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Nickel-Catalyzed *N*-Alkylation of both Acylhydrazines and Arylamines with Alcohols and Enantioselective Examples

Peng Yang, Caili Zhang, Yu Ma, Caiyun Zhang, Aijie Li, Bo Tang*[a] and Jianrong Steve Zhou*[b]

Abstract: *Borrowing hydrogen reaction between amines and alcohols is an atom-economic way to prepare alkylamines, with water as the sole byproduct ideally. Herein, we use nickel catalysts for direct N-alkylation of hydrazides and arylamines with 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 towards these chiral amines have been actively pursued.[2] Among extensively developed methods include metal-catalyzed asymmetric hydrogenation,[3] reductive amination,[4] and resolution of racemic alkylamines.[5] In recent years, biocatalytic amination using ketones[6] and even directly using 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.

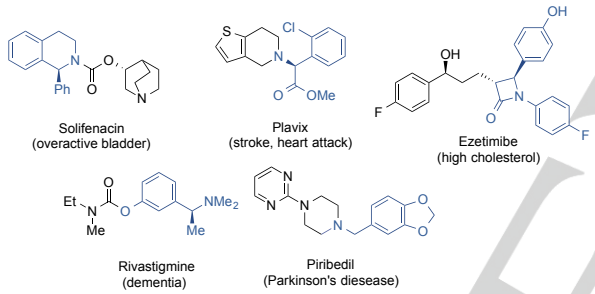
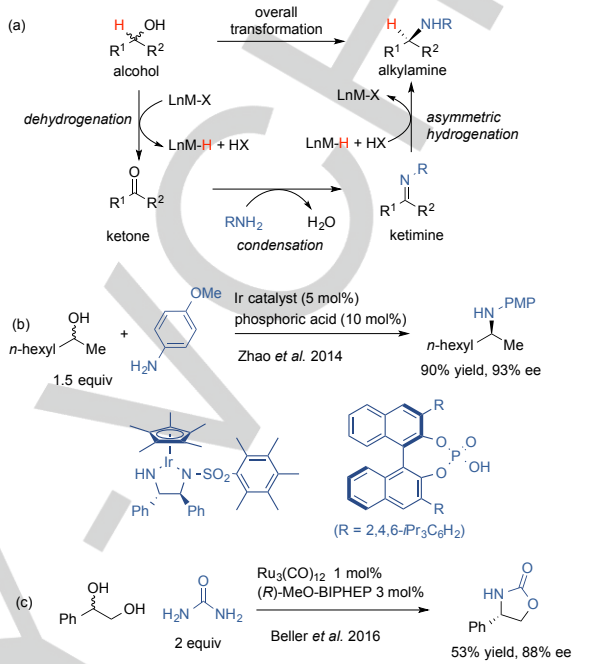


Figure 1. Examples of drugs containing benzylamines.

The most straightforward synthesis of chiral alkylamines is arguably direct *N*-alkylation of amines using cheap, readily available alcohols via so-called "borrowing hydrogen reaction" or hydrogen autotransfer reaction (Scheme 1a).[8] A typical process involves dehydrogenation of an alcohol to form a ketone by a metal catalyst, in situ condensation to an imine, 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, which allows better compatibility of polar groups.



Scheme 1. Asymmetric *N*-alkylation of amines using racemic alcohols via hydrogen borrowing: (a) a possible pathway and examples using anilines (b) and urea (c).

In previous studies on amination of alcohols, achiral catalysts based on expensive rare metals were developed extensively, in particular Ru[13] and Ir.[14] In recent years, much attention has been paid to catalytic applications of Earth-abundant, cheap *3d*-series metals, for example, homogeneous catalysts of Mn,[15] Fe,[16] Co,[17] and Cu.[18] Additionally, Raney Ni and nickel nanoparticles are also effective in simple *N*-alkylation of ammonia and amines with alcohols.[19] Nickel is produced in millions of tons yearly, but as a word of caution, nickel(II) salts is considerable toxicity in animal models.[20]

Today, only limited examples are available that deliver enantio-enriched alkylamines via the borrowing hydrogen pathway.[21] For example, Zhao *et al.* made a seminal discovery of *N*-alkylation of anilines, under dual catalysis of a chiral iridium catalyst and a large phosphoric acid (Scheme 1b).[22] Later, his group extended the 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 Ru catalyst.[25] Lately, Beller *et al.* also disclosed 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, rare metals, Ir and Ru in the catalysts.

During our previous study of nickel-catalyzed asymmetric reductive amination of arylamines,[27] *N*-isopropylaniline was isolated in moderate yield, which was derived from *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.

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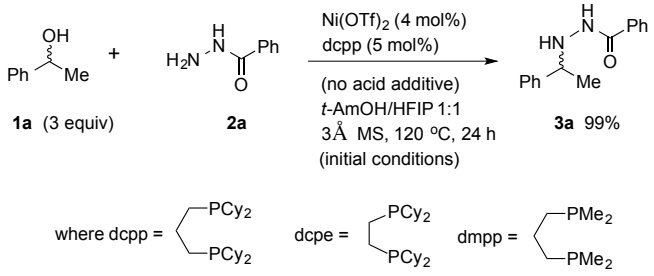
Table 1. Optimization of *N*-alkylation of benzohydrazide **2a** with 1-phenylethanol **1a**



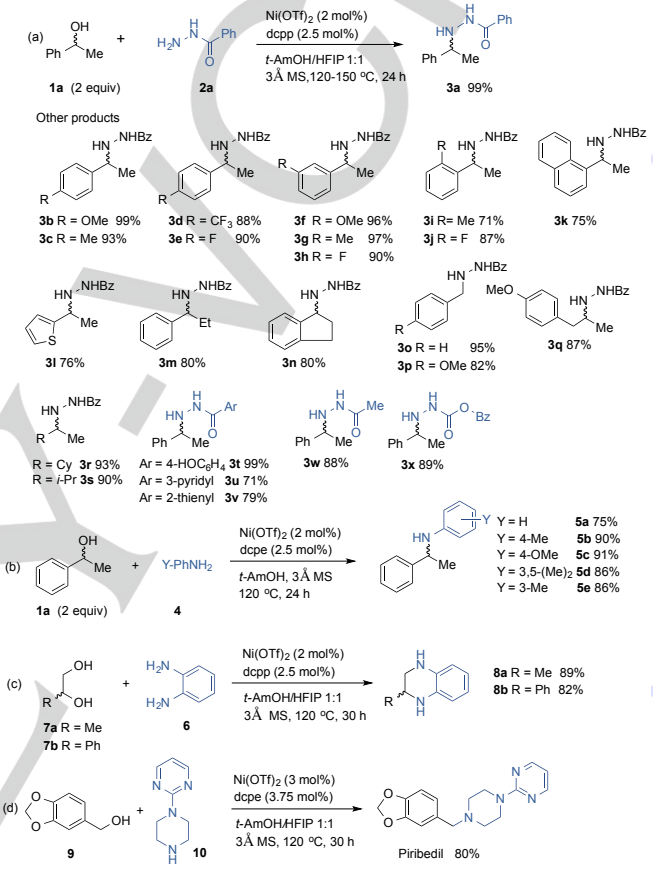
Entry	Changes from initial conditions	Yield (%)
1	*t*-BuOK (0.2 equiv) as additive in t-AmOH	0
2	*p*-TsOH (0.2 equiv) in *t*-AmOH	<5
3	AcOH (2 equiv) in t-AmOH	88
4	no acid in *t*-AmOH	6
5	no additive in HFIP	95
6	no additive in *t*-AmOH/HFIP 1:1 (initial conditions)	99
7	2% Ni and 2.5% dcpp; 2 equiv **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

In the beginning, we investigated *N*-alkylation of benzohydrazide **2a** with racemic 1-phenylethanol **1a** in the presence of 4 mol% of $Ni(OTf)_2$ and dcpp (Table 1). No desired product **3a** was observed under strongly basic or acidic conditions (entries 1-2). When acetic acid was used as an additive in *t*-amyl alcohol, good yields of **3a** was 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 (*p*Ka value of 9.3 in water) or in a 1:1 mixture of the two solvents, however, no acetic acid was needed to form product **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 solvent and molecular sieve (100 mg per 0.4 mmol of **2a**) are crucial for condensation of acetophenone to form the hydrazine in situ. When 2 mol% nickel catalyst and 2 equiv of **1a** were used, the yield was almost quantitative (entry 7). However, the use of 1 equiv of **1a** in the presence of 2 mol% and 1 mol% of the nickel catalyst led to 72% and 50% yields of **3a**, respectively (entries 8-9). Another bulky and electron-rich diphosphine, dcpe also formed an active nickel catalyst (entry 10). Notably, in the absence of strongly donating dcpp, no product **3a** was generated under catalytic conditions similar to entry 3 or 7. In comparison, dmpp wasn't electronically donating enough to form an active nickel catalyst and/or less hindered dmpp formed catalytic inactive $(P\text{-}P)_nNi^{2+}$ species where n is 2 or 3 (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 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 free phenol group (**3t**), pyridine and thiophene rings (**3u** and **3v**). Notably, Cbz-protected hydrazine also delivered **3x** in 89% yield.

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 nickel/dcpp catalyst led to only 60% yield of **5b**. Furthermore, double alkylation of *o*-phenylenediamine **6** with diols **7** successfully produced 2-substituted tetrahydroquinoxaline **8** in high yields (Scheme 2c).

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



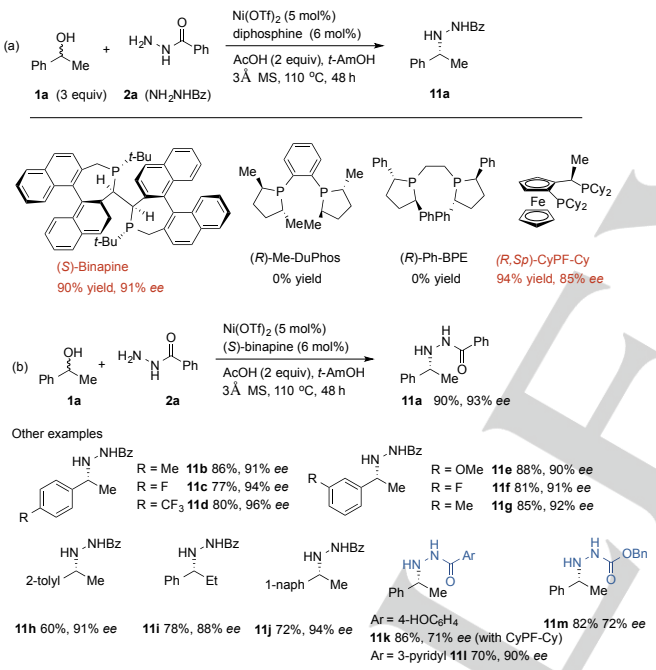
Scheme 2. Examples *of N*-alkylation of a) hydrazides and b) arylamines. c) Double alkylation of *o*-phenylenediamine with vicinal diols. d) Synthesis of piribedil.

Next, we explored a selected sample of chiral diphosphines in search for an asymmetric amination. Unfortunately, the reaction of 3 equiv of **1a** and *p*-anisylamine using a combination of 5% $Ni(OTf)_2$ and 6% (*R*)-Ph-BPE only provided **5c** in ~50% yield and 27% ee, under conditions similar to Scheme 2b. Later, we were gratified to find that the reaction of **1a** and benzohydrazide **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 a josiphos, CyPF-Cy also afforded high catalytic activity and 85% *ee*. In comparison, a similar catalyst of 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 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 <10% yield.

A diverse set of benzylic alcohols reacted efficiently with benzohydrazide to alkylate *N*-acylhydrazines 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, a *p*-MeO-substituted analog 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 didn't catalyze this amination reaction under the conditions described in Scheme 3.

On the hydrazides, pyridine and phenol groups were compatible, as well as a carbamate. In the reaction of 4-hydroxybenzohydrazide, *P*-cyclohexyl-substituted josiphos was the better ligand and provided product **11k** in 71% ee. The products are crystalline, which helps to upgrade their optical purity after a 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, compound **11e** contains the chiral amine fragment of a chiral drug, revastigmine.

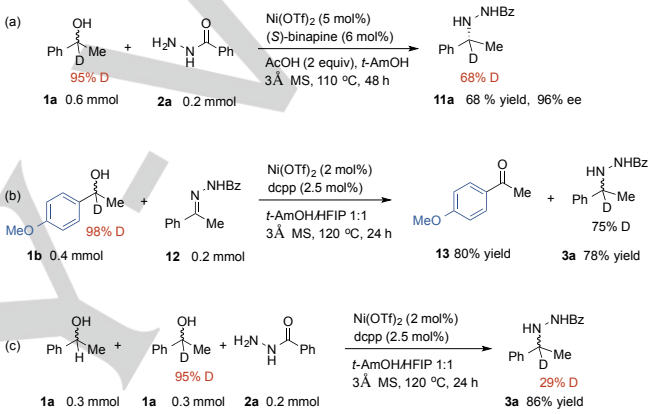


Scheme 3. (a) Effect of chiral ligands and (b) substrate scope in asymmetric *N*-alkylation of benzohydrazide.

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 (in 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 (in Scheme 2a) also argues against an alternative pathway involving η^3-benzylnickel species.[31] We have conducted other experiments to probe the reaction pathway. When deuterated **1a** reacted with benzohydrazide **2a**, it produced **11a** (68% D) in 68% yield and 96% *ee* (Scheme 4a), along with some unreacted hydrazone; 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 $[(L\text{-}L)NiD]^+$ with the proton of acids and alcohols.[32]

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

A competition of **1a** and *d*-labeled **1a** was conducted which resulted in **3a** in 29% D (Scheme 4c). By factoring in 75% retention of deuterium in a similar process in Scheme 4b, we estimated a KIE effect of the whole catalytic reaction is $k_H/k_D = 1.6$.



Scheme 4. Deuterium-labeling reactions.

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 in good enantioselectivity.

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Keywords: *N*-alkylation of amines • borrowing hydrogen reaction • nickel catalysis • hydrogen autotransfer reaction • amination

[1] Examples: a) J. M. Herbert, D. Frehel, E. Valee, G. Kieffer, D. Gouy, Y. Berger, J. Necciari, G. Defreyn, J. P. Maffrand, *Cardiovasc. Drug Rev.* **1993**, *11*, 180; b) C. M. Spencer, S. Noble, *Drugs Aging* **1998**, *13*, 391; c) R. A. Smulders, W. J. Krauwinkel, P. J. Swart, M. Huang, *J. Clin. Pharmacol.* **2004**, *44*, 1023; d) S. M. Grundy, H. Arai, P. Barter, T. P. Bersot, D. J. Betteridge, R. Carmena, A. Cuevas, M. H. Davidson, J. Genest, Y. A. Kesäniemi, S. Sadikot, R. D.

Santos, A. V. Susekov, R. G. Sy, S. LaleTokgözoglu, G. F. Watts, D. Zhao, *J. Clin. Lipidol.* **2014**, *8*, 29.

[2] a) Amines: Synthesis, Properties and Applications; S. A. Lawerence, Ed.; Cambridge University Press, 2005; b) Chiral Amine Synthesis; T. C. Nugent, Ed.; Wiley-VCH: Weinheim, 2010.

[3] Reviews: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291; c) H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo, T. Saito, *Acc. Chem. Res.* **2007**, *40*, 1385; d) W. Zhang, Y. Chi, X. Zhang, *Acc. Chem. Res.* **2007**, *40*, 1278; e) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2010**, *111*, 1713; f) C. Wang, B. Villa-Marcos, J. Xiao, *Chem. Commun.* **2011**, *47*, 9773; g) D. J. Ager, A. H. M. de Vries, J. G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340; h) H.-U. Blaser, B. Pugin, F. Spindler, *Top. Organomet. Chem.* **2012**, 1; i) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497; j) A. Bartoszewicz, N. Ahlsten, B. Martín-Matute, *Chem.-Eur. J.* **2013**, *19*, 7274; k) F. Foubelo, M. Yus, *Chem. Record* **2015**, *15*, 907.

[4] a) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788; *Angew. Chem.* **2004**, *116*, 806; b) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753; c) C. Wang, J. Xiao, *Top. Curr. Chem.* **2014**, *343*, 261.

[5] Example: J. H. Lee, K. Han, M.-J. Kim, J. Park, *Eur. J. Org. Chem.* **2010**, *2010*, 999.

[6] a) J. H. Schrittwieser, S. Velikogne, W. Kroutil, *Adv. Synth. Catal.* **2015**, *357*, 1655; b) J. Mangas-Sanchez, S. P. France, S. L. Montgomery, G. A. Aleku, H. Man, M. Sharma, J. I. Ramsden, G. Grogan, N. J. Turner, *Curr. Opin. Chem. Biol.* **2017**, *37*, 19; c) M. Sharma, J. Mangas-Sanchez, N. J. Turner, G. Grogan, *Adv. Synth. Catal.* **2017**, *359*, 2011.

[7] F. G. Mutti, T. Knaus, N. S. Scrutton, M. Breuer, N. J. Turner, *Science* **2015**, *349*, 1525.

[8] Reviews: a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555; b) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611; c) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681; d) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853; e) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305; f) A. Quintard, J. Rodriguez, *Chem. Commun.* **2016**, *52*, 10456.

[9] A review including detailed discussion of different pathways: X. Ma, C. Su, Q. Xu, *Top. Curr. Chem.* **2016**, *374*, 27.

[10] Example of Pd-catalyzed reaction path (DFT calculation): G.-M. Zhao, H.-l. Liu, X.-r. Huang, X. Yang, Y.-p. Xie, *ACS Catal.* **2015**, *5*, 5728.

[11] Example of Ir-catalyzed reaction path (DFT calculation): A. Bartoszewicz, G. González Miera, R. o. Marcos, P.-O. Norrby, B. Martín-Matute, *ACS Catal.* **2015**, *5*, 3704.

[12] Metal alkoxide as an actual hydride donor: H.-J. Pan, Y. Zhang, C. Shan, Z. Yu, Y. Lan, Y. Zhao, *Angew. Chem. Int. Ed.* **2016**, *55*, 9615; .

[13] Examples: a) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chemistry – Asian J.* **2007**, *2*, 403; b) C. Gunanathan, D. *Angew. Chem.* **2008**, *120*, 8789; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; c) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766; d) S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 8126; e) D. Pingen, C. Müller, D. Vogt, *Angew. Chem. Int. Ed.* **2010**, *49*, 8130; *Angew. Chem.* **2010**, *122*, 8307; f) M. Zhang, S. Imm, S. Bähn, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 11197; *Angew. Chem.* **2011**, *123*, 11393; g) J. J. A. Celaje, X. Zhang, F. Zhang, L. Kam, J. R. Herron, T. J. Williams, *ACS Catal.* **2017**, *7*, 1136.

[14] Examples: a) B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 749; b) R. Kawahara, K.-i. Fujita, R. Yamaguchi, *J. Am. Chem. Soc.* **2010**, *132*, 15108; c) J.-Q. Li, P. G. Andersson, *Chem. Commun.* **2013**, *49*, 6131; d) Q. Zou, C. Wang, J. Smith, D. Xue, J. Xiao, *Chem.-Eur. J.* **2015**, *21*, 9656.

[15] Examples: a) S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Comm.* **2016**, *7*, 12641; b) N. Deibl, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *129*, 1685.

[16] Examples: a) M. Bala, P. K. Verma, U. Sharma, N. Kumar, B. Singh, *Green Chem.* **2013**, *15*, 1687; b) H.-J. Pan, T. W. Ng, Y. Zhao, *Chem. Commun.* **2015**, *51*, 11907; c) T. Yan, B. L. Feringa, K. Barta, *ACS Catal.* **2016**, *6*, 381.

[17] Examples: a) S. Rösler, M. Ertl, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2015**, *54*, 15046; *Angew. Chem.* **2015**, *127*, 15260; b) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2016**, *55*, 14373; *Angew. Chem.* **2016**, *128*, 14585; c) M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016**, *18*, 3462; d) Z. Yin, H. Zeng, J. Wu, S. Zheng, G. Zhang, *ACS Catal.* **2016**, *6*, 6546; e) G. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2016**, *18*, 300; f) F. Freitag, T. Irrgang, R. Kempe, *Chem.-Eur. J.* **2017**, doi: 10.1002/chem.201701211.

[18] Examples: a) X. Cui, F. Shi, M. K. Tse, D. Gördes, K. Thurow, M. Beller, Y. Deng, *Adv. Synth. Catal.* **2009**, *351*, 2949; b) G.-m. Zhao, H.-l. Liu, D.-d. Zhang, X.-r. Huang, X. Yang, *ACS Catal.* **2014**, *4*, 2231.

[19] Examples: a) A. N. Parvulescu, P. A. Jacobs, D. E. De Vos, *Adv. Synth. Catal.* **2008**, *350*, 113; b) J. L. Garcia Ruano, A. Parra, J. Aleman, F. Yuste, V. M. Mastranzo, *Chem. Commun.* **2009**, 404; c) F. Alonso, P. Riente, M. Yus, *Acc. Chem. Res.* **2011**, *44*, 379; d) X. Cui, X. Dai, Y. Deng, F. Shi, *Chem.-Eur. J.* **2013**, *19*, 3665; e) K.-i. Shimizu, K. Kon, W. Onodera, H. Yamazaki, J. N. Kondo, *ACS Catal.* **2013**, *3*, 112.

[20] K. S. Egorova, V. P. Ananikov, *Angew. Chem. Int. Ed.* **2016**, *55*, 12150; *Angew. Chem.* **2016**, *128*, 12334.

[21] Examples: a) A. Eka Putra, Y. Oe, T. Ohta, *Eur. J. Org. Chem.* **2013**, *2013*, 6146; b) N. J. Oldenhuis, V. M. Dong, Z. Guan, *J. Am. Chem. Soc.* **2014**, *136*, 12548; c) O. El-Sepelgy, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 13602; *Angew. Chem.* **2016**, *128*, 13800.

[22] Y. Zhang, C.-S. Lim, D. S. B. Sim, H.-J. Pan, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 1399; *Angew. Chem.* **2014**, *126*, 1423.

[23] Z.-Q. Rong, Y. Zhang, R. H. B. Chua, H.-J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 4944.

[24] C. S. Lim, T. T. Quach, Y. Zhao, *Angew. Chem. Int. Ed.* **2017**, *56*, 7176; *Angew. Chem.* **2017**, *129*, 7282.

[25] L.-C. Yang, Y.-N. Wang, Y. Zhang, Y. Zhao, *ACS Catal.* **2017**, *7*, 93.

[26] M. Peña-López, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 7826; *Angew. Chem.* **2016**, *128*, 7957.

[27] a) H. Xu, P. Yang, P. Chuanprasit, H. Hirao, J. Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 5112; *Angew. Chem.* **2015**, *127*, 5201; b) P. Yang, L. H. Lim, P. Chuanprasit, H. Hirao, J. Zhou, *Angew. Chem. In. Ed.* **2016**, *55*, 12083; , *Angew. Chem.* **2016**, *128*, 12262.

[28] a) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 3509; *Angew. Chem.* **2003**, *115*, 3633; b) M. Chang, S. Liu, K. Huang, X. Zhang, *Org. Lett.* **2013**, *15*, 4354.

[29] a) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125; b) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062; c) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 1635; d) M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363; e) T. Imamoto, K. Tamura, Z. Zhang, Y. Horiuchi, M. Sugiya, K. Yoshida, A. Yanagisawa, I. D. Gridnev, *J. Am. Chem. Soc.* **2011**, *134*, 1754.

[30] a) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266; b) M. J. Burk, J. P. Martinez, J. E. Feaster, N. Cosforda, *Tetrahedron* **1994**, *50*, 4399; c) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452.

[31] H. Hikawa, T. Koike, K. Izumi, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* **2016**, *358*, 784.

[32] a) S. Guo, P. Yang, J. Zhou, *Chem. Commun.* **2015**, *51*, 12115; b) S. Guo, J. Zhou, *Org. Lett.* **2016**, *18*, 5344.

[33] Examples: a) Y. Zhao, S. W. Foo, S. Saito, *Angew. Chem. Int. Ed.* **2011**, *50*, 3006; *Angew. Chem.* **2011**, *123*, 3062; b) H. Hikawa, Y. Ijichi, S. Kikkawa, I. Azumaya, *Eur. J. Org. Chem.* **2017**, *2017*, 465.

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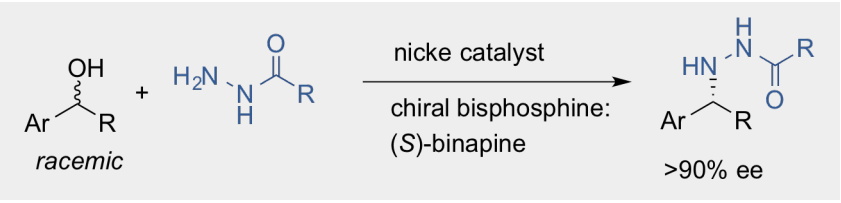

A nickel-catalyzed *N*-alkylation of hydrazides and arylamines with alcohols, including an asymmetric version, proceeds via hydrogen borrowing.

Peng Yang, Caili Zhang, Yu Ma, Caiyun Zhang, Aijie Li, Bo Tang and Jianrong Steve Zhou**

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Nickel-Catalyzed *N*-Alkylation of both Acylhydrazines and Arylamines with Alcohols and Enantioselective Examples