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Ruthenium-Catalyzed *N*-Alkylation of Amines and Sulfonamides Using Borrowing Hydrogen Methodology

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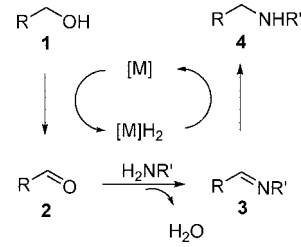
Abstract: The alkylation of amines by alcohols has been achieved using 0.5 mol % $[Ru(p\text{-cymene})Cl_2]_2$ with the bidentate phosphines dppf or DPEphos as the catalyst. Primary amines have been converted into secondary amines, and secondary amines into tertiary amines, including the syntheses of Piribedil, Tripelennamine, and Chlorpheniramine. *N*-Heterocyclization reactions of primary amines are reported, as well as alkylation reactions of primary sulfonamides. Secondary alcohols require more forcing conditions than primary alcohols but are still effective alkylating agents in the presence of this catalyst.

Introduction

The alkylation reaction of amines is typically achieved by reaction with an alkyl halide, although this procedure can be problematic due to overalkylation and the toxic nature of many alkyl halides and related alkylating agents.[1] The use of alcohols as direct alkylating agents for amines is generally limited due to the poor electrophilicity of most alcohols, although such a procedure is appealing since the only reaction byproduct is water. The alkylation of amines with alcohols is therefore potentially an atom economical and less hazardous process than the use of conventional alkylating agents. The use of the borrowing hydrogen strategy (Scheme 1) overcomes the lack of reactivity by the temporary removal of hydrogen from the starting alcohol **1** to give an intermediate aldehyde **2**. The aldehyde is much more reactive toward the amine, and the imine **3** is formed under the reaction conditions. The catalyst then returns the borrowed hydrogen, reducing the imine into the alkylated amine product **4**. Herein we report our use of $[Ru(p\text{-cymene})Cl_2]_2$ with diphosphines which successfully catalyze this process.[2] The alkylation of amines by alcohols with loss of water is a thermodynamically favored process where the loss of a C−O bond for a C−N bond is compensated by the gain of an O−H bond for an N−H bond. On the basis of the experimentally determined heats of enthalpy,[3] the conversion of $MeNH_2$ and MeOH into Me_2NH and H_2O has a reaction enthalpy of −7.7 kcal/mol (gas phase)/ −10.8 kcal/mol (liquid phase). Even for the formation of bulkier amines, the issue of reversibility does not appear to be a significant problem.

Scheme 1. Borrowing Hydrogen Strategy in the Alkylation of Amines with Alcohols



The first examples of homogeneous catalysts for the alkylation of amines by alcohols were published independently by Grigg[4] and Watanabe,[5] and there have been several ruthenium[6] and iridium[7] catalysts reported subsequently. Many of these catalysts require rather forcing conditions, although milder conditions have been employed by Yamaguchi and co-workers with Cp^*IrCl_2,[8] and by Beller's group using $Ru_3(CO)_{12}$ with bulky phosphines,[9] as well as a report on the use of $CpRuCl(PPh_3)_2$.[10] The borrowing hydrogen strategy has also been used in C-alkylation reactions, where the intermediate aldehyde is

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(1) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.
(2) (a) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725. (b) Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263.
(3) Heats of formation for a wide range of compounds are available from the National Institue of Standards and Technology (NIST) Chemistry WebBook at http://webbook.nist.gov/chemistry/.
(4) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611.
(5) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
(6) (a) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T.-A. *J. Org. Chem.* **1996**, *61*, 4214. (b) Ganguly, S.; Roundhill, D. M. *Polyhedron* **1990**, *20*, 2517. (c) Huh, K.-T.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449. (d) Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, *48*, 3367.
(7) (a) Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535. (b) Cami-Kobeci, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072. (c) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth Catal.* **2008**, *350*, 749.
(8) (a) Fujita, K.; Li, Z.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687. (b) Fujita, K.-I.; Yamaguchi, R. *Synlett* **2005**, *4*, 560. (c) Fujita, K.-I.; Enoki, Y.; Yamaguchi, R. *Org. Synth.* **2006**, *83*, 217. (d) Fujita, K.-I.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943. (e) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-I. *Org. Lett.* **2008**, *10*, 181.

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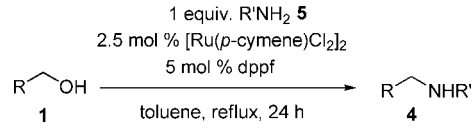
Scheme 2. Formation of Secondary Amines by *N*-Alkylation with Alcohols



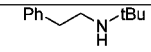
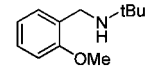
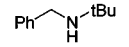
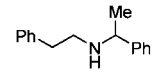
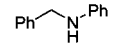
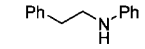
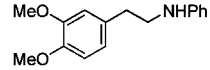
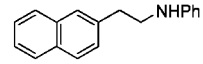
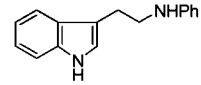
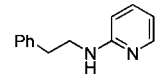
converted into an alkene which is then reduced by return of hydrogen.[11,12] Reactions involving borrowing hydrogen processes have recently been reviewed.[13]

Results and Discussion

The reaction of 2-phenylethanol **1** (R= $PhCH_2$) with *t*-butylamine **5** (R = *t*-Bu) was chosen as a model for establishing a competent catalyst for the alkylation of amines with alcohols (Scheme 2). $[Ru(p\text{-cymene})Cl_2]_2$ was selected as a readily available catalyst precursor, and the reaction was examined in the presence of a range of ligands. Using 2.5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ in the absence of any additional ligand afforded minimal consumption of starting material after 24 h at reflux in toluene. None of the alkylated amine product **4** was observed with the ester $PhCH_2CH_2O_2CCH_2Ph$ being formed with 8% conversion. The formation of this ester, along with the desired amine product, was also seen when the reaction was perfomed in the presence of several other phosphines, either as the sole (PCy_3), major (xantphos, BINAP), or minor (dppp, dippf) product component. However, we were pleased to find that the use of dppf[14] led to the exclusive formation of the desired alkylated amine product with no observable contamination by ester. DPEphos[15] was similarly effective and dppe also gave complete selectivity, although in this case the conversion into product was only 20%. The use of dppf with other catalyst precursors did not lead to any further improvement, with $Ru(OAc)_2(H_2O)_2$ being catalytically inactive, $Ru(CO)(PPh_3)_3H_2$ giving only ester (26%), and $Ru(PPh_3)_3Cl_2$ giving only alkylated amine but in low conversion (35%). In our initial experiments,[2] we used 10 mol% K_2CO_3 along with 3 Å molecular seives, although we subsequently demonstrated that these additives had a negligible effect on the reaction outcome.

Using the $[Ru(p\text{-cymene})Cl_2]_2$ with dppf combination, we applied these conditions to the formation of a range of secondary amines (Table 1). As well as the parent reaction (entry 1), the *N*-alkylation of *t*-butylamine was also successful with benzylic alcohols (entries 2 and 3) as was the *N*-alkylation of 1-phenylethylamine (entry 4). We examined the *N*-alkylation of aniline with a range of alcohols including benzyl alcohol (entry 5) and 2-arylethanols (entries 6−9), which were all successful. The use of 2-aminopyridine as substrate gave a reduced conversion into product with the formation of the amide $PhCH_2CONHPy$ as a significant byproduct, especially when the reaction was run in the presence of base. We assume that the intermediate

Table 1. Alkylation of Primary Amines with Alcohols

entry	Amine product[a]	conversion (%)[b] with K_2CO_3	conversion (%)[b] without K_2CO_3
1		96 (88)	94 (-)
2		73 (-)	87 (68)
3		84 (-)	62 (60)
4		100 (93)	100 (-)
5		100 (80)	95 (-)
6		94 (-)	100 (84)
7		100 (87)	100 (-)
8		100 (-)	100 (89)
9		100 (70)	100 (-)
10		69 (-)	93 (78)

[a] Reactions were performed using amine (1 mmol) and alcohol (1 mmol) in toluene (1 mL) using dppf as the ligand, as shown in Scheme 2. [b] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^1H NMR spectra. Figures in parentheses are isolated yields, where applicable.

(9) (a) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403. (b) Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881.
(10) Del Zotto, A.; Baratta, W.; Sandri, M.; Verardo, G.; Rigo, P. *Eur. J. Inorg. Chem.* **2004**, 524.
(11) For representative examples, see: (a) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedron Lett.* **1981**, *22*, 4107. (b) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020. (c) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72. (d) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662. (e) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913. (f) Yamada, Y. M. A.; Uozumi, Y. *Org. Lett.* **2006**, *8*, 1375. (g) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023. (h) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8982. (i) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988. (j) Löfberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, 5000. (k) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819. (l) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850.
(12) (a) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740. (b) Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90. (c) Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, *47*, 6787. (d) Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *4*, 116. (e) Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, *4*, 4367. (f) Burling, S.; Paine, B. M.; Nama, D.; Brown, V. S.; Mahon, M. F.; Prior, T. J.; Pregosin, P. S.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2007**, *129*, 1987. (g) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, *350*, 1975.
(13) (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Lamb, G. W.; Williams, J. M. J. *Chim. Oggi* **2008**, *26*, 17.
(14) dppf = 1,1′-bis(diphenylphosphino)ferrocene.
(15) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081. DPEphos = bis(2-diphenylphosphinophenyl)ether.

Scheme 3. Formation of Tertiary Amines by *N*-Alkylation with Alcohols

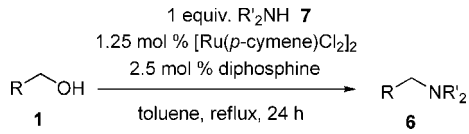
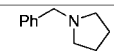
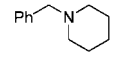
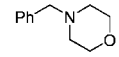
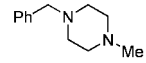
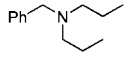
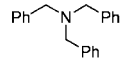
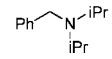


Table 2. *N*-Benzylation of Secondary Amines

entry	Amine[a]	conversion (%) DPEphos	conversion (%)[b] dppf
1		89	84 (71)
2		100	85 (72)
3		100	93 (84)
4		94	88 (80)
5		96	96 (87)
6		72	52 (44)
7		-	0

[a] Reactions were performed using amine (1 mmol) and alcohol (1 mmol) in toluene (1 mL) as shown in Scheme 3. [b] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields, where applicable.

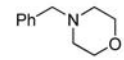
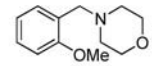
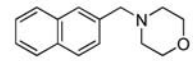
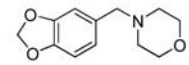
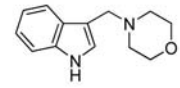
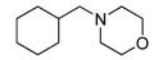
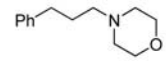
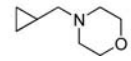
hemiaminal is stabilized by H-bonding to the pyridine nitrogen, which facilitates oxidation to the amide.[16]

In all of the reactions between alcohols and primary amines, only formation of the secondary amine product was seen, with no overalkylation to the tertiary amine. Although in one case, using excess ethanol (4.8 equiv) as the alkylating agent with aniline, *N*-ethylaniline was formed in 95% conversion, with 5% of diethylaniline as a side product, and we were encouraged from this result to see whether it may be possible to convert secondary amines directly into tertiary amines by alkylation with suitable alcohols.

Therefore, a range of tertiary amines **6** was prepared by the reaction of alcohols **1** with secondary amines **7** (Scheme 3). The ligands dppf and DPEphos were both found to be effective in this reaction.

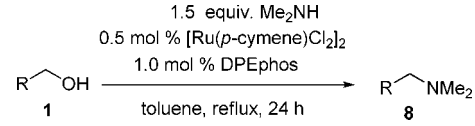
Benzyl alcohol was reacted with cyclic amines to give the corresponding *N*-benzyl heterocycles (entries 1−4) with good isolated yields (Table 2). The reaction was also successful for the *N*-benzylation of the acyclic amines dipropylamine and dibenzylamine (entries 5 and 6), although unreacted starting materials were returned when the *N*-alkylation of diisopropylamine (entry 7) was attempted, presumably due to the increased steric requirements of this substrate. We also chose to examine the alkylation of morpholine with other alcohols, and these results are summarized in Table 3. As well as the *N*-benzylation reaction (entry 1), other benzylic alcohols were successfully used as alkylating agents to give the products shown in entries 2−5. Aliphatic alcohols were also used successfully (entries 6−9), although a lower yield was obtained using cyclohexylmethanol (entry 6), presumably because of steric considerations.

Table 3. Alkylation of Morpholine with Alcohols

entry	product[a]	isolated yield (%)
1		84
2		74
3		78
4		89
5		85
6		62
7		77
8		85

[a] Reactions were performed using amine (1 mmol) and alcohol (1 mmol) in toluene (1 mL) using dppf as the ligand.

Scheme 4. Formation of *N,N*-Dimethylamino Compounds

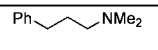
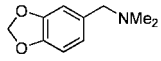
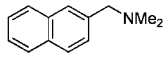
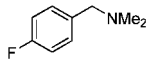
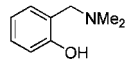
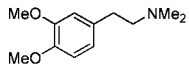
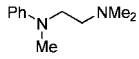
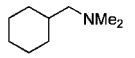
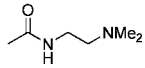


Given the widespread occurrence of the dimethylamino group, we were interested to apply this chemistry to the conversion of alcohols into *N,N*-dimethylamino compounds. The reaction of dimethylamine with alcohols **1** led to the formation of the corresponding dimethylamino compounds **8** (Scheme 4). Dimethylamine was prepared as a solution in toluene, by condensation of dimethylamine gas (bp 7 °C), and the exact concentration could be established by analysis of the integrals for the methyl peaks in the NMR spectrum. Dimethylammonium acetate was also a suitable reaction partner, and could be used in place of the toluene solution. Dimethylamine was then alkylated with various alcohols (Table 4), and a catalyst loading of only 0.5 mol % [Ru(*p*-cymene)Cl_2]$_2$ (equivalent to 1 mol % Ru) was sufficient for many of the simpler alcohols. Several benzylic alcohols (entries 2−5) were used successfully, as well as aliphatic amines including the amine-containing and amide-containing alcohols leading to the products shown in entries 7 and 10.

Since amine alkylation reactions are widely used in the preparation of pharmaceutical drugs and drug candidates, we wished to investigate the viability of preparing some pharmaceutical agents using the borrowing hydrogen amination methodology, which would employ alcohols in place of the more conventional, but often toxic, alkyl halides. Piribedil (**11**) is a piperazine dopamine agonist used in the treatment of Parkinson's

(16) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.

Table 4. Formation of Dimethylamino Compounds

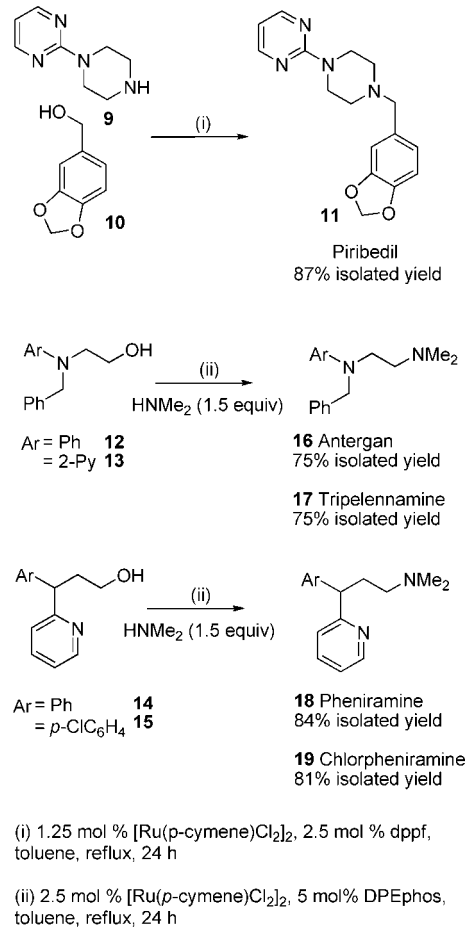
entry	amine product	catalyst (mol %)	conversion (%)[a]
1		0.5	100 (83)
2		0.5	96 (85)
3		0.5	100 (97)
4		0.5	100 (60)
5		0.5	100 (88)
6		0.5	100 (94)
7		1.25	88 (75)
8		1.25	100 (77)
9	n-$C_8H_{17}NMe_2$	1.25	100 (76)
10		2.5	100 (72)

[a] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields.

disease.[17] Piribedil (**11**) was prepared by the reaction of commercially available piperidine **9** with piperonyl alcohol **10** in a single synthetic transformation. The reaction proceeded to complete conversion after 24 h in toluene at reflux using 1.25 mol % of [Ru(*p*-cymene)Cl_2]$_2$, and dppf was found to be a suitable ligand in this reaction (Scheme 5).

There are many pharmaceuticals that contain the dimethylamino group, and we focused our attention on a family of anti-inflammatory agents, **16**−**19**. Antergan (**16**)[18] was among the first antihistamine drugs to be sold and its structure provided the framework for subsequent antihistamine agents, and Tripelennamine (**17**) is an example of a closely related antihistamine drug.[19] Pheniramine (**18**)[20] and chlorpheniramine (**18**)[21] (commonly marketed as Chlor-Trimeton or Piriton) are similar structures with an all-carbon backbone. Alcohols **12** − **15** were reacted with dimethylamine and converted into the desired products in good isolated yields. In these examples, a catalyst loading of 2.5 mol% [Ru(*p*-cymene)Cl_2]$_2$ with DPEphos was used, and we speculate that the higher loading was required because the starting materials and products could function as ligands for the ruthenium complex.

Scheme 5. *N*-Alkylation of Amines by Alcohols in the Preparation of Pharmaceuticals



(i) 1.25 mol % [Ru(p-cymene)Cl_2]$_2$, 2.5 mol % dppf, toluene, reflux, 24 h

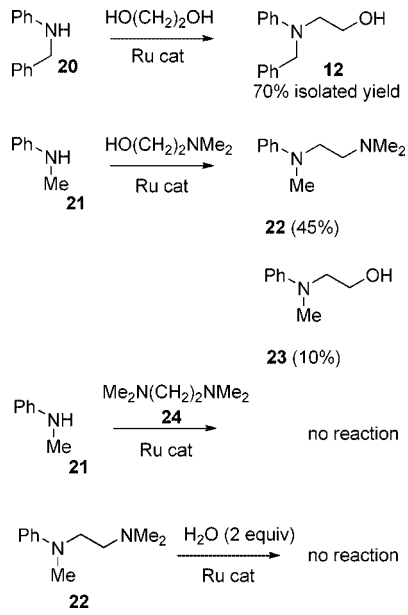
(ii) 2.5 mol % [Ru(*p*-cymene)Cl_2]$_2$, 5 mol% DPEphos, toluene, reflux, 24 h

The aminoalcohol **12** used in Scheme 5 was initially prepared by conventional alkylation of *N*-benzylaniline **20** with 2-bromoethanol,[22] but as shown in Scheme 6 it could also be prepared using ethylene glycol to alkylate amine **20** (which could be prepared by the alkylation of aniline with benzyl alcohol, see Table 1, entry 5). We reasoned that an alternative approach to related structures involving the alkylation of amine **21** with *N,N*-dimethylaminoethanol could also be considered. However, under the standard conditions, we discovered that as well as forming the expected diamine **22**, the amino alcohol **23** was also formed as a significant byproduct, initially suggesting that there may have been oxidation of the amine as well as the alcohol (Scheme 6). However, the reaction of amine **21** with tetramethylethylenediamine (TMEDA) led to no product formation under these conditions, implying that direct amine oxidation was not occurring. In addition, diamine **22** did not undergo conversion into an amino alcohol when subjected to the reaction conditions in the presence of added water.

We suggest that in the case of using *N,N*-dimethylaminoethanol as an alkylating agent, the intermediate amino aldehyde is in equilibrium with a reactive iminium species which undergoes transimination with the incoming amine, prior to return of hydrogen to give the product, as shown in Scheme 7. This sequence accounts for amine exchange in an amino alcohol without a direct C−N oxidation step.

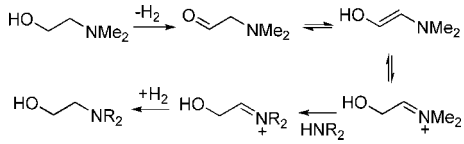
(17) (a) Jaber, M.; Robinson, S. W.; Missale, C.; Caron, M. G. *Neuropharmacology* **1996**, *35*, 1503. (b) Duncton, M. A. J.; Roffey, J. R. A.; Hamlyn, R. J.; Adams, D. R. *Tetrahedron Lett.* **2006**, *47*, 2549.
(18) Kaye, I. A.; Parris, C. L.; Weiner, N. *J. Am. Chem. Soc.* **1953**, *75*, 745.
(19) Petersenn, A. *Arch. Pharm. (Weinheim)* **1991**, *324*, 411.
(20) (a) Isaac, L.; Goth, A. *J. Pharmacol. Exp. Ther.* **1967**, *156*, 463. (b) Azzena, U.; Melloni, G.; Fenude, E.; Finà, C.; Marchetti, M.; Sechi, B. *Synth. Commun.* **1994**, *24*, 591.
(21) Charlton, B. G. *Med. Hypotheses* **2005**, *65*, 823.
(22) Powell, N. A.; Clay, E. H.; Holsworth, D. D.; Bryant, J. W.; Ryan, M. J.; Jalaie, M.; Zhang, E.; Edmunds, J. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2371.

Scheme 6. Alkylation Reactions Involving Diols and Amino Alcohols[a]



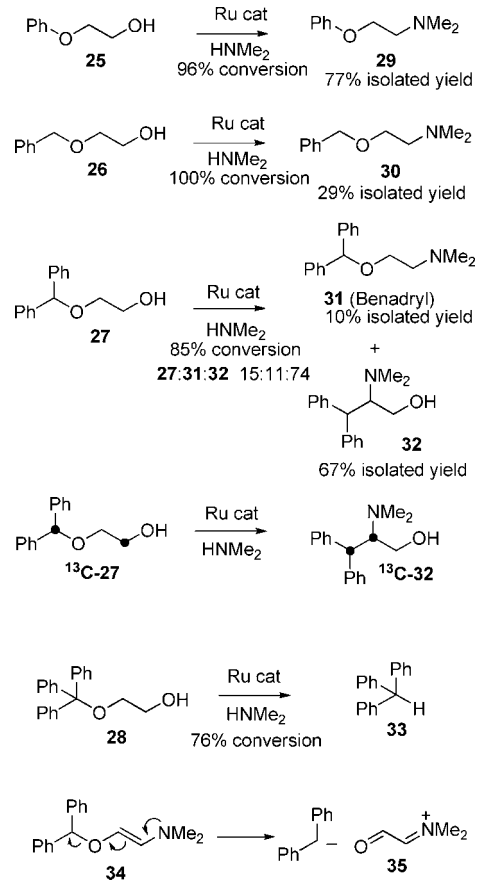
[a] All reactions were run with 2.5 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 5 mol% DPEphos, toluene, reflux, 24 h.

Scheme 7. Rationalization of the Reactivity of *N,N*-Dimethylethanolamine



Another unexpected reaction was observed in the case of some hydroxy ethers. While phenyl ether **25** and benzyl ether **26** were converted into the corresponding dimethylamino compounds **29** and **30** (Scheme 8), we observed that in the attempted conversion of the hydroxy ether **27**,[23] the expected product **31** (diphenhydramine, Benadryl)[24] was only a minor product of the reaction, and that the rearranged product **32** was formed as the major component. When hydroxy ether **27** was treated under the reaction condition in the absence of dimethylamine (or in the presence of the tertiary amine triethylamine), the starting material was recovered unchanged. A doubly ^{13}C labeled **27** was prepared by the reaction of PhMgBr with $Ph^{13}CHO$ to give $Ph_2{}^{13}CHOH$ which was O-alkylated with $BrCH_2{}^{13}CO_2Et$ and the ester group then reduced with $LiAlH_4$. The reaction of ^{13}C-**27** with dimethylamine under the same conditions led to the formation of product **32** where the ^{13}C labeled atoms were in adjacent positions. The ^{13}C NMR spectrum contained doublets at δ 67.1 and 52.2 with $J = 34.7$ Hz, corresponding to the ^{13}C labels at the positions indicated. The reaction was repeated using a 1:1 mixture of unlabeled **27** and doubly labeled **27**. Analysis of the same signals revealed that the ratio of the doubly labeled product (both peaks doublets) to the singly labeled product (singlets) was 82:18, indicating that an intramolecular rearrangement pathway predominated. We speculate that a plausible mechanism involves oxidation of the alcohol to an aldehyde which condenses with dimethylamine

Scheme 8. Reactions Involving Hydroxyether Substrates[a]



[a] All reactions were run with 2.5 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 5 mol% DPEphos, toluene, reflux, 24 h.

to give the enamine **34**. This enamine could then eject Ph_2CH^-, mainly as an ion pair, which then recombines by addition to the iminum species **35**, which after return of the hydrogen generates the amino alcohol **32**. When the reaction was examined using the trityl ether **28**,[25] only triphenylmethane **33** was observed, suggesting that the trityl anion (Ph_3C^-) could be formed by a similar fragmentation, but that it is too bulky to recombine with the iminium species **35**, and instead is simply protonated.

The reaction of diols with amines is an attractive route for the formation of *N*-heterocycles, and has been investigated by others using iridium[26] and ruthenium[27] catalysts. Given the success of amine alkylation with alcohols using $[Ru(p\text{-cymene})Cl_2]_2$ with diphosphines, we chose to investigate the reaction of amines **5** with diols **36** using this catalyst for the synthesis of a range of heterocycles **37** (Scheme 9). Preliminary experiments established that the use of 2.5 mol % $[Ru(p\text{-cymene})Cl_2]_2$ with DPEphos was an effective catalyst. The use of triethylamine (10 mol %) was found to provide consistent results, and this was used as an additive in all cyclization reactions.

(23) Sasaki, M.; Miyake, H.; Fujimura, M.; Tsumura, T. *Chem. Lett.* **2006**, *35*, 778.
(24) Brummel, R. N.; Vande Vusse, J. UK Pat. Appl. 1986, GB2176477A.
(25) Hirao, I.; Koizuma, M.; Ishido, Y.; Andrus, A. *Tetrahedron Lett.* **1998**, *39*, 2989.
(26) (a) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365. (b) Huh, K.-T.; Shim, S. C.; Doh, C. H. *Bull. Korean Chem. Soc.* **1990**, *11*, 45. (c) Marsella, J. A. *J. Organomet. Chem.* **1991**, *407*, 97. (d) Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282.
(27) (a) Fujita, K.-I.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (b) Eary, C. T.; Clasen, D. *Tetrahedron Lett.* **2006**, *47*, 6899. (c) Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034.

Scheme 9. Reaction of Diols with Amines to Form *N*-Heterocycles

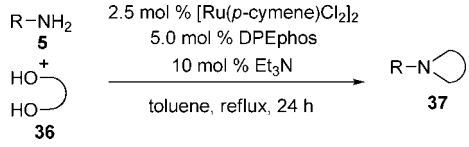
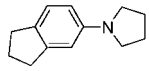
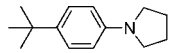
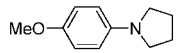
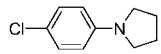
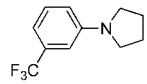
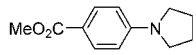
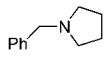
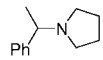
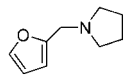
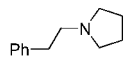
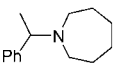


Table 5. *N*-Heterocyclization of Amines with Diols

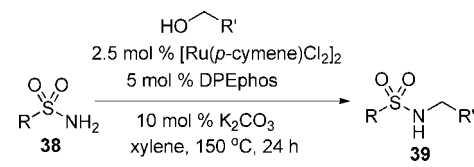
entry	product	conversion (%)[a,b]
1		100 (78)
2		94 (74)
3		92 (85)
4		100 (70)
5		100 (87)
6		61 (60)
7		50 (33)
8		81 (72)
9		100 (82)
10		77 (63)
11		100 (69)
12		87 (72)
13		100 (65)

[a] Reactions were performed using 1 mmol of amine and 1.2 mmol of diol using DPEphos as the ligand. [b] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields.

Aniline was reacted with 1,4-butanediol to give *N*-phenylpyrrolidine (entry 1, Table 5), and other substituted anilines were also found to be effective (entries 2−7), although the more electron poor anilines (entries 6 and 7) gave lower conversions under these conditions. Aliphatic primary amines (entries 8−11) were also effective, including the branched primary amine used for entry 9. The use of alternative diols also led to cyclization to the corresponding *N*-heterocycle, with the use of 1,5-pentanediol and 1,6-hexanediol leading to the products given in entries 12−13.

Sulfonamides are found in many pharmaceutical drugs (e.g., Sumatripan, Viagra, Furosemide) and have also been used as protecting groups for nitrogen.[28] We were interested in investigating whether primary sulfonamides **38** would react with alcohols to give *N*-alkylated sulfonamides **39** using the ruthenium-catalyzed borrowing hydrogen approach, a process which has not been reported previously, although Lewis acid catalysts have recently been reported to effect this transformation (Scheme 10).[29] We chose to examine the alkylation of *p*-toluenesulfonamide with one equivalent of benzyl alcohol as a model reaction. Using 2.5 mol% [Ru(*p*-cymene)Cl_2]$_2$ with 5 mol% DPEphos we only observed a 32% conversion into the alkylated product, *N*-benzyltoluenesulfonamide, when the reaction was performed at 110 °C for 24 h in toluene in the absence of base. However, by performing the reactions in *p*-xylene at 150 °C the reaction proceeded to 44% conversion (in the absence of base) and to 95% conversion (in the presence of 10 mol% K_2CO_3) after 6 h. After 24 h at 150 °C, these reactions had essentially gone to completion whether base was present or not. The results of these reactions are given in Table 6, where the reaction of benzyl alcohol with arylsulfonamides (entries 1−6) led to the corresponding secondary sulfonamides in good yields. The *p*-methoxy substrate (entry 4) provided the highest conversion and yield, while the *p*-nitro substrate (entry 5) was the least reactive. The alkylation of methanesulfonamide with benzyl alcohol was also successful (entry 7). Other benzylic alcohols could be used to alkylate *p*-toluenesulfonamide (entries 8−10), and the aliphatic alcohols tryptophol (entry 11) and cyclohexylmethanol (entry 12) and cyclopropylmethanol (entry 13) were also effective.

Scheme 10. *N*-Alkylation Reactions of Sulfonamides



Since the use of higher temperatures was effective in the *N*-alkylation reactions of sulfonamides, we chose to use the same approach for the reactions of secondary alcohols **40** with amines **41** to give *N*-alkylation products **42**. Preliminary results obtained at 110 °C had been unsatisfactory, with low conversions under these conditions. For example, the reaction of cyclohexanol with morpholine using 2.5 mol% Ru(*p*-cymene)Cl_2]$_2$ with 5 mol% DPEphos in toluene at 110 °C for 24 h only gave 51% conversion, but when this reaction was repeated in xylene at 150 °C, 100% conversion was achieved.

Cyclic amines were alkylated with cyclohexanol under these conditions to give the products with good conversions (Table 7, entries 1−4). Primary amines were also successful (entries 5−6), although in the case of *t*-butylamine, which was easily alkylated by primary alcohols, the reaction proceeded with low conversion with cyclohexanol, presumably for steric reasons.

Our attention turned to the use of other secondary alcohols as alkylating agents for amines, and these results are summarized in Table 8. We chose 1-phenylethanol (R = Ph, R′ = Me), 1-phenylpropan-2-ol (R = $PhCH_2$, R′ = Me) and pentan-2-ol (R = CH_2CH_2Me, R′ = Me) as representative alcohols. The benzylic alcohol, 1-phenylethanol, was the least reactive of these alcohols, providing only moderate yields of the tertiary amine product under these conditions (Scheme 11). However, the non-benzylic alcohols both showed higher reactivity and the products were obtained with higher conversion. To examine whether the

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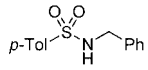
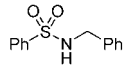
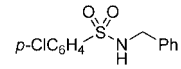
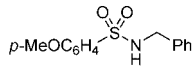
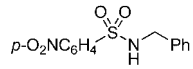
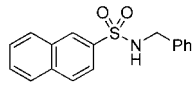
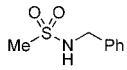
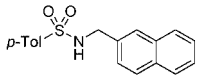
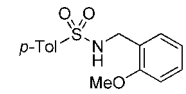
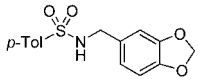
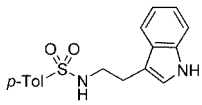
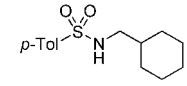
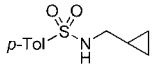
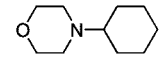
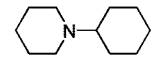
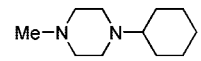
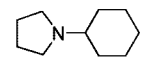
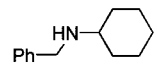
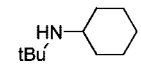
(29) (a) Qin, H.; Yoaagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409. (b) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetrahedron Lett.* **2007**, *48*, 8174.

Table 6. *N*-Alkylation of Sulfonamides

entry	sulfonamide product	conversion (%)[a]
1		95 (84)
2		92 (79)
3		89 (78)
4		99 (92)
5		72 (66)
6		90 (83)
7		91 (76)
8		100 (80)
9		73 (72)
10		100 (88)
11		89 (78)
12		91 (84)
13		100 (92)

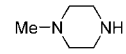
[a] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields.

Table 7. *N*-Alkylation of Amines with Cyclohexanol

entry	product	conversion (%)[a]
1		100 (84)
2		100 (98)
3		79 (75)
4		89 (81)
5		70 (63)
6		18

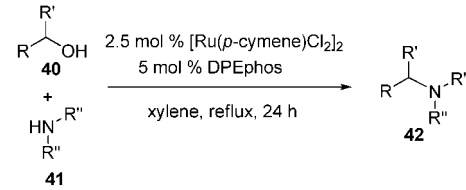
[a] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields, where applicable.

Table 8. *N*-Alkylation of Amines with Other Secondary Alcohols

entry	amine **41**	Conversion (%) of **42** from alcohols **40**[a]		
				
1-3		73 (65)	95 (86)	100 (88)
4-6		78 (69)	98 (91)	96 (85)
7-9		36	90 (82)	95 (80)
10-12		35	74 (69)	83 (72)

[a] Values given are conversions with respect to unreacted alcohol, as determined by analysis of the ^{1}H NMR spectra. Figures in parentheses are isolated yields, where applicable.

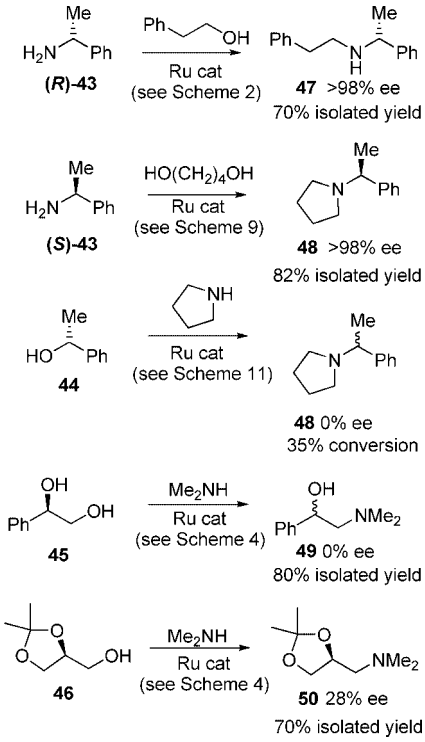
Scheme 11. *N*-Alkylation with Secondary Alcohols



reactions could be reversible, or under equilibrium conditions, we resubjected the piperazine product in entry 8, Table 8 to the reaction conditions. A large excess of water was required to observe formation of 1-phenyl-2-propanol, and only 10% conversion was observed in the ^{1}H NMR spectrum of the reaction mixture after treatment with 22 equiv of water under the reaction conditions used for the initial alkylation process.

We were interested in determining whether the stereochemical purity of the amine and alcohol components in the alkylation process would be retained during the course of the reaction, and these experiments are summarized in Scheme 12 (all reactions were run under the equivalent conditions from the scheme indicated). Enantiomerically pure 1-phenylethylamine **43** underwent alkylation with 2-phenylethanol to give the alkylated product **47** with complete retention of stereochemistry. In a similar way, *N*-heterocyclization of amine **43** with 1,4-butanediol to give product **48** was also achieved without loss of stereochemical integrity. Potential pathways for loss of stereochemistry include transient amine (C−N) to imine (C=N) oxidation,[30] or isomerization of the imine formed when the amine reacts with the intermediate aldehyde. However, under these conditions, it is clear that these pathways do not operate. As expected, the reaction of an enantiomerically pure secondary alcohol **44** with an amine leads to product with 0% ee—this

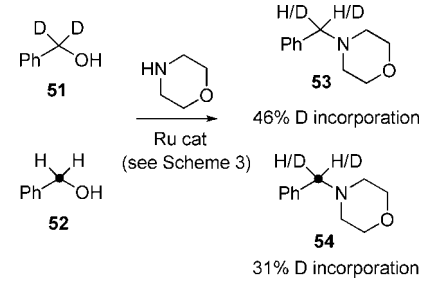
Scheme 12. *N*-Alkylation Reactions Involving Enantiomerically Pure Substrates



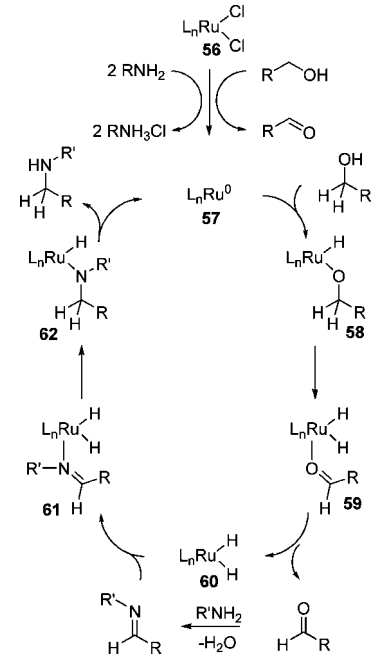
observation is consistent with the necessary loss of stereochemistry in the conversion of alcohol into achiral ketone in the oxidation step. The reaction of enantiomerically pure diol **45** with dimethylamine occurs selectively with the primary alcohol to give the racemic amino alcohol **49** as product. This is consistent with reversible oxidation of the secondary alcohol to the achiral ketone, as noted in racemization reactions of secondary alcohols in the presence of appropriate ruthenium catalysts.[31] Racemization of the intermediate aldehyde or iminium species may also be responsible. In the case of the amination of enantiomerically pure alcohol **46**, the majority of the stereochemical integrity is lost in the formation of the product **50**, and this observation is consistent with racemization occurring by enolization of the intermediate aldehyde or iminium species.[32] Presumably, stereochemistry positioned further away from the alcohol would be stereochemically stable, although this has not been investigated.

In the borrowing hydrogen mechanism, the intermediate aldehyde could either remain complexed to the metal during the imine-forming process or it could dissociate and form the imine/iminium away from the metal center. We performed a crossover experiment in order to gain evidence for either of these possible mechanisms. Thus, the deuterated alcohol **51** and the ^{13}C labeled alcohol **52** were reacted with morpholine to provide the *N*-benzylated morpholine adducts **53** and **54** (Scheme 13). Deuterium incorporation was observed in both the unlabeled product **53** and the labeled product **54**. The fact

Scheme 13. Hydrogen/Deuterium Crossover Study in Morpholine Alkylation



Scheme 14. Mechanistic Proposal for the *N*-Alkylation of Alcohols with Amines



that there is crossover of the deuterium to the ^{13}C labeled benzyl group implies that the intermediate aldehyde can dissociate from the ruthenium and that imine formation does not necessarily take place while coordinated. However, since water is formed in the oxidation process, either as H_2O or HOD, a mechanism involving H/D exchange of the water with the starting alcohols **52** and **53** cannot be entirely ruled out. The higher deuterium incorporation in compound **53** is consistent with the fact that only one of the two C−D bonds needs to be broken in order for the reaction to take place.

A plausible mechanism for the alkylation of an amine by alcohol using the [Ru(*p*-cymene)Cl_2]$_2$ /diphosphine combination is given in Scheme 14. Complexation of a diphosphine with the ruthenium would lead to the formation of the cationic 18 electron complex [Ru(P−P)(*p*-cymene)Cl]Cl[33] which needs to generate a free co-ordination site to become catalytically active. We have previously shown[34] that the reaction of [Ru(*p*-cymene)Cl_2]$_2$ with BINAP and the diamine DPEN leads to the formation of the Noyori complex Ru(BINAP)(DPEN)Cl_2[35] and we believe that *p*-cymene is dissociated in the active complex. *p*-Cymene is also observed in the crude ^1H NMR spectra at the end of *N*-alkylation reactions. We therefore believe that complex

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56 is generated where L_n represents the bidentate phosphine and probably amine ligands. Activation of complex **56** can be considered to give a ruthenium(0) complex **57** by exchange of a chloride with alcohol, and loss of HCl. β-Hydride transfer from the alkoxy complex to give $L_nRuHCl(O{=}CHR)$ then leads to complex **57** by loss of the aldehyde and HCl. Oxidative addtion of the alcohol provides the alkoxy hydride complex **58**, which can then undergo β-hydride transfer to form the aldehyde complex **59**. Dissociation of the aldehyde, imine formation and recomplexation leads to the imine complex **61**, presumably by the dihydride complex **60**. β-Hydride transfer to give the amido complex **62** and reductive elimination affords the amine product and regenerates the ruthenium(0) complex **57**. When the reaction involves the *N*-alkylation of a secondary amine, the intermediate iminium species would not be able to bind through the nitrogen, and the reaction could proceed either via an η^2 iminium complex, or via the enamine.

Conclusion

We have demonstrated that the use of $[Ru(p\text{-cymene})Cl_2]_2$ with either dppf or DPEphos provides a catalyst capable of alkylating amines with alcohols. The reaction is most readily accomplished using unbranched primary alcohols with sterically unencumbered amines, although other substrates could also be used successfully. The chemistry has been applied to the synthesis of some simple pharmaceutical drugs, as well as to cyclization reactions and the *N*-alkylation of sulfonamides.

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Supporting Information Available: Further details of experimental procedures, along with analytical and spectroscopic data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675.