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Letter

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Method for the Direct Enantioselective Synthesis of Chiral Primary α-Amino Ketones by Catalytic α-Amination

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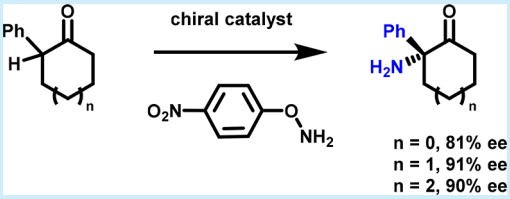
Supporting Information

ABSTRACT: A useful catalytic enantioselective approach has been developed for the synthesis of chiral ketamine analogs using Rh(II)-catalyzed amination of triisopropylsilyl enol ethers to form α-amino ketones with *O*-(4-nitrophenyl)hydroxylamine as nitrogen donor in 81−91% ee.



The recent finding that ketamine (**1**; Figure 1), a long-used injectable general anesthetic,[1] can also promptly relieve treatment-resistant depression[2] has provided synthetic chemistry with a unique opportunity to help with one of the world's most pressing problems. Amine **1** is far from an ideal therapeutic agent. Although a subanesthetic dose of ketamine can sometimes lift refractory depression in as little as 1 h, the response rate is moderate and side effects may be significant. It has been suggested that a metabolite of ketamine 2*R*,6*R*-hydroxy norketamine (**2**; Figure 1) may possibly be superior to it,[3−5] but this has not been tested by *in vivo* clinical studies. The mechanism by which ketamine lifts depression is unclear, but there is evidence that inhibition of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate activated synaptic receptor is involved. In addition, recent evidence indicates that the lateral habenula region in the brain may be a key site of NMDA receptor inhibition by ketamine.[6] We describe in this Letter a study aimed at development of a new enantioselective route to ketamine and a variety of structural analogs by direct α-amination of suitable cyclic ketones. This area of synthetic methodology is relatively undeveloped. The most actively studied approach to the enantioselective synthesis of α-amino ketone derivatives involves the Michael addition of a ketone enolate or equivalent to an azodicarboxylic ester.[7−10] In our previous work on the enantioselective synthesis of ketamine, its metabolites, and its analogs, the α-amino ketone subunit was accessed via a chiral epoxide and an α-azido ketone.[10−12]

At the outset the best option for a direct attachment of NH_2 alpha to the ketonic carbonyl function appeared to be the use of a transition metal nitrene complex, especially with rhodium

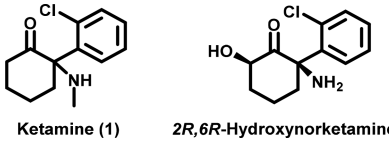
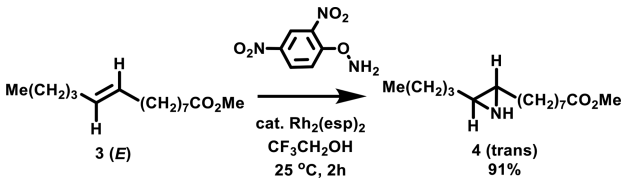


Figure 1. Structure of ketamine (**1**) and 2*R*,6*R*-hydroxynorketamine (**2**).

Scheme 1. Kürti−Falck Amination of 3 to 4



as metal.[13,14] Of special relevance was the Kürti−Falck process[14] for the amination of olefins by Rh(II) carboxylate catalyzed transfer of NH from *O*-(2,4-dinitrophenyl)-hydroxylamine (2,4-DNPONH$_2$), for example, as illustrated by the reaction in Scheme 1. Although the report that the reaction did not occur with useful enantioselectivity using several chiral Rh(II) complexes was not encouraging,[14a] we decided to investigate this approach with the trimethylsilyl enol ether of 2-phenylcyclohexanone as the test substrate by screening of a set of chiral Rh(II) complexes under essentially the conditions used by Kürti et al. (CF_3CH_2OH as solvent at ambient temperature of 23 °C). The results of these early studies are summarized in Scheme 2, which shows the structures of the chiral ligands attached to Rh(II). The Rh(II) complexes were homogeneous by chromatographic and ^{1}H NMR analysis and are likely to have the sequential NNOO arrangement about each rhodium of the Rh_2 complex.[15] The yield of the product 2-amino-2-phenylcyclohexanone (**5**) was determined by isolation, and the ee values were measured by HPLC analysis using a Chiral Technologies AD-H column. On the basis of the yields and ee values shown in Scheme 2, it was decided to advance the Rh(II) complex **21**[15] (Figure 2) derived from ligand **16** (an ester of (+)-menthol) for further study.

The ligand **16** can readily be synthesized from (+)-menthol and (*S*)-pyroglutamic acid by coupling with DCC and DMAP in CH_2Cl_2/DMF (8:1). The complex **21** was prepared by

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Scheme 2. Chiral Ligands Used in the Screening of Rh_2 Complexes for Enantioselectivity

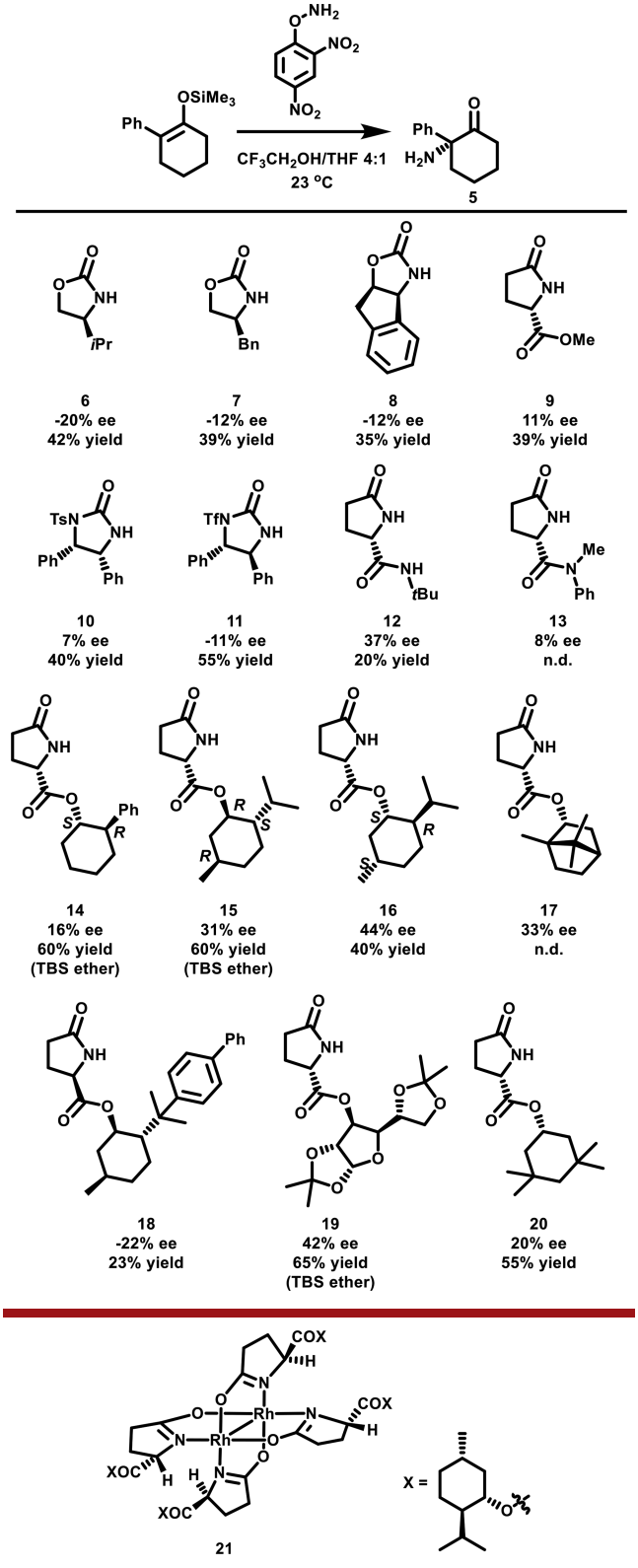
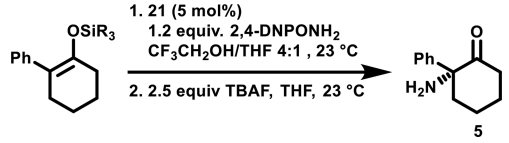


Figure 2. Structure of Rh complex **21**.

reaction of $Rh_2(OAc)_4$ and excess ligand **16** in chlorobenzene at reflux using a Soxhlet extraction apparatus with a mixture of Celite 545 and CaH_2 to remove HOAc as formed. Purification of **21** was carried out by flash column chromatography on silica gel; for details, see Supporting Information.

A definite improvement in the enantioselectivity of the α-amination process with 2-phenylcyclohexanone was found by

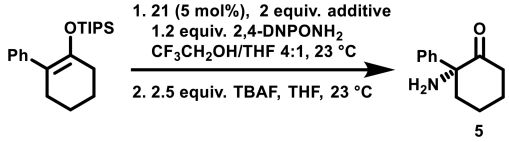
Table 1. Enantioselective Amination of Various Silyl Enol Ether of 2-Phenylcyclohexanone[16]



R_3Si	yield (%)[b]	ee (%)[c]
TMS	35	44
TES	44	46
TBS	40	52
Ph_3Si	30	55
TIPS	46	58

[a]Reactions conducted on a 0.1 mmol scale. [b]Isolated yield. [c]Determined by HPLC.

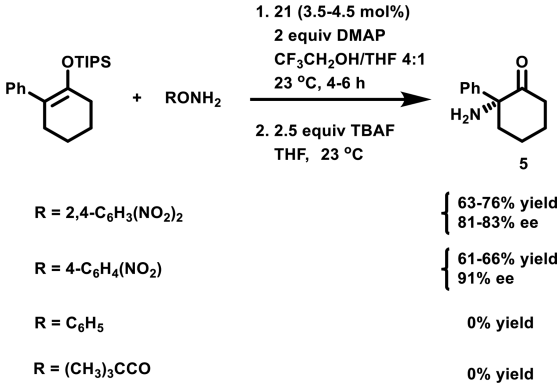
Table 2. Effect of Additives on the Enantioselective Amination



additives	yield (%)[b]	ee (%)[c]
none	41	58
HOAc	40	40
K_2CO_3	30	51
2,6-lutidine	56	69
pyridine	60	74
DMAP (2 equiv)	76	81
DMAP (3 equiv)	70	81
DBU	56	64
imidazole	53	78
dabco	48	74
N-Me-imidazole	40	80
1,1,3,3-tetramethylguanidine	63	73
TMEDA	56	76
4-pyrrolidinopyridine	56	82

[a]Reactions conducted on a 0.1 mmol scale. [b]Isolated yield. [c]Determined by HPLC.

Scheme 3. Yield and Enantioselectivity vs. $RONH_2$



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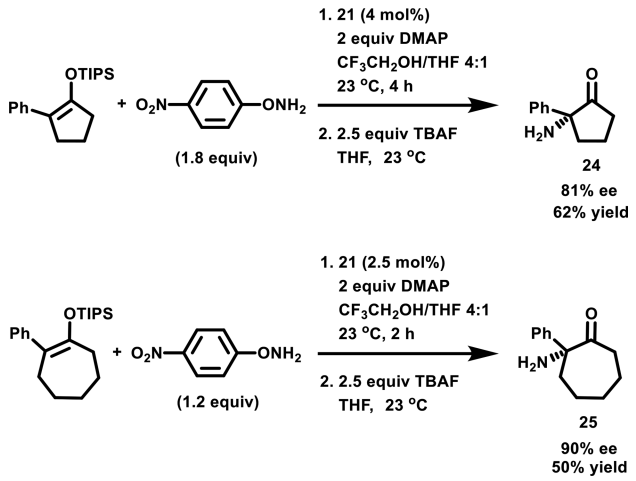
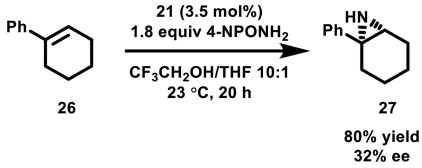
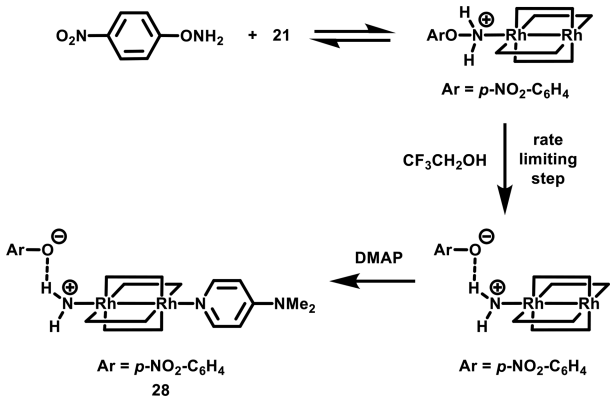
Scheme 4. Simple Enantioselective Synthesis of (*R*)-Nor- and (*R*)-Homoketamine



Scheme 5. Aziridination of 26 to 27 Using Catalyst 21



Scheme 6. One Route to 28, a Possible Amination Intermediate (Ligands Not Shown)



examining the reaction of a series of silyl enol ethers with varying steric properties, as shown in Table 1. The triisopropylsilyl (TIPS) enol ether provided the best combination of yield and ee.

We next examined the effect of added amine bases on the α-amination reaction of the TIPS enol ether of 2-phenylcyclohexanone. The results of these experiments are summarized in Table 2 , which reveals a beneficial effect of certain amines, especially 4-*N*,*N*-dimethylamino pyridine (DMAP) on both the yield and enantioselectivity of the enantioselective Kürti−Falck amination process with the TIPS enol ether of 2-phenylcyclohexanone, even though the rate of amination is a little slower when DMAP is present. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), a considerably stronger base than DMAP, is definitely less effective in terms of the enhancement of yield and enantioselectivity. Imidazole and *N*-methyl imidazole markedly improve enantioselectivity, but not yield. The rate of amination of the TIPS-enol ether of 2-phenylcyclohexanone is not noticeably accelerated by DMAP or the other bases.

We were pleasantly surprised to find that the replacement of *O*-(2,4-dinitrophenyl)hydroxylamine by *O*-(4-nitrophenyl)-hydroxylamine (4-NPONH$_2$) under the optimized conditions shown in Table 2 with the TIPS enol ether and DMAP as base provided even higher enantioselectivity, as summarized in Scheme 3 (data from repeated experiments). It is noteworthy that *O*-phenylhydroxylamine and *O*-pivaloylhydroxylamine were unreactive under the same conditions (Scheme 3). The rate of disappearance of the starting enol ether was somewhat slower with the *O*-(4-nitrophenyl)hydroxylamine reagent than with *O*-(2,4-dinitrophenyl)hydroxylamine. The rate of reaction of TIPS enol ether decreases markedly as the ratio of CF_3CH_2OH to THF is lowered from 4:1, becoming very slow below 1:1. Because ethanol is not an effective replacement for trifluoroethanol, it seems likely that the role of the latter is to assist amino transfer to rhodium by solvation of or hydrogen bonding to the aryloxide leaving group. Neither *N*-amino-4-(dimethylamino)pyridinium 2,4-dinitrophenolate nor *N*-aminopyridinium iodide were reactive as a nitrogen donor to rhodium of **21** under the conditions that worked with the 2,4-DNPONH$_2$ or 4-NPONH$_2$ reagents.

When the conditions indicated in Scheme 3 were applied to the five- and seven-membered homologues of the TIPS enol ether of 2-phenylcyclohexanone (**22** and **23**) using *O*-(4-nitrophenyl)hydoxylamine as reagent, the desired products, *nor*- and *homo*-ketamine analogs **24** and **25**, were obtained enantioselectively as shown in Scheme 4.

When we applied catalyst **21**, *O*-(4-nitrophenyl)-hydroxylamine, and DMAP to the Kürti−Falck amination of 1-phenylcyclohexene (**26**), we found that aziridine **27** was formed in good yield (80%), but with poor enantioselectivity (32% ee), as summarized in Scheme 5. The rate of reaction was approximately one-third that with the TIPS enol ether of 2-phenylcyclohexanone.

In summary, we have described a useful new method for the direct enantioselective conversion of certain silyl enol ether of cyclic ketones to α-amino ketones using the chiral Rh(II) catalyst **21** with *O*-(4-nitrophenyl)hydroxylamine as amine donor in the presence of 4-*N*,*N*-dimethylamino pyridine (DMAP). The reaction is highly accelerated when trifluoroethanol is utilized as the reaction medium, which appears to indicate that hydrogen bonding of CF_3CH_2OH to the *O*-arylhydroxylamine and transfer of NH_2 to the Rh(II) catalyst **21** is likely to be the rate-limiting step. The favorable effects of DMAP and *O*-(4-nitrophenyl)hydroxylamine on enantioselectivity may be due to their presence in the active amination Rh complex, such as expressed by formula **28**,[17−19] wherein **28** may be either a hydrogen bonded or contact ion pair. A possible route to **28** is depicted in Scheme 6. Further discussion of the mechanistic basis of enantioselectivity requires a more detailed study.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03733.

Synthetic procedures, NMR, and HPLC (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Rush, A. J.; Trivedi, M. H.; Wisniewski, S. R.; Nierenberg, A. A.; Stewart, J. W.; Warden, D.; Niederehe, G.; Thase, M. E.; Lavori, P. W.; Lebowitz, B. D.; McGrath, P. J.; Rosenbaum, J. F.; Sackeim, H. A.; Kupfer, D. J.; Luther, J.; Fava, M. Am *Am. J. Psychiatry* **2006**, *163*, 1905−1917.

(2) Elia, N.; Tramer, M. R. *Pain* **2005**, *113*, 61−70.

(3) Zarate, C. A., Jr.; Singh, J. B.; Carlson, P. J.; Brutsche, N. E.; Ameli, R.; Luckenbaugh, D. A.; Charney, D. S.; Manji, H. K. *Arch. Gen. Psychiatry* **2006**, *63*, 856−864.

(4) Duman, R. S.; Aghajanian, G. K.; Sanacora, G.; Krystal, J. *Nat. Med.* **2016**, *22*, 238−249.

(5) (a) Zanos, P.; Moaddel, R.; Morris, P. J.; Georgiou, P.; Fischell, J.; Elmer, G. I.; Alkondon, M.; Yuan, P.; Pribut, H. J.; Singh, N. S.; Dossou, K. S. S.; Fang, Y.; Huang, X.-P.; Mayo, C. L.; Wainer, I. W.; Albuquerque, E. X.; Thompson, S. M.; Thomas, C. J.; Zarate, C. A., Jr.; Gould, T. D. *Nature* **2016**, *533*, 481−486. (b) The absolute configuration and structure of **2** were established by X-ray diffraction analysis of the hydrochloride salt.

(6) Yang, Y.; Cui, Y.; San, K.; Dong, Y.; Ni, Z.; Ma, S.; Hu, H. *Nature* **2018**, *554*, 317−322.

(7) (a) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevid, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254−6255. (b) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306−15309.

(8) Trost, B. M.; Tracy, J. S.; Saget, T. *Chem. Sci.* **2018**, *9*, 2975−2980.

(9) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044−16045.

(10) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205−3208.

(11) Han, Y.; Mahender Reddy, K.; Corey, E. J. *Org. Lett.* **2017**, *19*, 5224−5227.

(12) da Silva Gomes, R. S.; Mahender Reddy, K.; Corey, E. J. *Org. Lett.* **2018**, *20*, 6310−6313.

(13) See, for example, (a) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758−762. (b) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042−3051. (c) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911−922.

(14) See (a) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kgrti, L.; Falck, J. R. *Science* **2014**, *343*, 61−65. (b) Ma, Z.; Zhou, Z.; Kürti, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 9886−9890.

(15) The structure of the methyl ester corresponding to complex **21** has been established by X-ray crystallographic analysis; see (a) Wang, Y.; Wolf, J.; Zavalij, P.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1439−1442. (b) Xu, X.; Wang, X.; Liu, Y.; Doyle, M. P. *J. Org. Chem.* **2014**, *79*, 12185−12190.

(16) The α-amination reaction of the silyl enol ethers of 2-phenylcyclohexanone formed a mixture of 2-amino-2-phenylcyclohexanone (**5**) and the corresponding silyl enol ether, 1-amino-1-phenyl-2-silyloxycyclohex-2-ene. Treatment of the reaction mixture with TBAF converts the latter to the desired product **5**.

(17) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223−14230.

(18) The Lewis acid character of Rh in complexes such as **21** is clear from catalysis (ref 15) and numerous studies of such coordination compounds.

(19) The ^{1}H NMR spectrum of the complex **21** undergoes change in the presence of DMAP (see SI).

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