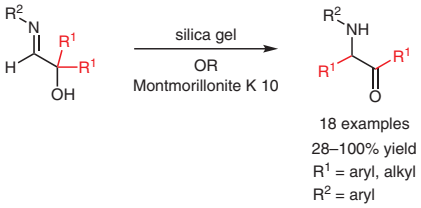
Synlett X. Zhang et al. Letter

The Acceleration of the Rearrangement of α-Hydroxy Aldimines by Lewis or Brønsted Acids

Xin Zhang
Yijing Dai
William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA
wulff@chemistry.msu.edu



Received: 03.08.2018
Accepted after revision: 05.08.2018
Published online: 28.08.2018
DOI: 10.1055/s-0037-1610262; Art ID: st-2018-b0374-l

Abstract An efficient method was developed for the synthesis of α-amino ketones from α-hydroxy imines. The reaction occurs through an α-iminol rearrangement involving the migration of a substituent of the carbinol carbon to the imine carbon. The optimal catalysts were found to be silica gel or montmorillonite K 10, which effected migration of a variety of aryl and alkyl substituents in high yields. The rearrangement can also be carried out on imines generated in situ from aldehydes and amines in essentially the same yields as those from the preformed imines.

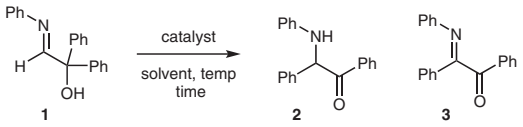
Key words iminol rearrangement, silica gel, montmorillonite, catalysis, amino ketone, hydroxy imines

The α-iminol rearrangement converts an α-hydroxy imine into an α-amino ketone. The history and the development of this reaction have been documented in a review that appeared in 2003;[1] subsequently, there have been many additional examples of this reaction.[2,3] The rearrangement is reversible and the equilibrium can lie either with the ketone or the imine; although this very much depends on the structure of the substrate, typically the equilibrium lies with the ketone. In the presence of a protic acid the equilibrium is driven toward the α-amino ketone because the amine salt is not an active participant in the equilibrium. Most examples reported in the literature involved thermal conditions (about 150–200°C), but the reaction can be accelerated by simple Brønsted acids,[1,2] transition-metal Lewis acids,[2f,j,r] or, in some cases, by alkoxide bases.[1]

We recently reported the first catalytic asymmetric α-iminol rearrangement promoted by a VANOL (3,3′-diphenyl-2,2′-binaphthalen-1-ol) complex of zirconium.[4]

All the reported examples of the α-iminol rearrangement involve imines derived from ketones and therefore it was of interest to study the rearrangement of α-hydroxy aldimines in the presence or absence of simple Brønsted and Lewis acids.[5] The test substrate **1** was subjected to strictly thermal conditions in the presence of air, and it was found that the product **2** could not be detected after heating at 80°C for 42h (Table1, entry 1). Increasing the temperature to 150°C for two hours gave the rearrangement product **2** in 20% yield, along with a 30% recovery of **1** and a 50% yield of the imine **3**, which presumably results from the aerial oxidation of the amine **2**. Acetic acid and sulfuric acid were not effective catalysts, except when the latter was used in DMF as solvent, which gave a 90% yield of **2** in the presence of air (entry 8). One equivalent of 4-toluenesulfonic acid hydrate gave a 56% yield of **2** along with a 44% yield of the aldehyde resulting from the hydrolysis of **1** (entry 10). Lewis acids including zinc, copper, and scandium triflates gave moderate yields under certain conditions, but the none of these reactions could be optimized to provide useful levels of product. A useful outcome was also not realized with the reaction mediated by sodium ethoxide, which gave 100% conversion to a complex mixture of products. Finally, it was found that a very efficient and clean rearrangement of **1** could be affected with either silica gel or montmorillonite K 10 as catalyst, which gave 95 and 100% yields at 80 and 60°C, respectively (entries 22 and 23).

Table 1 Effects of Brønsted and Lewis acids on the α-Iminol Rearrangement[a]



1 2 3

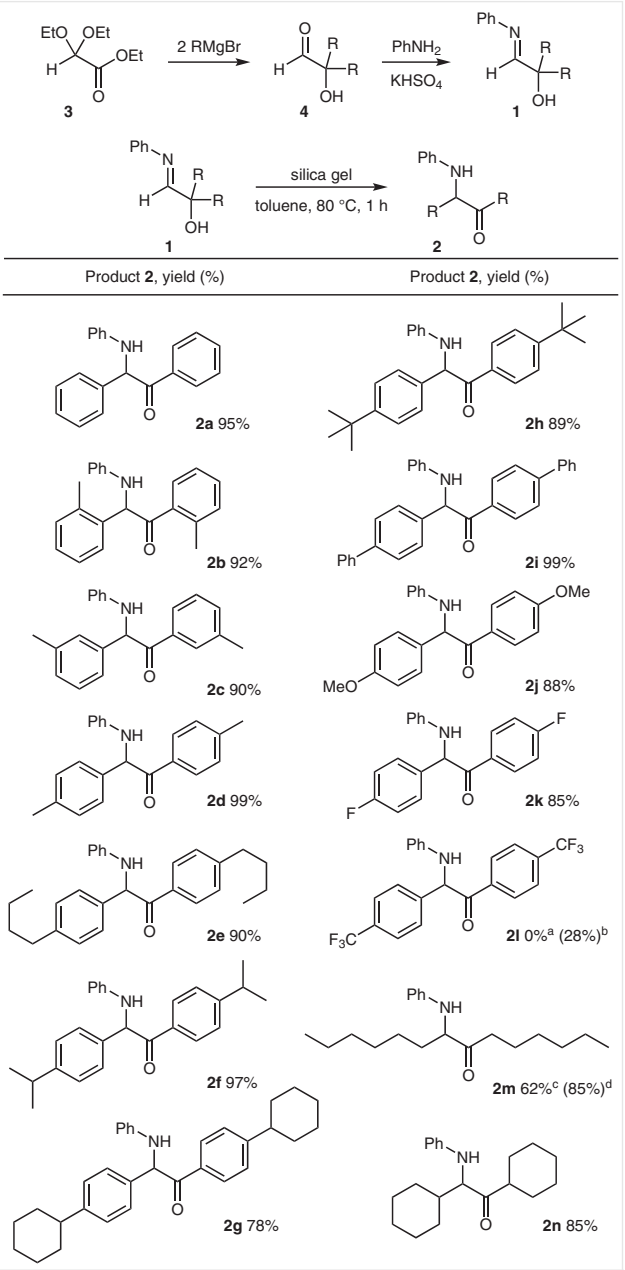
Entry	Catalyst	Catalyst amount	Solvent	T (°C)	Time (h)	Yield[b] (%) of **2**
1	–	–	toluene	80	42	0
2	–	–	mesitylene	150	2	20[c]
3	HOAc	10 equiv	toluene	80	10	–[d]
4	HOAc	1 equiv	toluene	80	15	<1[e]
5	HOAc	1 equiv	DMF	80	1	0[f]
6	H_2SO_4	1 equiv	toluene	80	1	–[g]
7	H_2SO_4/SiO_2	1 equiv	toluene	60	1.5	13
8	H_2SO_4	1 equiv	DMF	80	1	90
9	H_2SO_4	0.1 equiv	DMF	80	3.5	0[f]
10	$TsOH·H_2O$	1 equiv	DMF	80	1	56[h]
11	$Zn(OTf)_2$	1 equiv	DMF	80	2	9[i]
12	$Zn(OTf)_2$	1 equiv	DMF	80	1	–[j]
13	$Zn(OTf)_2$	1 equiv	toluene	80	1	25[k]
14	$Zn(OTf)_2$	1 equiv	$PhCF_3$	80	1	30
15	$Cu(OTf)_2$	1 equiv	DMF	80	1	0[l]
16	$Cu(OTf)_2$	1 equiv	toluene	80	1	–[m]
17	$Cu(OTf)_2$	1 equiv	$PhCF_3$	80	1	38
18	$Sc(OTf)_2$	1 equiv	DMF	80	1	71
19	$Sc(OTf)_2$	1 equiv	$PhCF_3$	80	1	50
20	NaOEt	1 equiv	EtOH	80	1	–[n]
21	silica gel	100 wt%	toluene	60	2	30[o]
22	silica gel	100 wt%	toluene	80	1	95[p]
23	K 10[q]	100 wt%	toluene	60	1.5	100

[a] Unless otherwise specified, all reactions were carried out on 0.1 mmol scale in the presence of air.
[b] Yield determined from the ^1H NMR spectrum of the crude reaction mixture with triphenylmethane as internal standard.
[c] A 30% recovery of **1** and a 50% yield of **3** were obtained.
[d] A 40% recovery of **1** and a 60% yield of **3** were obtained.
[e] >99% recovery of **1**;<1% formation of **2**.
[f] 100% recovery of **1**.
[g] This reaction gave an insoluble black resin.
[h] A 44% yield of aldehyde **4** from hydrolysis of **1** was also obtained.
[i] 91% recovery of **1**.
[j] 70% recovery of **1**.
[k] 100% conversion.
[l] 30% recovery of **1**.
[m] 50% recovery of **1**
[n] 100% conversion; complex mixture obtained.
[o] 70% conversion.
[p] With a different batch of silica gel, the yield was 87% after 2h.
[q] Montmorillonite K 10.

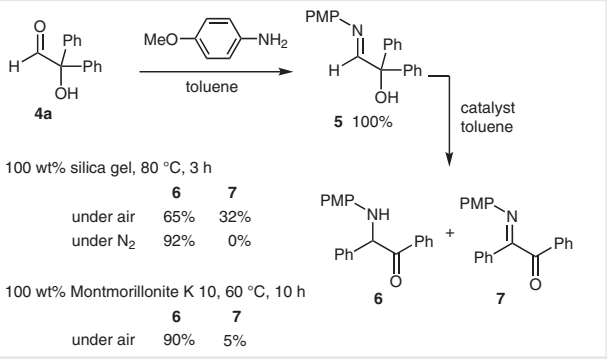
We then turned our attention to investigating the scope of the silica gel-mediated rearrangement with a variety of α-iminols **1**, and the results are presented in Scheme 2.[6] The syntheses of the rearrangement precursors **1** all began from the commercially available ethyl diethoxyacetate (**3**) and the appropriate Grignard reagent.[4] The silica gel-mediated rearrangements were carried out at 80°C for one hour in the presence of air. A variety of aryl groups in the iminol gave excellent yields when a methyl group was incorporated in any of the three positions of the arene, including the *ortho*-position. Incorporation of larger groups such as phenyl and isobutyl in the *para*-positions also resulted in excellent yields (89–99%). An excellent yield was also observed with the electron-rich *para*-anisyl group (88%), but the reaction of the electron-withdrawing *para*-trifluoromethyl-substituted reactant was particularly problematic. Under the standard conditions, none of the expected α-amino ketone **2l** was obtained, and the reaction was very slow, going only to 20% completion in 24 hours. The only product observed was the α-ketoimine resulting from air oxidation of **2l**. It was surprising that the electron-rich α-amino ketone **2j** was not more susceptible to air oxidation to an imine. When the rearrangement of **1l** was carried out under nitrogen, ketone **2l** was isolated, but only in 28% yield with montmorillonite K-10 as catalyst. The reaction of alkyl-substituted iminols also gave good yields. The biscyclohexyl iminol **1n** gave the α-amino ketone **2n** in 85% yield. The rearrangement of the bishexyl iminol **1m** was a little slower and required a temperature of 90°C to go to completion, giving **2m** in 62% yield. The yield was increased to 85% by using montmorillonite K-10 (60°C, 10h).

It was determined that this method could be extended to the synthesis of α-amino ketones with a removable protecting group on the nitrogen atom. Reaction of aldehyde **4a** with 4-methoxyaniline gave the imine **5** quantitatively; heating this compound at 80°C with silica gel gave the desired α-amino ketone **6** in 65% yield, along with the oxidized product **7** in 32% yield (Scheme 2). The oxidation product **7** was clearly the result of aerial oxidation, because it was completely absent when the same reaction was performed under a nitrogen atmosphere, where a 92% yield of **6** was obtained. Oxidation with air was much less of a problem with montmorillonite K 10 as catalyst, because this gave α-amino ketone **6** in 90% yield along with only a 5% yield of **7**.

An additional advantage of the present protocol for the α-iminol rearrangement over those with more-conventional catalysts is its toleration of acid-sensitive groups, as illustrated by the rearrangement of iminol **8** bearing a TBS ether group (Table2). With sulfuric acid as catalyst, the rearrangement occurred at 80°C with concomitant loss of the TBS group to give the alcohol **10** in 56% yield. In contrast, the rearrangement with montmorillonite K 10at 70°C gave a 96% yield of the α-amino ketone **9** with an intact TBS group.

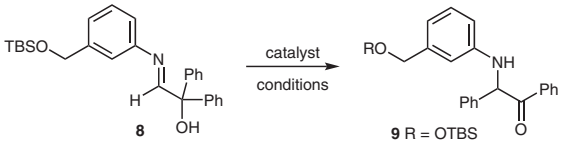


Scheme 1 Substrate scope for the α-iminol rearrangement of iminols **1** with silica gel. Unless otherwise specified, all reactions were carried out with imine **1** (0.1 mmol) and silica gel (100 wt%) gel in toluene at 80 °C for 1 h in the presence of air. The reported yield is that of the isolated material purified by silica gel chromatography. [a] The reaction time was 24 h and the conversion was 20%. The only product observed was the α-keto imine resulting from aerial oxidation of **2l**. [b] Reaction with 100 wt% montmorillonite K 10 at 70 °C for 24 h under a N_2 atmosphere. [c] Reaction temperature: 90 °C. [d] Reaction with 100 wt% montmorillonite K 10 at 60 °C for 10 h.



Scheme 2 α-Iminol rearrangement of imine **5**

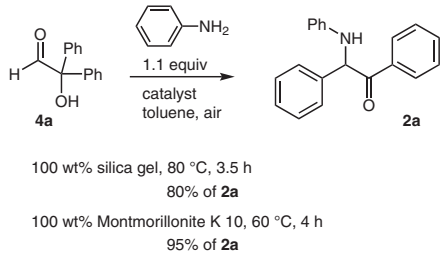
Table 2 α-Iminol Rearrangement in the Presence of a Silyl Ether



Catalyst	Catalyst amount	Solvent	T (°C)	Time (h)	Yield[b] (%) of **9**	Yield[b] (%) of **10**
H_2SO_4	1 equiv	DMF	80	1	–	56
silica gel	100 wt%	toluene	80	1	70	–
K 10[c]	100 wt%	toluene	70	2	96	–

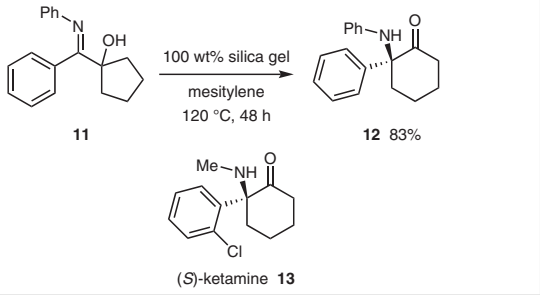
[a] Unless otherwise specified, all reactions were carried out on a 0.1 mmol scale in the presence of air.
[b] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture with triphenylmethane as internal standard.
[c] Montmorillonite K 10.

It was also found that the protocol for the α-iminol rearrangement can be greatly simplified by combining the imine formation and subsequent rearrangement in a single step (Scheme 3). Heating the aldehyde **4a** with 1.1 equivalents of aniline at 80 °C in air in the presence of silica gel or montmorillonite K 10 gave the α-amino ketone **2a** in 80% and 95% yield, respectively.



Scheme 3 Concomitant imine formation and α-iminol rearrangement

We were able to extend this rearrangement to the ketimine **11**, prepared according to the method reported by Stevens et al.[7] Heating imine **11** with silica gel at 120°C led to ring expansion and the formation of the α-amino ketone **12** in 83% yield (Scheme 4). This transformation demonstrates that the α-iminol rearrangement can be used to access analogues of ketamine **13**, which has been used since 1963 as a short-term anesthetic.[2a,8]



Scheme 4 Synthesis of a ketamine analogue through an α-iminol rearrangement

In conclusion, we found that the α-iminol rearrangement of aldimines and ketimines can be affected with silica gel or montmorillonite K 10 to give the corresponding α-amino ketones in excellent yields at moderate temperatures (60–80°C) in the presence of air. The reaction scope is general for the migration of a variety of aryl and alkyl groups, the only exception observed being that of the 4-trifluoromethyl group.These catalysts also are effective for the rearrangement of imines generated in situ from aldehydes and an amine. The conditions are sufficiently mild to accommodate a silyl enol ether without cleavage or to permit extension to imines of ketones, as illustrated for the synthesis of an analogue of the anesthetic ketamine.

Funding Information

This work was supported by a grant from the National Institute of General Medical Sciences (GM094478).

References and Notes

(1) Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477.
(2) (a) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2177. (b) Liu, Y.; McWhorter, W. W. Jr; Hadden, C. E. *Org. Lett.* **2003**, *5*, 333. (c) Liu, Y.; McWhorter, W. W. Jr *J. Org. Chem.* **2003**, *68*, 2618. (d) Liu, Y.; McWhorter, W. W. Jr *J. Am. Chem. Soc.* **2003**, *125*, 4240. (e) Binder, J. T.; Crone, B.; Kirsch, S. F.; Liébert, C.; Menz, H. *Eur. J. Org. Chem.* **2007**, 1636. (f) Movassaghi, M.; Schmidt, M. A.; Ashenjurst, J. A. *Org. Lett.* **2008**, *10*, 4009. (g) Fuji, H.; Ogawa, R.; Ohata, K.; Nemoto, T.; Makajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem.* **2009**, *17*, 5983. (h) Lu, G.; Katoh, A.; Zhang, Z.; Hu, Z.; Lei, P.; Kimura, M. *J. Heterocycl. Chem.* **2010**, *47*, 932. (i) Yang, T.-F.; Shen, C.-H.; Hsu, C.-T.; Chen, L.-H.; Chuang, C.-H. *Tetrahedron* **2010**, *66*, 8734. (j) Qi, X.; Bao, H.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 10050. (k) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768. (l) Liu, S.; Hao, X.-J. *Tetrahedron Lett.* **2011**, *52*, 5640. (m) Harayan, A. R. N.; Sarpong, R. *Org. Biomol. Chem.* **2012**, *10*, 70. (n) Fustero, S.; Albert, L.; Maten, N.; Chiva, G.; Miró, J.; González, J.; Aceña, J. L. *Chem. Eur. J.* **2012**, *18*, 3753. (o) Yang, T.-F.; Chen, L.-H.; Kao, L.-T.; Chuang, C.-H.; Chen, Y.-Y. *J. Chin. Chem. Soc. (Weinheim, Ger.)* **2012**, *59*, 378. (p) Hays, P. A.; Casale, J. F.; Berrier, A. L. *Microgram J.* **2012**, *9*, 3. (q) Ahmadi, A.; Khalili, M.; Hajikhani, R.; Hosseini, H.; Afhin, N.; Nahri-Niknafs, B. *Med. Chem. (Sharjah, United Arab Emirates)* **2012**, *8*, 246. (r) Liu, S.; Scotti, J. S.; Kozmin, S. A. *J. Org. Chem.* **2013**, *78*, 8645. (s) Zhang, Z.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2013**, *15*, 4822. (t) Frongia, A.; Secci, F.; Capitta, F.; Piras, P. P.; Sanna, M. L. *Chem. Commun.* **2013**, *49*, 8812.
(3) For recent examples of other methods for the synthesis of α-amino ketones, see: (a) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852. (b) Liu, L.; Zheng, Y.; Hu, X.; Lian, C.; Yuan, W.; Zhang, X. *Chem. Res. Chin. Univ.* **2014**, *30*, 235. (c) Farahi, M.; Tamaddon, F.; Karami, B.; Pasdar, S. *Tetrahedron Lett.* **2015**, *56*, 1887. (d) Wen, W.; Zeng, Y.; Peng, L.-Y.; Fu, L.-N.; Guo, Q.-X. *Org. Lett.* **2015**, *17*, 3922. (e) Tamaddon, F.; Tafti, A. D. *Synlett* **2016**, *27*, 2217. (f) Lin, L.; Bai, X.; Ye, X.; Zhao, X.; Tan, C.-H.; Jiang, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 13842.
(4) Zhang, X.; Staples, R. J.; Rheingold, A. L.; Wulff, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 13971.
(5) Our recent report on catalytic asymmetric α-iminol rearrangement is the single exception in the case of aldimines (see ref. 4).
(6) **1,2-Diphenyl-2-(phenylamino)ethanone (2a); Typical Procedure**
A slurry of imine **1a** (0.0287 g, 0.100 mmol) and silica gel (0.0280 g) in toluene (0.3 mL) was placed in a 20 mL vial under air, and the vial was sealed with a screw-cap and heated at 80 °C for 1 h. Alternatively, a slurry of **1a** (0.0287 g, 0.100 mmol) and montmorillonite K (0.0285 g) in toluene (0.3 mL) was placed in a 20 mL vial under air, and the vial was sealed with a screw-cap and heated at 60 °C for 1.5 h. After the solution had cooled to r.t., it was concentrated on a rotary evaporator and the residue was purified by flash column chromatography [silica gel, hexane–$CHCl_3$ (1:2)] to give a yellow solid; yield: 0.0272 g (95%, 0.0948 mmol) (with silica gel) or 0.0287 g (100%) (with montmorillonite K 10); mp = 89–92 °C.^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.62 (br s, 1 H), 6.04 (s, 1 H), 6.70–6.72 (m, 3 H), 7.14 (t, *J* = 8.0 Hz, 2 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 2 H), 7.42–7.46 (m, 4 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 8.00 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.88, 113.72, 118.04, 128.11, 128.15, 128.66, 128.85, 129.04, 129.22, 133.49, 135.05, 137.56, 145.90, 196.97.
(7) Stevens, C. L.; Thuillier, A.; Daniher, F. A. *J. Org. Chem.* **1965**, *30*, 2962.
(8) Yokoyama, R.; Matsumoto, S.; Momura, S.; Higaki, T.; Yokoyama, T.; Kiyooka, S.-i. *Tetrahedron* **2009**, *65*, 5181.