JOC*Note*

One-Step $RhCl_3$-Catalyzed Deprotection of Acyclic *N*-Allyl Amides

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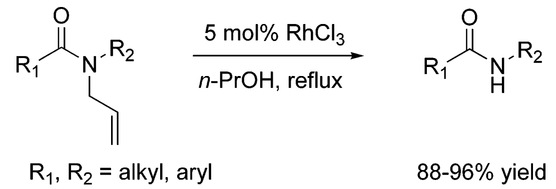
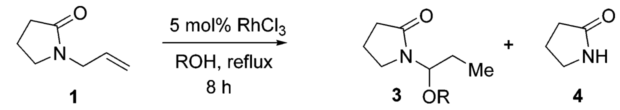
Received March 16, 2007



A convenient one-step $RhCl_3$-catalyzed deprotection of acyclic *N*-allyl amides is described. Preliminary mechanistic studies reveal that the key to the success of the one-step deprotection process is the dual function of $RhCl_3$ in alcohol solvents. Reaction of $RhCl_3$ with *n*-PrOH not only provides an active rhodium hydride species to catalyze isomerization of *N*-allyl amides to corresponding enamides but also generates a crucial catalytic amount of HCl to convert the enamides to deallylated amides through *N*,*O*-acetal exchange.

The prevalence of amides in natural products and pharmaceuticals underscores the need for practical methods for their synthesis, including protecting group strategies. Among the more versatile of protecting groups for multistep organic synthesis is the allyl group. While allyl deprotection of alcohols and amines is a facile process that can be carried out with a wide variety of reagents and conditions, the deprotection of allyl amides is considerably more challenging,[1] and few methods are currently available. The most common approach is a two-step procedure involving isomerization of the double bond to an enamide by the action of Rh[2] or Ru[2a,3] catalysis[4] and subsequent acidic[2d,e] or oxidative[2c,3b] cleavage of the isolated enamide. By contrast, one-step direct deprotection procedures are relatively rare. The use of π-allyl chemistry for direct amide deprotection is limited to one report involving $Ni(dppp)Cl_2$ and $AlMe_3$ in refluxing toluene.[5] Recently, a one-step oxidative cleavage protocol was developed that involved the use of excess oxidizing agents.[6] Given considerations of functional group compatibility, a convenient one-step deprotection process that operated under orthogonal conditions would improve the attractiveness of the allyl protecting group for amide synthesis.

TABLE 1. Reactivity Profile of 1 as a Function of Alcohol Solvent[a]



R	**3:4**
Me	1:0
Et	4:1
n-Pr (**3**)	2:1

[a] Molar ratios based on HPLC analysis of crude reaction mixture measured against known samples.

Despite the absence of any reports using Pd π-allyl chemistry for direct amide deprotection, we briefly investigated this reaction by subjecting *N*-allyl-2-pyrrolidone (**1**) to conditions that were recently successful for the deallylation of a pyrrolidine.[7] In this event, the use of 1 mol % $Pd_2(dba)_3$, 2 mol % dppb, and 1.1 equiv of thiosalicylic acid in THF failed to afford any reaction products. Given this result, our focus shifted toward the known Rh- and Ru-catalyzed reactions. We envisioned that the mild conditions of these metal-catalyzed olefin isomerizations could be combined in situ with a mild acidic cleavage of the enamide intermediate.[8] In this Note, we report the successful development of this strategy into a one-step deprotection of *N*-allyl amides and provide preliminary mechanistic features of this transformation.

Our investigations focused on rhodium catalysts due to their high functional group tolerance. *N*-Allyl-2-pyrrolidone (**1**) was subjected to conditions reported for the isomerization of an *N*-allyl protected lactam to an enamide. A screen of catalysts revealed that $(Ph_3P)_4RhH$ gave the expected enamide **2**[2e,4e] in 85% yield (eq 1), whereas by comparison, Wilkinson's catalyst afforded **1** in only 40% yield (50% conversion). The use of H_2O or dilute HCl as a cosolvent, as a means of hydrolyzing the enamide in situ, did not affect the product distribution and resulted in lower yields and conversion. The addition of anhydrous acids such as benzenesulfonic acid

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New York, 2006. For example, while Pd catalysis is well known for the deprotection of *N*-allyl amines, there are no reports for the use of Pd catalysis the deprotection of *N*-allyl amides.

(2) (a) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (b) Nemeto, H.; Jimenez, H. N.; Yamamoto, Y. *Chem. Commun.* **1990**, 304. (c) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173. (d) Cainelli, G.; Giacomini, D.; Galetti, P. *Synthesis* **2000**, 289. (e) Cainelli, G.; DaCol, M.; Galetti, P.; Giacomini, D. *Synthesis* **1997**, 923. (f) Chiusoli, G. P.; Costa, M.; Fiore, A. *Chem. Commun.* **1990**, 303.

(3) (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Tetrahedron Lett.* **2003**, *43*, 8693. (c) For a report on the Ru-catalyzed isomerization but not applied to *N*-allyl deprotection, see: Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257.

(4) Only one report for the use of Pd in this isomerization process has appeared: (a) Dallavalle, S.; Merlini, L. *Tetrahedron Lett.* **2002**, *43*, 1835. For Fe, see: (b) Sergeyev, S.; Hesse, M. *Synlett* **2002**, 1313 and (c) Hubert, A. J., Feron, A.; Goebbels, G.; Warin, R.; Teyssie, P. *J. Chem. Soc., Perkin Trans. 2* **1997**, 11. For Co, see: (d) Onishi, M.; Oishi, S.; Sakaguchi, M.; Takaki, I.; Kiraki, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3925. For Ir, see: (e) Neugnot, B.; Cintrat, J.-C.; Rousseau, B. *Tetrahedron* **2004**, *60*, 3575.

(5) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679.

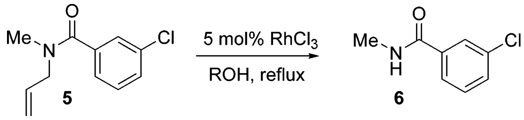
(6) Kitov, P. I.; Bundle, D. R. *Org. Lett.* **2001**, *3*, 2835. For an application of this reaction, see: Clement, E. C.; Carlier, P. R. *Tetrahedron Lett.* **2005**, *45*, 3633.

(7) Xu, F.; Murry, J. A.; Simmons, B. A.; Corley, E.; Fitch, K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *8*, 3885. See Experimental Section.

(8) A similar strategy has been documented for the deallylation of allyl ethers but has not been applied to amides: Boss, R.; Scheffold, R. *Angew. Chem. Int. Ed.* **1976**, *88*, 578.

10.1021/jo070553t CCC: $37.00

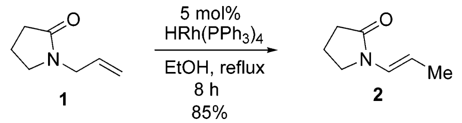
TABLE 2. Reactivity Profile of 5 as a Function of Alcohol Solvent



R	time (h)	yield (%)[a]
Me	8	18
Et	8	90
n-Pr	4	99

[a] Assay yield determined by HPLC by reference of the reaction solution to a solution prepared from analytically pure **4e**.

or HCl similarly resulted in unclean reactions. Interestingly, when $RhCl_3$ was employed under anhydrous conditions without added acid, the observed products were *N*,*O*-acetal **3** and 2-pyrrolidone (**4**) (Table 1). This transformation has not been described thus far in the allylamide literature during olefin isomerization reactions,[9,10] and the observation of **4** signaled the potential to achieve a one-step allyl deprotection process.

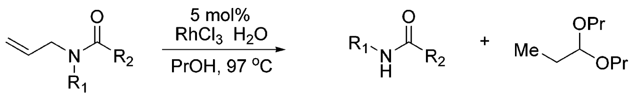


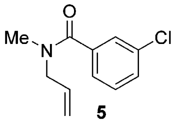
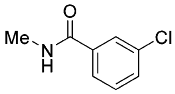
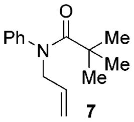
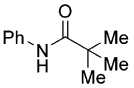
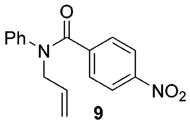
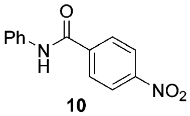
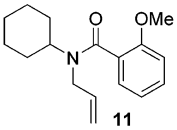
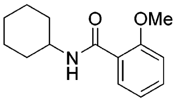
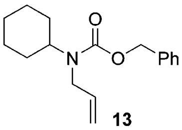
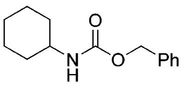
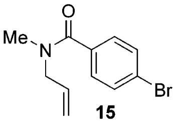
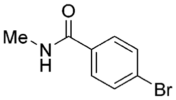
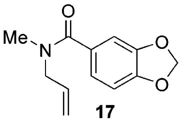
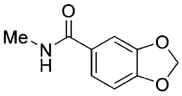
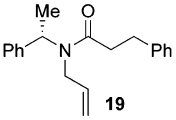
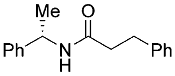
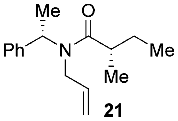
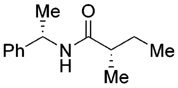
(1)

When acyclic tertiary allylamide **5** was subjected to the $RhCl_3$ reaction conditions in EtOH, the only observed product was the deprotected amide **6** in 90% assay[11] yield (Table 2). Whereas the use of MeOH as the solvent led to poor conversion and only 18% assay yield of **6**, the use of *n*-PrOH afforded **6** in 99% assay yield in 4 h. The identical reactivity profiles observed between *i*-PrOH and *n*-PrOH suggest that the observed solvent effect reflects the function of reaction temperature.[12]

With these results in hand, we set out to establish the generality of the reaction protocol by examining the deallylation of various tertiary amides under $RhCl_3$ catalysis in *n*-PrOH (Table 3). The reaction is tolerant of a wide range of steric and electronic environments. The active catalyst, which is believed to be a rhodium hydride species,[13] is tolerant of aromatic nitro[14] functionalities (entry 3) as well as aryl bromides (entry 6) and Cbz groups (entry 5). The piperonlyoyl acetal group (entry 7), as well as a potentially epimerizable center (entry 9), were also unaffected. For small scale work, the use of a 5 mol % catalyst was convenient for affording high yields of product in relatively short periods of time (<6 h). In cases where the cost of the catalyst or the generation of heavy metal waste is of concern, the catalyst loading can be reduced. For example, deprotection of **7** on a 4 g scale using 2 mol % $RhCl_3$ afforded **8** in 95% yield after 14 h of reaction time.

TABLE 3. Deallylation of *N*-Allylamides[a]



entry	*N*-allyl amide	product	yield (%)[b]
1	 **5**	 **6**	92
2	 **7**	 **8**	96
3	 **9**	 **10**	90
4	 **11**	 **12**	92
5	 **13**	 **14**	93
6	 **15**	 **16**	88
7	 **17**	 **18**	94
8	 **19**	 **20**	96
9	 **21**	 **22**	91

[a] Conditions: 0.5 M solution of *N* = allylamide in *n*-PrOH, heated at reflux. [b] Isolated yield.

The byproduct of these reactions was propionaldehyde dipropyl acetal, which was found in equimolar quantities relative to the secondary amide product as observed by ^{1}H NMR of the

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(9) A structure similar to **2** was observed under HRh(PPh$_3$)$_4$ catalysis but only derived from secondary allyl amides (ref 2b), whereas tertiary allyl amides were shown not to form *N*,*O*-acetals (e.g., **2**). There are no known reports of products resulting from complete deallylation under Rh catalysis.

(10) Use of EtOH as a solvent resulted in a 4:1 ratio, whereas use of MeOH resulted in the exclusive formation of the *N*,*O*-acetal.

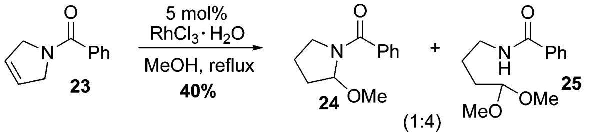
(11) Assay yield is determined by HPLC, comparing the reaction solution to a solution of known concentration prepared from an analytically pure authentic product.

(12) When a MeOH reaction was heated to 100 °C in a sealed tube, a reactivity similar to PrOH was observed. For relevant observations, see ref 2c.

(13) For relevant observations, see: (a) Cramer, R. *J. Am. Chem. Soc.* **1967**, *89*, 1633 and references therein. (b) Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B.; Moore, D. W. *J. Organomet. Chem.* **1967**, *9*, 153. (c) Hirai, H.; Sawai, H.; Ochiai, E.-I.; Makishima, S. *J. Catal.* **1970**, *17*, 119. (d) Su, A. C. *Adv. Organomet. Chem.* **1979**, *17*, 269. These mechanistic studies, including deuterium labeling experiments, suggest rhodium hydride as the active catalyst. A Rh(I) species is likely, as Rh(III) is reduced to Rh(I) in the presence of olefins and alcohol solvents.

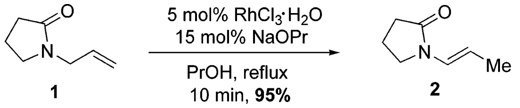
(14) Liou, K. F.; Cheng, C. H. *J. Org. Chem.* **1982**, *47*, 3018. $RhCl_3$ in the presence of alcohols and KOAc reduces nitro-arenes to anilines.

crude reaction mixture. This observation suggested that an initially formed *N*,*O*-acetal undergoes acid-catalyzed acetal exchange with *n*-PrOH to produce the deallylated secondary amide. An interesting illustration of this point was the conversion of allyl amide **23** to a mixture of **24** and **25** (eq 2).[15] Additional evidence in support of this pathway comes from the observation that the *N*,*O*-acetal **3** in Table 1 was the kinetically observed product, while **4** was observed only after prolonged reaction times.



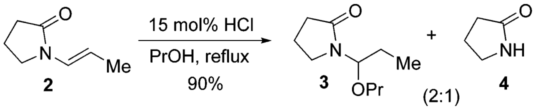
(2)

The conversion of **3** to **4** (eq 1) and **24** to **25** (eq 2) suggests the presence of acid in solution, and indeed, this was observed experimentally as an apparent pH of 4.[16] The acid was presumably in the form of HCl, as $RhCl_3$ liberates HCl in the presence of olefins and alcohol solvents.[13] The role of acid in the overall transformation was probed by subjecting *N*-allyl-2-pyrrolidone (**1**) to modified conditions including 15 mol % NaOPr. In this event, the substrate was rapidly converted to the enamide **2** in 95% yield (eq 3).[17] No other products were observed, even upon prolonged heating.



(3)

Since *N*,*O*-acetal **3** was not observed in the presence of base, we speculated that under the reaction conditions, HCl is responsible not only for acetal exchange but also for acetal formation. Support for this hypothesis was garnered when **2** was converted to a 2:1 mixture of **3** and **4** when subjected to 15 mol % HCl in PrOH at 97 °C in the absence of a rhodium catalyst (eq 4). Interestingly, this is the same ratio observed in Table 1.[18] On the basis of these results, it appears that the essential role of the rhodium catalyst is the isomerization of the double bond.



(4)

In conclusion, we have developed a one-step deprotection of acyclic *N*-allyl amides to secondary NH amides catalyzed by $RhCl_3$ in alcohol solvents. The key to the success of this method is the use of a simple rhodium complex unadorned with ligands and in the absence of base, such that HCl is evolved under the reaction conditions. Following olefin isomerization, at elevated temperatures, HCl catalyzes the conversion of the enamide intermediate to the secondary amide. This convenient procedure improves the utility of the allyl group as a protecting group in amide synthesis.

Experimental Section

General Procedure. A 0.5 M solution of the *N*-allyl amide in anhydrous *n*-PrOH was degassed via N_2 sparging, then $RhCl_3$ (5 mol %) was charged under positive N_2 pressure. The resulting solution was then heated to reflux for 4−6 h, until judged complete by TLC or HPLC. After cooling to room temperature, the solution was diluted with H_2O, and the product was extracted with CH_2Cl_2. The NH amide could be purified by silica gel chromatography, eluting with EtOAc/hexanes. Alternatively, the reaction mixture could be concentrated and directly loaded onto a silica gel column.

Supporting Information Available: General experimental procedures and characterization of **3**, **5**, **6**, **8**−**14**, **16**, and **18**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Determined by ^{1}H NMR analysis of the crude reaction mixture, referring to reported characterization data of **24** and **25**: Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 9483. After 10 h, the combined yield of **6** and **7** was ∼40%. When *n*-PrOH was used as solvent, the combined yield of the analogous products was ∼75%.

(16) Apparent pH was measured by preparing a 1:1 (by volume) solution of the reaction solution and H_2O.

(17) As was the case with the use of Et_3N, $^{i}PrNEt_2$, and Na_2CO_3, the only observed product was **1**.

(18) After 8 h. In the presence of HCl in PrOH, enamide **1** was rapidly converted to *N*,*O*-acetal **2**, which slowly converted to the observed 2:1 mixture. In the case of lactams, the observed ratios may reflect an equilibrium. For example, see: Afinogenov, V. A.; Filimonov, V. D.; Sirotkina, E. E. *Zh. Org. Khim.* **1978**, *14*, 1723.