

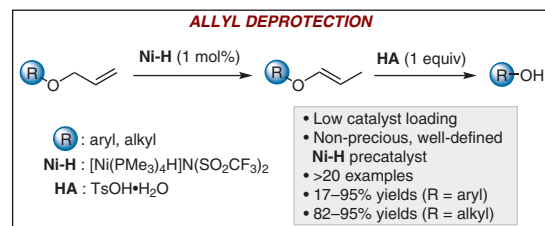
Nickel Hydride Catalyzed Cleavage of Allyl Ethers Induced by Isomerization

Prasad M. Kathe^aAndreas Berkefeld^{*b}Ivana Fleischer^{*a} 

^a Institute of Organic Chemistry, Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
ivana.fleischer@uni-tuebingen.de

^b Institute of Inorganic Chemistry, Faculty of Science and Mathematics, Eberhard Karls University Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
andreas.berkefeld@uni-tuebingen.de

Published as part of the Cluster
Modern Nickel-Catalyzed Reactions



Received: 04.11.2020
Accepted: 27.12.2020
Published online: 22.01.2021
DOI: 10.1055/s-0040-1706683; Art ID: st-2020-k0584-c



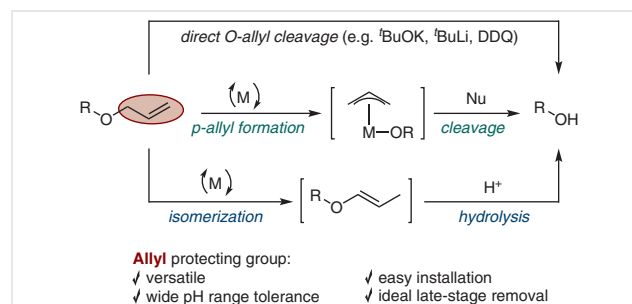
Abstract This report discloses the deallylation of O- and N-allyl functional groups by using a combination of a Ni-H precatalyst and excess Brønsted acid. Key steps are the isomerization of the O- or N-allyl group through Ni-catalyzed double-bond migration followed by Brønsted acid induced O/N–C bond hydrolysis. A variety of functional groups are tolerated in this protocol, highlighting its synthetic value.

Key words nickel catalysis, deprotection, allylic ethers, isomerization, selectivity

The use of protecting groups undoubtedly permits the development of synthetic routes toward desired organic scaffolds. Depending on the requirements in a synthesis, numerous protecting groups for acidic functional groups can be used. The ideal protecting group is complementary to the requisite conditions in the relevant synthetic steps, such as a certain pH range or reagents, and it should not affect the overall desired reactivity. In turn, the protection and deprotection steps should be selective for the particular functionality. Owing to their ubiquitous nature and reactivity in target molecules and intermediates, the presence of hydroxy groups often requires the employment of protecting groups. To address the many needs, a wide range of acetal-, ether- and ester-based protecting groups for hydroxy functionality have been developed.¹

A particularly attractive O-protecting group is allyl, thanks to several factors such as its ease of installation, use of inexpensive and readily available reagents, and stability under various reaction conditions (Scheme 1).² Beside the methods reported for the direct cleavage of allyl groups by using nucleophiles or oxidants,³ those using homogeneous metal catalysts stand out due to their mild reaction conditions and often high selectivity. This has been impressively

demonstrated in several total syntheses of natural compounds.⁴ These reactions usually follow two main mechanisms. The first is based on the formation of a metal allyl intermediate by oxidative addition in the presence of a nucleophile or reducing agent.⁵ The underlying principle in other cases is an initial olefin isomerization (single-bond transposition) to an enol ether, followed by hydrolysis.⁶ Although the isomerization of allylic alcohols, ethers, and related substrates has been studied extensively,⁷ its application or suggested involvement in the deallylation is much less well investigated. Furthermore, the use of nonprecious metals in allyl deprotection methods is rare but clearly desirable.



Scheme 1 General principle and deallylation methodologies

An important feature in deprotection chemistry is the concept of orthogonality, based on the selective removal of a protecting group through differential reactivity and stability.⁸ Recently, Yamada and co-workers reported an elegant method for orthogonal oxidative deprotection of *p*-methylbenzyl ethers in the presence of a *p*-methoxybenzyl group, and vice-versa.⁹ In this context, the chemoselective removal of an allyl group in the presence of a benzyl protecting group is of interest.

During our investigations of nickel hydride/ Brønsted acid catalyzed tandem reactions of allyl ethers for the generation of oxacyclic scaffolds, we observed an unexpected loss of an allyl group under the reaction conditions in some cases.¹⁰ A plausible explanation was an initial isomerization to form an alkenyl ether, as later proven by independent experiments, and subsequent acidic hydrolysis owing to the presence of water in the acid.

Having obtained this result and based on our interest in isomerization reactions¹¹ and nickel catalysis,¹² we envisaged developing a general catalytic process for O-deallylation of ethers. To investigate this further, we chose the O-allylated phenol **1a** as a substrate and the complex nickel hydride $[\text{Ni}(\text{PMe}_3)_4\text{O}]\text{N}(\text{SO}_2\text{CF}_3)_2$ from our original study as a precatalyst, due to its structural simplicity (Table 1). The precatalyst can be synthesized in two steps from bis(cycloocta-1,5-dienyl)nickel(0), the appropriate ligand, and bistriflimidic acid on a gram scale, and can be stored under argon on the bench.¹³ In line with our previous investigations, partial isomerization to the corresponding enol ether occurred. This was followed by subsequent addition of a Brønsted acid in an attempt to obtain 2-methoxyphenol (**2a**). Initial experiments using catalytic amounts of diphenylphosphoric and triflic acid gave only a mixture of the starting material and its isomer (Table 1, entries 1 and 2). Increasing the amount of precatalyst and the use of a weaker acid gave only traces of **2a** (entries 3 and 4). The use of triflic acid (10 mol%) with a prolonged reaction time led to formation of **2a** in a moderate yield of 38% (entry 5).

Upon screening of additional Brønsted acids, we found that a stoichiometric amount of *p*-toluenesulfonic acid monohydrate ($\text{TsOH}\cdot\text{H}_2\text{O}$) gave complete conversion into the phenol (isolated yield 73%) within 30 minutes (Table 1, entry 6). $\text{TsOH}\cdot\text{H}_2\text{O}$ is an attractive option owing to its bench stability, its ease of handling, and its straightforward removal through aqueous workup, after which the product **2a** was determined to be spectroscopically pure without the need for column chromatographic purification. This reaction was also demonstrated at 5 mmol scale (entry 6). A control experiment with $\text{TsOH}\cdot\text{H}_2\text{O}$ in the absence of the catalyst led to complete recovery of unreacted **1a** (entry 7). The precatalyst loading could be decreased to 0.5 mol% without any loss in activity (entry 8). Unfortunately, longer reaction times were deemed necessary to achieve complete conversion when 0.5 equiv of $\text{TsOH}\cdot\text{H}_2\text{O}$ were used (entry 9), and only traces of product were detected when using 1 mol% of acid (entry 10). In addition, we examined whether a catalytic amount of acid could be used in the presence of water to promote the hydrolysis, but we found this not to be the case (entry 11). Addition of all components at the onset of the reaction resulted in 1:1 mixture of **1a** and **2a** (entry 12). Furthermore, the use of slightly weaker camphorsulfonic acid (CSA) required longer reaction times for complete conversion (entry 13).

Table 1 Optimization of the Reaction Conditions for the Ni-Catalyzed Deallylation^a

Entry	Ni-H (mol%)	Acid (mol%)	Time (h)	Yield ^b (%) of 2a
1	1	(PhO) ₂ P(O)OH (8)	1	— ^c
2	1	MeSO ₃ H (8)	1	— ^c
3	5	(PhO) ₂ P(O)OH (120)	0.5	traces
4	5	(PhO) ₂ P(O)OH (200)	0.5	traces
5 ^d	2	F ₃ CSO ₃ H (10)	15	38
6	1	TsOH·H ₂ O (100)	0.5	73 (79) ^e
7	—	TsOH·H ₂ O (100)	1	— ^f
8	0.5	TsOH·H ₂ O (100)	1	84
9	0.5	TsOH·H ₂ O (50)	15	75
10	1	TsOH·H ₂ O (1)	1	traces
11 ^g	0.5	TsOH·H ₂ O (10)	5	traces
12 ^h	0.5	TsOH·H ₂ O (100)	1	(1:1) ⁱ
13	1	CSA (100)	5	(1:4) ⁱ

^a Reaction conditions: **1a** (0.25 mmol), $[\text{Ni}(\text{PMe}_3)_4\text{H}]\text{N}(\text{SO}_2\text{CF}_3)_2$, Brønsted acid, THF (0.16 M), 30 min, RT with Ni-H, then 60 °C for the indicated time with acid.

^b Isolated yield.

^c Mixture of olefin isomers (unreacted **1a** along with enol ethers).

^d 30 min at RT with Ni-H then 15 h at RT with F₃CSO₃H.

^e Yield at 5 mmol scale.

^f **1a** was recovered.

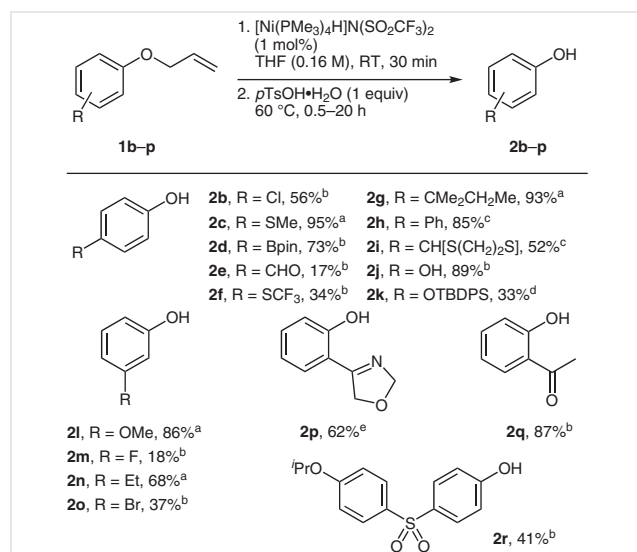
^g With H₂O (1 equiv).

^h All reaction components were added at the start.

ⁱ Ratio **1a**/**2a** determined by ¹H NMR analysis.

Therefore, a system consisting of 1 mol% of Ni-H and 1 equivalent of $\text{TsOH}\cdot\text{H}_2\text{O}$ was chosen for further study of the transformation. With an operationally simple and straightforward protocol in hand, we proceeded to evaluate its generality through deprotection of a variety of substituted O-allylated compounds, starting with aryl allyl ethers **1b–p** (Scheme 2). First, the influence of substituents in the 3- and 4-positions of the phenyl ring was evaluated. Compounds containing electron-donating groups performed much better under the catalytic conditions than those with electron-withdrawing substituents. Ethers **1c**, **1g**, **1h**, **1l**, and **1n** were smoothly deallylated to the corresponding phenols in yields of 68–95%. Note that no column chromatographic purification was necessary to obtain phenols **2c** and **2g** in adequate purity (>95%). The boronate ester **1d** was converted in a satisfactory 73% yield, albeit with a longer reaction time of 20 hours. The 4-trifluoromethylsulfanyl ether **1f** underwent deallylation to give **2f** in 34% yield. Upon testing the halide-substituted ethers **1b**, **1m**, and **1o**, we obtained the corresponding phenols in low to moderate yields of 56,

18, and 37%, respectively. A competing dehalogenation was not observed; low yields are therefore attributable to lower reactivity in both steps. Note that the isomerization to an enol ether was more closely investigated in our previous work; although it was never complete (usually 50%), it did not impact the overall yield if both reactions were successful.



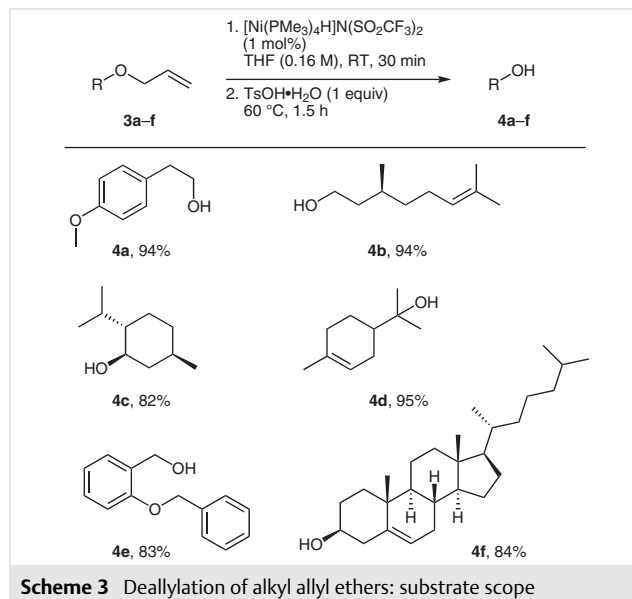
Scheme 2 Substrate scope of Ni-catalyzed deprotection of aryl allyl ethers. Reaction time for the second step: ^a 6 h, ^b 15 h, ^c 10 h, ^d 22 h [camphersulfonic acid (1 equiv)], ^e 15 h [TsOH·H₂O (2 equiv)].

Although the aldehyde **1e** displayed poor reactivity and gave **2e** in only 17% yield, its protected derivative **1i** underwent deallylation to give a 52% yield of **2i**. The allyl group could be successfully removed from the monoprotected hydroquinone **1j**. A selective allyl deprotection was observed in the presence of a *tert*-butyl(diphenyl)silyl group by using a weaker acid (CSA); however, the reaction was slow, and only a 33% yield of **2k** was obtained.

In the presence of an oxazole motif, deallylation to the phenol **2p** occurred in 62% yield; an additional equivalent of TsOH·H₂O was used in this case. In contrast to other substrates with electron-withdrawing groups, the 2-acetyl-substituted ether **1q** was converted into the product in good yield (87%). Moreover, it was found that a sulfone functionality, which is often found in biologically active compounds, can be present in the molecule, as **2r** was obtained in 41% yield.

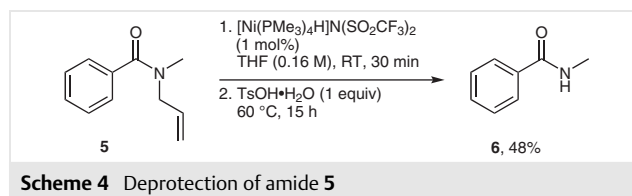
Primary, secondary and tertiary alkyl allyl ethers **3** also underwent facile C–O bond cleavage (Scheme 3). The homobenzylic alcohol **4a**, citronellol (**4b**), (–)-menthol (**4c**), and α -terpenol (**4d**) were obtained from the corresponding allyl ethers in appreciable yields of 82–95%. Note that the allyl protecting group was removed selectively in the presence of a benzyl group in the case of **4e**. Moreover, the protected cholesterol derivative **3f** gave cholesterol (**4f**) with-

out any racemization in 84% yield. The internal double bonds in substrates **3b**, **4d**, and **4f** did not isomerize during the transformation. It is noteworthy that, apart from **4e**, all aliphatic compounds were obtained in high yields without the need for chromatographic purification.



Scheme 3 Deallylation of alkyl allyl ethers: substrate scope

In addition, we also examined the feasibility of deallylation of amides, which has received less attention in the literature¹⁴ despite its potential in, for example, the synthesis of immobilized DNA oligomers, where allyl groups are used to protect the nucleotide bases.¹⁵ Employing our *O*-deallylation method, the deprotection of *N*-allylated benzamide **5** was possible and gave the corresponding product **6** in 48% yield (Scheme 4). To the best of our knowledge, there are no previous reports on the deallylation of amides by employing a nickel catalyst.



Scheme 4 Deprotection of amide **5**

In summary, we have developed a rapid and straightforward protocol for a nickel hydride catalyzed, Brønsted acid promoted deprotection of allyl ethers.¹⁶ The transformation occurs through an initial nickel-catalyzed isomerization of the terminal double bond to the enol ether, which, in turn, is hydrolytically cleaved by the Brønsted acid. The deprotection of the allyl ether moiety occurs chemoselectively in the presence of internal double bonds and other protecting groups, such as the widely used benzyl group. The low catalyst loading along with the generality of the substrate

scope, point to the robustness of the protocol, which is suitable for both aryl and alkyl ethers. Moreover, a deprotection of an *N*-allylamide has been achieved.

Funding Information

Financial support from the German Academic Exchange Service New Delhi, the Deutscher Akademischer Austauschdienst (fellowship for P.K.), and the University of Tübingen is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1706683>.

References and Notes

- (1) (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed; Wiley-Interscience: Hoboken, **2006**, 16. (b) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, 61, 7833.
- (2) Guibé, F. *Tetrahedron* **1997**, 53, 13509.
- (3) (a) Kitov, P. I.; Bundle, D. R. *Org. Lett.* **2001**, 3, 2835. (b) Bailey, W. F.; England, M. D.; Mealy, M. J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* **2000**, 2, 489. (c) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, 37, 6603. (d) Atienza, B. J. P.; Truong, N.; Williams, F. J. *Org. Lett.* **2018**, 20, 6332.
- (4) (a) Walia, M.; Teijaro, C. N.; Gardner, A.; Tran, T.; Kang, J.; Zhao, S.; O'Connor, S. E.; Courdavault, V.; Andrade, R. B. *J. Nat. Prod.* **2020**, 83, 2425. (b) Liu, Z.; Meng, Y.; Yuan, P.; Wang, Z.; Gao, J.-M.; Zheng, H. *Org. Lett.* **2020**, 22, 520. (c) Praveen Kumar, V.; Kishi, Y. *J. Am. Chem. Soc.* **2020**, 142, 14743.
- (5) (a) Gärtner, D.; Konnerth, H.; von Wangelin, A. J. *Catal. Sci. Technol.* **2013**, 3, 2541. (b) Tanaka, S.; Suzuki, Y.; Saburi, H.; Kitamura, M. *Tetrahedron* **2015**, 71, 6559. (c) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, 68, 1146. (d) Taniguchi, T.; Ogasawara, K. *Angew. Chem. Int. Ed.* **1998**, 37, 1136. (e) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, 62, 8932. (f) Mao, Y.; Liu, Y.; Hu, Y.; Wang, L.; Zhang, S.; Wang, W. *ACS Catal.* **2018**, 8, 3016. (g) Hemming, D. S.; Talbot, E. P.; Steel, P. G. *Tetrahedron Lett.* **2017**, 58, 17. (h) Chouhan, M.; Kumar, K.; Sharma, R.; Grover, V.; Nair, V. A. *Tetrahedron Lett.* **2013**, 54, 4540. (i) Giedyk, M.; Turkowska, J.; Lepak, S.; Marculewicz, M.; Proinsias, K.; Gryko, D. *Org. Lett.* **2017**, 19, 2670. (j) Meng, C.; Niu, H.; Ning, J.; Wu, W.; Yi, J. *Molecules* **2020**, 25, 602.
- (6) (a) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, 43, 1839. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, 38, 3224. (c) Varela-Álvarez, A.; Sordo, J. A.; Piedra, E.; Nebra, N.; Cadierno, V.; Gimeno, J. *Chem. Eur. J.* **2011**, 17, 10583.
- (7) (a) Huang, G.; Ke, M.; Tao, Y.; Chen, F. *J. Org. Chem.* **2020**, 85, 5321; corrigendum: *J. Org. Chem.* **2020**, 85, 6830. (b) Gao, W.; Zhang, X.; Xie, X.; Ding, S. *Chem. Commun.* **2020**, 56, 2012. (c) Trost, B. M.; Cregg, J. J.; Quach, N. *J. Am. Chem. Soc.* **2017**, 139, 5133. (d) Bolyog-Nagy, E.; Udvardy, A.; Barczáné-Bertók, A.; Joó, F.; Kathó, A. *Inorg. Chim. Acta* **2017**, 455, 514. (e) Li, H.; Mazet, C. *J. Am. Chem. Soc.* **2015**, 137, 10720. (f) Erbing, E.; Vázquez-Romero, A.; Bermejo Gómez, A.; Platero-Prats, A. E.; Carson, F.; Zou, X.; Tolstoy, P.; Martín-Matute, B. *Chem. Eur. J.* **2016**, 22, 15659.
- (8) Ghosh, B.; Kulkarni, S. S. *Chem. Asian J.* **2020**, 15, 450.
- (9) Ikeuchi, K.; Murasawa, K.; Ohara, K.; Yamada, H. *Org. Lett.* **2019**, 21, 6638.
- (10) Kathe, P. M.; Caciuleanu, A.; Berkefeld, A.; Fleischer, I. *J. Org. Chem.* **2020**, 85, 15183.
- (11) Kathe, P. M.; Fleischer, I. *Org. Lett.* **2019**, 21, 2213.
- (12) (a) Gehrtz, P. H.; Geiger, V.; Schmidt, T.; Sršan, L.; Fleischer, I. *Org. Lett.* **2019**, 21, 50. (b) Gehrtz, P. H.; Kathe, P.; Fleischer, I. *Chem. Eur. J.* **2018**, 24, 8774.
- (13) (a) Neary, M. C.; Quinlivan, P. J.; Parkin, G. *Inorg. Chem.* **2018**, 57, 374. (b) Koch, F.; Berkefeld, A. *Dalton Trans.* **2018**, 47, 10561. (c) Tolman, C. A. *Inorg. Chem.* **1972**, 11, 3128.
- (14) (a) Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem.* **2008**, 2008, 5042. (b) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, 72, 6298. (c) Kamijo, S.; Huo, Z.; Jin, T.; Kanazawa, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, 70, 6389. (d) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, 58, 6109.
- (15) Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, 112, 1691.
- (16) **2-Methoxyphenol (2a): Typical Procedure**
In a glove box, a flame-dried 15 mL Schlenk tube was charged with [Ni(PMe₃)₄H]N(SO₂CF₃)₂ (1.6 mg, 2.48 μmol, 1 mol%). The Schlenk tube was removed from the glove box and anhyd THF (1.5 mL, 0.16 M) was added. 1-(Allyloxy)-2-methoxybenzene (**1a**; 41.1 mg, 0.250 mmol, 1 equiv) was then added under an argon counterflow and the mixture was stirred at RT for 30 min. TsOH·H₂O (1 equiv) was added, and the mixture was refluxed for 1 h. The reaction was quenched by addition of EtOAc (2 mL) and H₂O (2 mL), and the mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were dried (MgSO₄). Rotary evaporation gave pure **2a**, without any chromatographic purification, as a light-brown oil; yield: 26.1 mg (0.21 mmol, 84%). The NMR spectral data matched those reported in the literature.¹⁷ **Note:** The glove box setup for the reaction is not necessary: the catalyst can be stored on the bench under an inert atmosphere.
- (17) Song, L. X.; Wang, H. M.; Yang, Y.; Xu, P. *Bull. Chem. Soc. Jpn.* **2007**, 80, 2185.