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Potassium Base-Catalyzed Michael Additions of Allylic Alcohols to α,β-Unsaturated Amides: Scope and Mechanistic Insights

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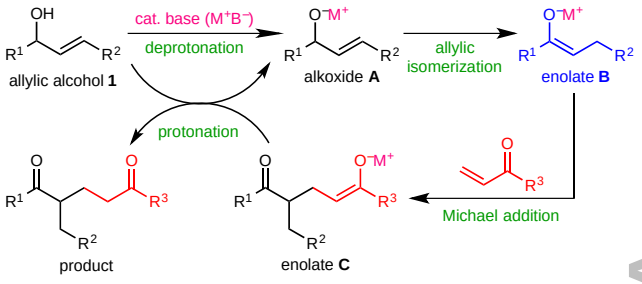
Abstract. We report herein the first KHMDS-catalyzed Michael additions of allylic alcohols to α,β-unsaturated amides through allylic isomerization. The reaction proceeds smoothly in the presence of only 5 mol% of KHMDS to afford a variety of 1,5-ketoamides in high yields. Mechanistic investigations, including experimental and computational studies, reveal that the KHMDS-catalyzed in-situ generation of the enolate from the allylic alcohol through a tunneling-assisted 1,2-hydride shift is the key to the success of this transformation.

Keywords: allylic alcohols; enolates; Michael addition; hydride shift; tunneling

Introduction

Allylic alcohols are versatile synthetic precursors that can participate in a variety of transformations.[1] Among them, isomerization is particularly important because it provides carbonyl compounds in an atom-economical manner. Therefore, a variety of catalytic systems that enable such transformations have been developed, but most use transition-metal catalysts.[2] Although the development of transition-metal-free base-mediated protocols is highly desirable from the viewpoint of green chemistry, they have only been studied sporadically, and most require a stoichiometric or excess amount of a base.[3] In 2015, Kang et al. first reported the NaO^{t}Bu/phenanthroline-catalyzed allylic isomerization under transition-metal-free conditions;[4a] they also conducted a detailed mechanistic study and revealed that the reaction proceeds through a radical pathway. The base-mediated allylic isomerization is also applicable to tandem reactions; i.e., allylic isomerization followed by electrophilic trapping of the in-situ generated enolate.[5,6] However, this type of reaction still requires stoichiometric amounts of base, and a catalytic variant remains unexplored.[7] Our continuing interest in the transformations of unsaturated alcohols[8] prompted us to develop a base-catalyzed tandem allylic isomerization/electrophilic trapping reaction. As outlined in Scheme 1, our working hypothesis for a base-catalyzed tandem reaction relies on the use of α,β-unsaturated carbonyl compounds as electrophiles. Enolate **B**, which is generated from alkoxide **A** through allylic isomerization, undergoes Michael addition to the α,β-unsaturated carbonyl compound to form enolate **C**, which is sufficiently basic to smoothly abstract the OH proton of the next substrate **1**, to give the desired Michael adduct and regenerate **A**. Thus, a catalytic amount of a base (M^+B^-) drives the catalytic cycle even though the base itself is not regenerated.[9] In this paper, we describe the first base-catalyzed tandem allylic isomerization/Michael addition reaction under transition-metal-free conditions. The mechanism of the allylic isomerization process is also discussed based on experimental and computational studies.



Scheme 1. Working hypothesis for a base-catalyzed tandem allylic-isomerization/Michael-addition sequence.

Results and Discussion

Initially, we aimed to identify the appropriate base for the isomerization of an allylic alcohol to the corresponding enolate or homoenolate. To this end, allylic alcohol **1a** was reacted with various bases for 1 h and then trapped with benzyl bromide. The

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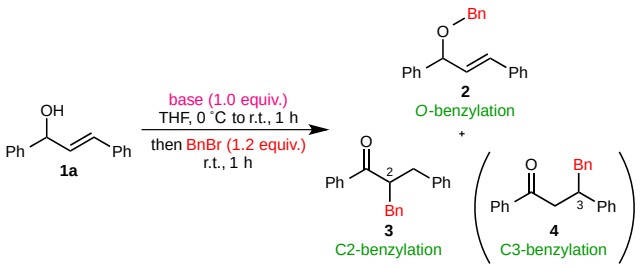
product distribution was monitored by ^{1}H NMR spectroscopy (Table 1). The use of lithium bases led to no observable reaction (entries 1 and 2). When sodium bases were used, large amounts of **1a** were again recovered, while *O*-benzylated ether **2** and C2-benzylated ketone **3** were obtained in low yields (entries 3 and 4). In contrast, we found that **3** was formed in high yields with almost complete consumption of **1a** when potassium bases were employed (entries 5 and 6).[10] In particular, KHMDS was effective for the allylic isomerization of **1a** to the corresponding enolate and its subsequent reaction with benzyl bromide. No C3-benzylated ketone **4** was observed in any reaction.

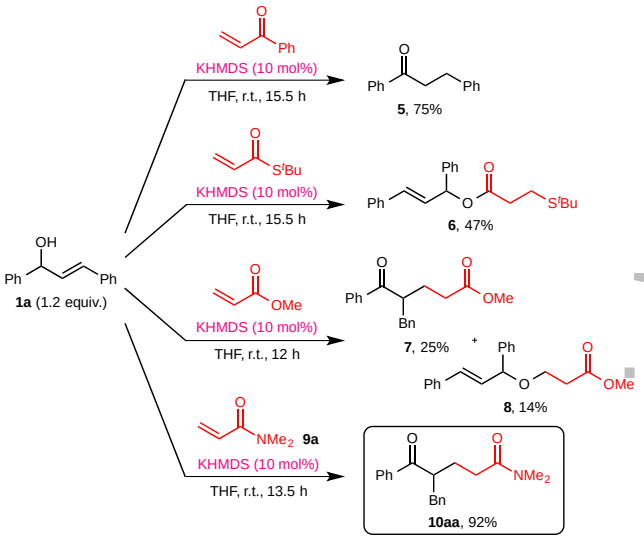
Table 1. Benzylation of allylic alcohol **1a** in the presence of various bases.[a]



Entry	Base	Yield [%][b]		
		1a	**2**	**3**
1	^{n}BuLi	>99	0	0
2	LHMDS	94	0	0
3	NaH[c]	49	17	17
4	NaHMDS	77	15	4
5	KH[c]	0	3	71
6	KHMDS	1	3	94

[a] Conditions: **1a** (0.2 mmol) and base (0.2 mmol) in THF (2 mL) at room temperature for 1 h followed by trapping with benzyl bromide (0.24 mmol) for 1 h. [b] Determined by ^{1}H NMR analysis. [c] With 1.5 equiv. of base.

We next explored the feasibility of the working hypothesis outlined in Scheme 1, using various α,β-unsaturated carbonyl compounds (Scheme 2). When an α,β-unsaturated ketone was selected as the electrophile, no Michael adduct was observed, and only ketone **5** derived from **1a** was obtained in 75% yield. Ester **6** was formed in 47% yield when the α,β-unsaturated thioester was used; **6** was formed by the 1,2-addition of the alkoxide of **1a** to the thioester followed by the thia-Michael addition of KS^{t}Bu to the in-situ-generated α,β-unsaturated ester. While the reaction of **1a** with the α,β-unsaturated ester provided a 25% yield of the desired Michael adduct **7** for the first time, inseparable oxa-Michael adduct **8** was also generated. Gratifyingly, the use of α,β-unsaturated amide **9a** delivered Michael adduct **10aa** in 92% isolated yield without the formation of any side products. The high yield and chemoselective formation of **10aa** is likely due to the lower reactivity of **9a**,[11] which retards the oxa-Michael addition of the alkoxide of **1a** and provides an opportunity for allylic isomerization. It should be noted that this represents the first example of the base-catalyzed *C*-addition of an allylic alcohol to an electrophile other than a proton.



Scheme 2. The KHMDS-catalyzed tandem allylic-isomerization/Michael-addition reaction.

We next investigated the allylic alcohol substrate scope (Table 2). Optimization studies revealed that the reaction of **1a** with **9a** was complete in 1.5 h in the presence of only 5 mol% of KHMDS.[12] A wide range of allylic alcohols **1** underwent successive allylic isomerization and Michael addition to **9a**, to provide the corresponding 1,5-ketoamides **10** in good-to-excellent yields. This reaction tolerates a variety of functionalities, such as ether, halo, trifluoromethyl, cyano, furyl, thienyl, and pyridyl groups.[13] Although the reaction of **1q** devoid of substituent at the 3-position was sluggish, giving **10qa** in only 20% yield,[14] the yield improved to 88% when the aryl group was changed from phenyl to 2-pyridyl, as in **10ra**. Methyl-substituted allylic alcohol **1s** was also a suitable substrate. Unfortunately, allylic alcohols bearing an alkyl group at the C1 position could not be employed in this reaction because such substrates did not undergo the allylic isomerization.[15]

Table 2. Substrate scope of allylic alcohols **1**.[a]

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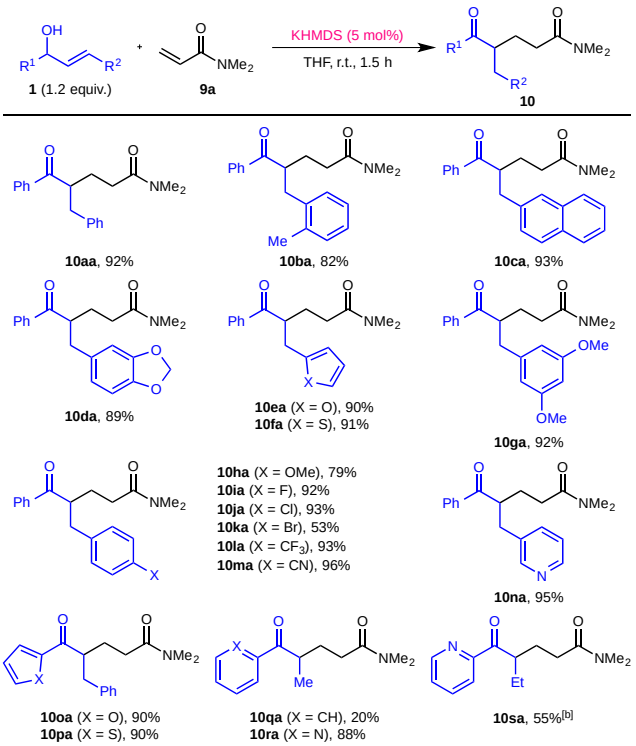
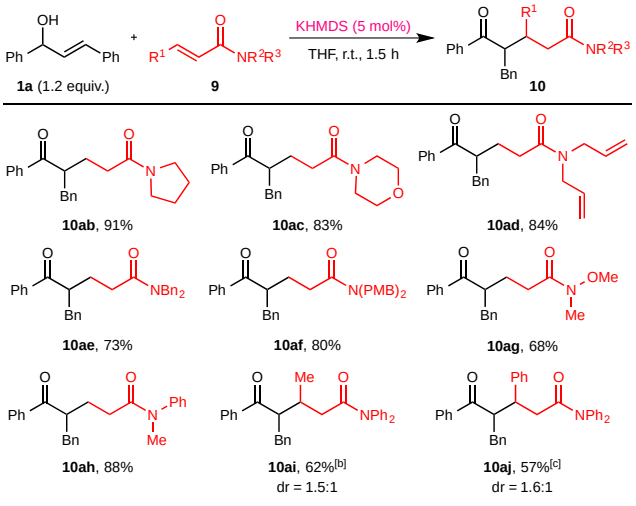


[a] Conditions: **1** (0.36 mmol), **9a** (0.3 mmol), and KHMDS (5 mol%, 0.5 M in toluene) in THF (3 mL) at room temperature for 1.5 h. Yields of isolated products are shown. [b] With 20 mol% of KHMDS for 2 h.

We also examined the generality of reactions involving α,β-unsaturated amides **9** (Table 3), and various substituents on the nitrogen atom were evaluated. *N*,*N*-Dialkylamides reacted well to afford the desired products **10ab** and **10ac**. *N*,*N*-diallyl-, *N*,*N*-dibenzyl-, and *N*,*N*-di(*p*-methoxybenzyl)amides, with possible subsequent deprotection in mind, were well tolerated and gave the corresponding products **10ad**–**10af** in high yields. Weinreb-type amide **9g** and *N*-arylamide **9h** were also suitable substrates. α,β-Unsaturated amides **9i** and **9j** bearing alkyl or aryl substituents at their β-positions could also be employed in this reaction.

Table 3. Substrate scope of α,β-unsaturated amides **9**.[a]



[a] For general reaction conditions, see Table 2. Yields of isolated products are shown. [b] With 7.5 mol% of KHMDS. [c] With 2.0 equiv. of **1a** and 20 mol% of KHMDS.

The key step in this transformation is the isomerization of the allylic alcohol to the corresponding enolate. Therefore, to elucidate the isomerization mechanism, we performed a series of control experiments (Scheme 3). First, **1a** was reacted with **9a** in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to investigate if the mechanism is radical-based as proposed by Kang and co-workers.[4a] The reaction afforded **10aa** in 80% yield even in the presence of TEMPO. In addition, radical-clock substrate **1t** was reacted with **9a**, which afforded **10ta** in 67% yield without any formation of ring-opening byproducts. These results provide strong evidence against a radical mechanism. Because a direct 1,2-proton shift is symmetry-forbidden and unlikely to occur,[16,17] we believe that the allylic isomerization proceeds via a hydride-shift mechanism. We performed a deuterium-labeling experiment to distinguish between 1,2- and 1,3-hydride shifts.[3e] When **1a**-*d* was reacted with 10 mol% of KHMDS, 31% deuterium was incorporated at the C2 position in **5**-d^2, and only 4% was incorporated at the C3 position. Because the erosion of deuterium content at the C2 position can be explained by base-catalyzed D/H exchange,[18,19] this result indicates that a 1,2-hydride shift is likely to be operative in the allylic-isomerization process. Next, we reacted **1a**-*d* with **9a** in the presence of 5 mol% KHMDS, which furnished a 5.3:1 mixture of **10aa**-*d* (26% D) and **11aa**-*d* (99% D). The detection of oxa-Michael adduct **11aa**-*d* was in sharp contrast to the outcome observed with **1a** and suggests that the incorporation of deuterium significantly retards the 1,2-hydride-shift process. An alternative pathway that involves direct C1–H deprotonation is conceivable because the difference between the pK_a values of the OH and the C1–H in **1a** may not be significant in organic solvents. To test this hypothesis, **1a**-*d* was reacted with a stoichiometric amount of KH. If KH directly abstracts the C1–D in **1a**-*d*, the reaction should not afford deuterated ketone **5**-*d* because the deuterium at the C1 position is lost from the reaction system as HD gas. Surprisingly, 76% of the deuterium was transferred to the C3 position of ketone **5**-d^3 although no deuterium incorporation at the C2 position was observed. A similar reaction using KHMDS as the base produced **5**-d^3 (82% D at C3). The fact that deuterium content was well preserved during the reaction ruled out a direct C1–H deprotonation pathway. An explanation for the change in position of the deuteration that is dependent on the amount of base is presented as follows (Scheme 4): For cases with a catalytic amount of a base, homoenolate **B** is generated from alkoxide **A** through a 1,2-deuteride shift undergoing rapid C3-protonation by the OH group of **1a**-*d*, thus producing C2-deuterated ketone **5**-d^2, which is

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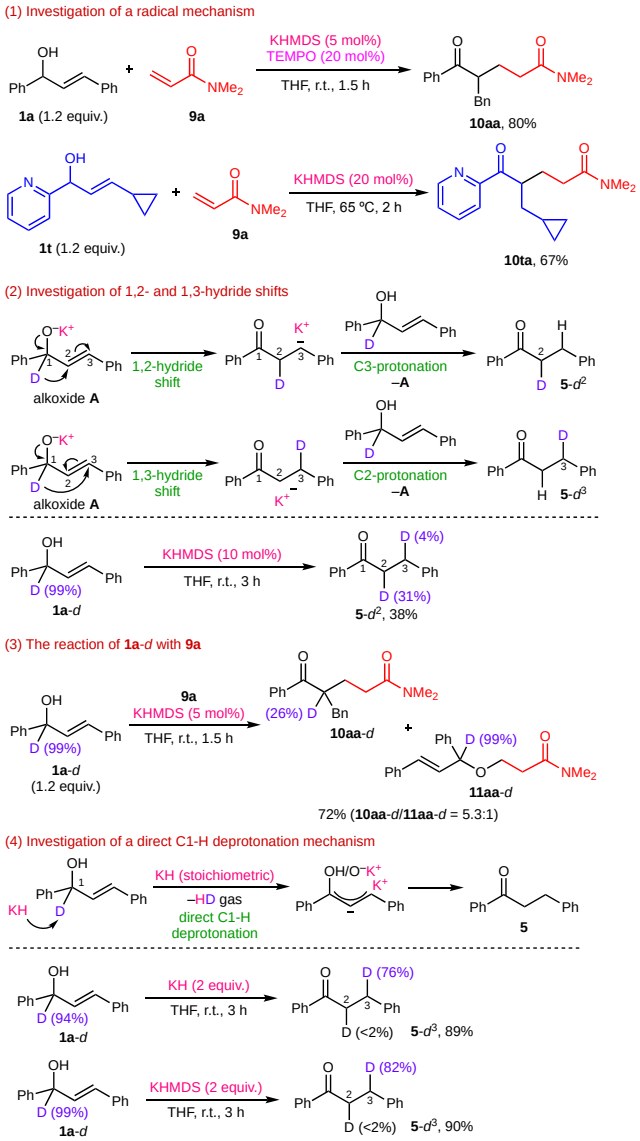
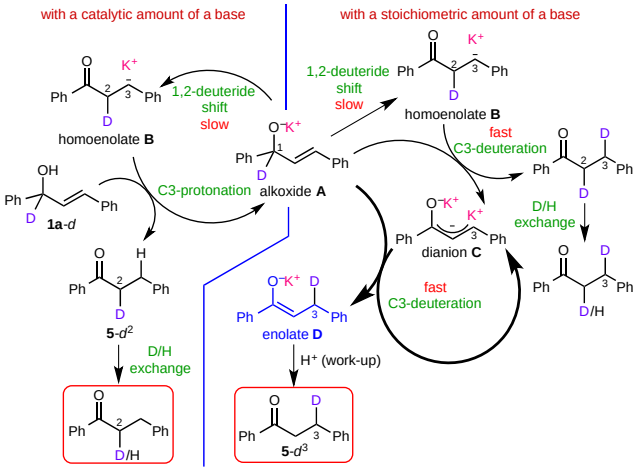
susceptible to base-catalyzed C2–D/H exchange. However, when a stoichiometric amount of base is used, homoenolate **B** abstracts the C1–D of alkoxide **A** affording dianion **C** because there is no OH group of **1a**-*d*. Dianion **C** also abstracts the C1–D of alkoxide **A** to give enolate **D** and regenerate **C**. Enolate **D** is converted into C3-deuterated ketone **5**-d^3 after aqueous work-up.[20,21]

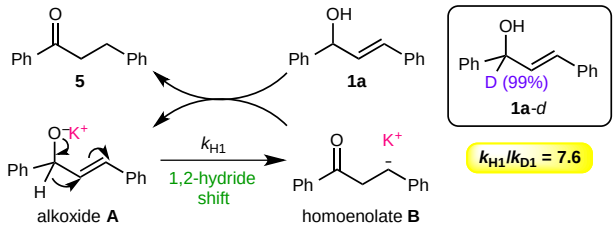


Scheme 3. Control experiments.



Scheme 4. A plausible mechanism of the base-catalyzed isomerization of allylic alcohol **1a**-*d*.

We turned to kinetics studies to acquire more information on this allylic-isomerization process. We first reacted **1a** with 5 mol% of KHMDS to measure rate constant k_{H1} (Scheme 5). This reaction is catalytic; hence the concentration of alkoxide **A** is essentially constant and the same as that of the added KHMDS. However, we found that the reaction clearly slowed as the reaction proceeded, which is probably due to the equilibrium between **A**, ketone **5**, **1a**, and the corresponding enolate, which decreases the concentration of **A**. Accordingly, we performed initial-rate kinetics studies to measure k_{H1}. On the basis of these experiments,[22] k_{H1} was determined to be 3.33×10^{-3} s^{-1}. We also conducted similar kinetics experiments using **1a**-*d* bearing 99% deuterium at the 1-position and consequently observed a large KIE of 7.6 ($k_{D1} = 4.39 \times 10^{-4}$ s^{-1}). These results indicate that the 1,2-hydride shift (C–H bond cleavage step) is rate-determining and that tunneling[23] is involved in this event.



Scheme 5. Kinetics studies for the KHMDS-catalyzed isomerizations of allylic alcohols **1a** and **1a**-*d*.

To further probe the validity of the 1,2-hydride-shift mechanism, the rate of the reaction and KIE were determined computationally using canonical variational transition state theory (CVT) with small-curvature tunneling (SCT) correction. These calculations were carried out on the M06-2X/6-31+G* potential energy surface using GAUSSRATE[24] as the interface between

POLYRATE[25] and Gaussian16.[26] The SMD model was used to include solvent effects.[27] Of all possible allylic-isomerization processes, the 1,2-hydride shift was found to be the fastest, both with and without considering tunneling (Figure 1). The CVT/SCT-predicted reaction rate constant at 294.15 K of 1.57×10^{-3} s^{-1} is in good agreement with the experimentally determined rate constant (3.33×10^{-3} s^{-1}). The KIE was calculated by comparing the calculated reaction rate constant for the 1,2-deuteride shift of 1.94×10^{-4} s^{-1} (CVT/SCT) with the above-mentioned value for the analogous hydride shift; the CVT/SCT KIE value of 8.1 is close to the experimental value. The CVT KIE value of 4.2 (without tunneling correction) is significantly different from the experimental value. These computational results support the notion that the 1,2-hydride shift is the rate-determining step in this reaction and that tunneling accelerates this hydride shift.

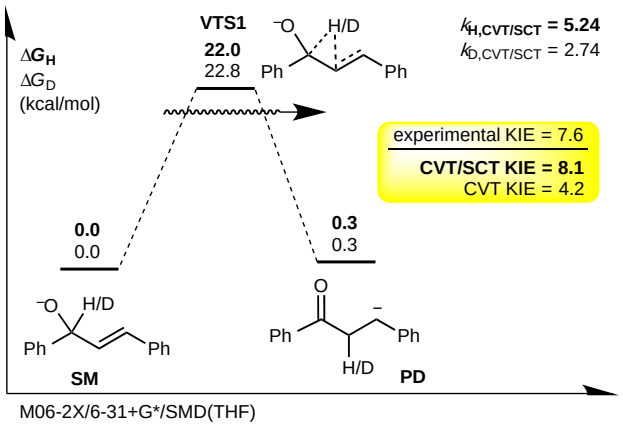
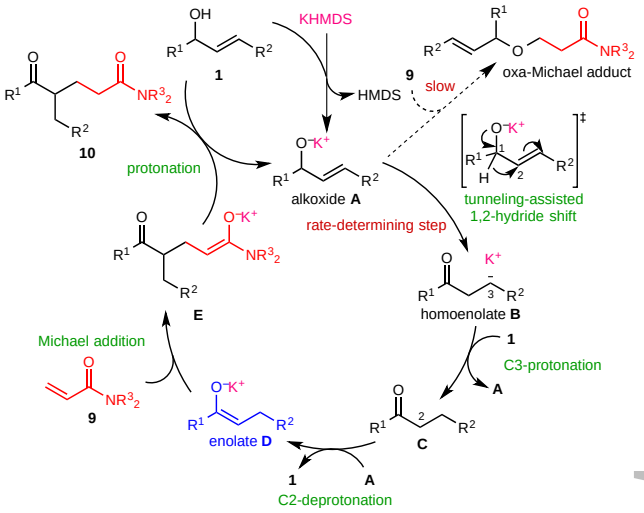


Figure 1. Free energy profile for the 1,2-hydride/deuteride shift in the alkoxide of **1a**. Transmission coefficient values (κ) are also shown. VTS = variational transition state.

On the basis of the experimental and computaional studies, we propose the reaction mechanism shown in Scheme 6. The OH proton of **1** is initially abstracted by KHMDS to form alkoxide **A**. Due to the low electrophilicity of the α,β-unsaturated amide **9**, **A** is reluctant to undergo oxa-Michael addition to **9** and is therefore transformed into the homoenolate **B** through a 1,2-hydride shift, which is the rate-determining step and in which tunneling is involved. **B** is rapidly protonated by **1** prior to reaction with **9**, and the α-proton of the resulting ketone **C** is deprotonated by **A** to generate enolate **D**, which then undergoes Michael addition to **9** to give enolate **E**, which is protonated by **1** to afford product **10** and regenerate **A**.



Scheme 6. Proposed catalytic cycle.

Conclusion

In conclusion, we developed novel KHMDS-catalyzed Michael-addition chemistry of allylic alcohols with α,β-unsaturated amides that involves allylic isomerization. A series of mechanistic studies, including radical-inhibition, deuterium-labeling, kinetics, and KIE experiments, along with a computational study led us to propose that the in-situ generation of the enolate from the allylic alcohol through a tunneling-assisted 1,2-hydride shift is the key step in this transformation. Further investigations into the reaction mechanism and applications of this protocol to the use of allylic alcohols as homoenolates are currently underway in our laboratory.

Experimental Section

Allylic alcohol **1** (0.36 mmol) was placed in an oven-dried vial equipped with a magnetic stir bar. The vial was flushed with argon and sealed with a rubber septum. To the vial were added THF (3 mL), α,β-unsaturated amide **9** (0.30 mmol), and KHMDS (0.5 M in toluene, 0.015 mmol, 30 μL), and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aq. NH_4Cl solution and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give the corresponding product **10**.

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[10] According to the reaction mechanism, the high efficiency of potassium bases toward allylic isomerization is likely due to the strong basicity, which facilitates the 1,2-hydride shift.

[11] For a recent report on the electrophilicities of α,β-unsaturated carbonyl compounds, see: D. S. Allgäuer, H. Jangra, H. Asahara, Z. Li, Q. Chen, H. Zipse, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.

[12] We also tested other potassium and cesium bases. The use of KO^{t}Bu gave a somewhat lower yield (65%) of **10aa**. The use of $CsOH{\cdot}H_2O$ provided a mixture of oxa-Michael adduct (32%) and **10aa** (22%) probably due to the enhanced nucleophilicity of a cesium alkoxide.

[13] The structure of **10ma** was unambiguously identified by spectroscopic and X-ray crystallographic analysis. CCDC 1944310 contains the supplementary crystallographic data for **10ma**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] In this case, oxa-Michael adduct was detected in 53% NMR yield. The poor reactivity of **1q** for the allylic isomerization is probably due to the absence of an anion-stabilizing substituent at the 3-position.

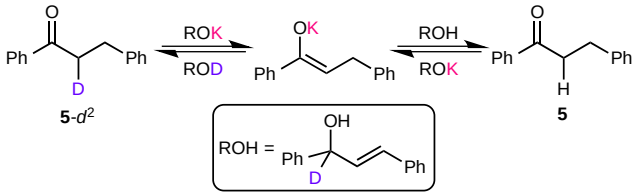
[15] The reaction of (*E*)-1-phenylhept-1-en-3-ol with amide **9a** under the standard reaction conditions resulted in a 57% yield of the corresponding oxa-Michael adduct.

[16] Yates et al. suggested that a direct 1,2-proton shift was a symmetry forbidden process and calculated to have a barrier of 39.1 kcal/mol in a model stetter reaction. a) K. J. Hawkes, B. F. Yates, *Eur. J. Org.*

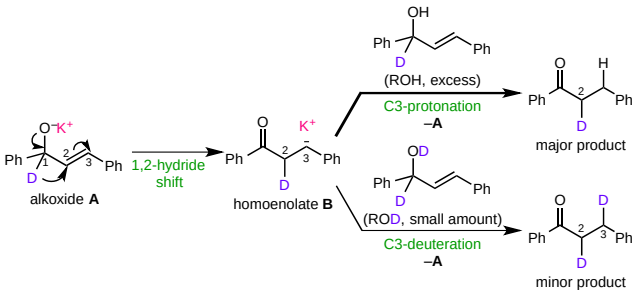
Chem. **2008**, 5563–5570. For DFT calculations on a direct 1,2-proton shift, also see: b) B. Goldfuss, M. Schumacher, *J. Mol. Model.* **2006**, *12*, 591–595; c) M. Schumacher, B. Goldfuss, *Tetrahedron* **2008**, *64*, 1648–1653.

[17] We also conducted DFT calculations of a direct 1,2-proton shift pathway, which had a high energy of 44.9 kcal/mol (see the Supporting Information).

[18] The mechanism of base-catalyzed D/H exchange at the C2 position in **5**-d^2 is as follows:



[19] Incorporation of a small amount of deuterium at the C3 position is likely owing to the reaction of homoenolate **B** with deuterated substrate ROD, which is generated as C2–D/H exchange of **5**-d^2 (see ref 17).



[20] This mechanism is consistent with the results reported in Table 1 where benzylation of **1a** occurs exclusively at the C2 position (**3**) and not at the C3 position (**4**) even in the presence of a stoichiometric amount of a base.

[21] The abstraction of C1–D of alkoxide **A** by homoenolate **B** and dianion **C** would be much faster than a 1,2-deuteride shift. This explains the negligible amount of deuteration at the C2 position in **5**-d^3.

[22] See the Supporting Information for details of the kinetics studies.

[23] For reviews on tunneling in organic chemistry, see: a) R. S. Sheridan in *Reviews of Reactive Intermediate Chemistry* (Eds.: M. S. Platz, R. A. Moss, M. Jones Jr.), John Wiley & Sons, Hoboken, New Jersey, **2007**, pp. 415–463; b) J. T. Hynes, J. P. Klinman, H.-H. Limbach, R. L. Schowen in *Hydrogen-Transfer Reactions*, Wiley-VCH, Weinheim, **2007**; c) D. Ley, D. Gerbig, P. R. Schreiner, *Org. Biomol. Chem.* **2012**, *10*, 3781–3790; d) P. R. Schreiner, *J. Am. Chem. Soc.* **2017**, *139*, 15276–15283.

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[25] J. Zheng, J. L. Bao, R. Meana-Pañeda, S. Zhang, B. J. Lynch, J. C. Corchado, Y.-Y. Chuang, P. L. Fast, W.-P. Hu, Y.-P. Liu, G. C. Lynch, K. A. Nguyen, C. F. Jackels, A. Fernandez Ramos, B. A. Ellingson, V. S. Melissas, J. Villà, I. Rossi, E. L. Coitiño, J. Pu, T. V. Albu, A. Ratkiewicz, R. Steckler, B. C. Garrett, A. D. Isaacson, D. G. Truhlar, POLYRATE, version 2017-B, University of Minnesota, Minneapolis, MN **2017**.

[26] M. J. Frisch, et al., Gaussian 16, Revision B.01, Gaussian, Inc., Wallingford, CT, **2016**. For the full citation as well as the full computational details, see the Supporting Information.

[27] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys Chem. B.* **2009**, *113*, 6378–6396.

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FULL PAPER

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