afforded high catalytic activity and 85% *ee*. In comparison, a similar catalyst, CyPF-*t*Bu, was completely inactive, although it was known to effectively catalyze transfer hydrogenation of an *N*-benzohydrazone of acetophenone in 99% *ee*, in the presence of formic acid.[27] Thus, we suspect that this catalyst of CyPF-*t*Bu has a problem in the dehydrogenation of **1a**. Furthermore, other electron-rich diphosphines, including Me-DuPhos, Ph-BPE, and QuinoxP* were also catalytically inactive.[29] Acetic acid was a necessary additive to promote condensation of hydrazones under the catalytic conditions. Without it, the nickel/binapine catalyst afforded **11a** in less than 10% yield.

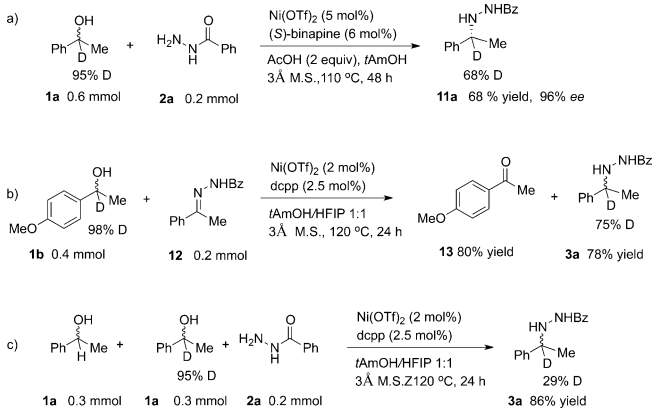
A diverse set of benzylic alcohols reacted efficiently with **2a** in the presence of the nickel/binapine catalyst (Scheme 3b). The electron-withdrawing and mild electron-donating groups were well tolerated in aryl rings of alcohols. However, the *p*-MeO-substituted analogue of **1a** provided a racemic product, surprisingly. Control experiments indicated that $Ni(OTf)_2$ alone catalyzed the background reaction (80% yield after 24 h), while acetic acid itself did not catalyze this amination reaction under the reaction conditions described in Scheme 3.

On the hydrazides, pyridine and phenol groups were compatible, as well as a carbamate (Scheme 3b). In the reaction of 4-hydroxybenzohydrazide, *P*-cyclohexyl-substituted josiphos was the better ligand than binapene, and provided the product **11k** in 71% *ee*. The products are crystalline, which helps to upgrade their optical purity after simple crystallization. Furthermore, the N–N single bonds in the products can be cleaved to release free benzylamines by treatment with SmI_2 or Raney nickel.[30] Notably, the compound **11e** contains the chiral amine fragment of the chiral drug revastigmine.

In our previous studies in transfer hydrogenation of hydrazones using formic acid,[27] binapine was the optimal ligand. This parallelism with the borrowing hydrogen reaction of acylhydrazines herein (Scheme 3a) supports the putative borrowing-hydrogen mechanism through the intermediacy of hydrazones. Additionally, the fact that the nickel-catalyzed amination proceeded well with aliphatic alcohols (Scheme 2a) also argues against an alternative pathway involving η^3-benzylnickel species.[31] We then conducted other experiments to probe the reaction pathway. When deuterated **1a** reacted with **2a**, it produced **11a** (68% D) in 68% yield and 96% *ee* (Scheme 4a), along with some unreacted hydrazine, and no acetophenone was detected. Notably, no deuteration occurred at the methyl group and phenyl ring of **11a**. The partial loss of deuterium during the transfer is consistent with a parasitic equilibrium between (L-L)Ni^0 and cationic $[(L\text{-}L)NiD]^+$ in the presence of proton of acids and alcoholic solvents.[32]



Scheme 3. a) Effect of chiral ligands. b) Substrate scope in asymmetric N-alkylation of benzohydrazide.



Scheme 4. Deuterium-labeling reactions.

Moreover, in a hydride-transfer reaction of the 1-(4-anisyl)ethanol **1b** and hydrazone **12**, the **3a** was produced in 78% yield and 75% D incorporation, along with 80% of the ketone **13** (Scheme 4b), which directly supports a hydrogen-transfer pathway and discredits both direct nucleophilic substitution and a radical pathway.[33] The partial loss of deuterium can be attributed to the equilibrium between the nickel(II) deuteride and proton of alcoholic solvents. No other byproducts were detected, including a hydrazone from **13**, aldol condensation of **13**, reductive byproducts of aldol condensation, and acetophenone from **12**.

A competition of **1a** and deuterium-labeled **1a** was conducted and resulted in **3a** with 29% D (Scheme 4c). By factoring in 25% loss of deuterium in a similar process in Scheme 4b, we estimate the KIE effect of the whole catalytic reaction to be $k_H/k_D = 1.6$, which does not support nucleophilic displacement pathways.

In summary, we discovered nickel/bis(alkylphosphine) catalysts for selective N-monoalkylation of both hydrazides and anilines with racemic alcohols. Furthermore, an asymmetric N-alkylation of acylhydrazides was realized to afford medicinally important benzylamines with good enantioselectivities.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · amination · hydrogen transfer · nickel · P ligands

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