Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 7662

Received 11th September 2013,
Accepted 3rd October 2013

DOI: 10.1039/c3ob41857j

www.rsc.org/obc

NaH mediated isomerisation–allylation reaction of 1,3-substituted propenols†

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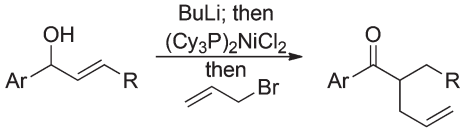
A base mediated isomerisation–allylation protocol of 1,3-disubstituted propenols has been established. The use of diaryl and arylsilyl substrates is reported alongside the use of substituted allyl bromides. Mechanistic experiments have also been conducted to elucidate the reaction pathway.

The isomerisation of allylic alcohols to ketones and aldehydes can be a useful transformation that avoids the use of both oxidants and reductants.[1] The most common strategy to achieve this operation is to utilise a transition metal catalyst that isomerises the alkene moiety into an enol (or enolate) which upon tautomerisation (or workup) affords the corresponding carbonyl functionality.[2] In most cases, the reaction is driven by a thermodynamic preference for the enol (or enolate) over the allylic alcohol (or alkoxide) with up to 25 kcal mol^{-1} difference between the two.[3]

Many of these processes have also been rendered enantioselective.[4] The allyl amine variant is generally superior producing significantly higher levels of enantiomeric enrichment.[5] Motherwell also demonstrated that enolates derived from rhodium or nickel catalysed isomerisations of allylic alkoxides could be intercepted by electrophiles such as aldehydes or allylic bromides to form α-branched products (eqn (1)).[6]

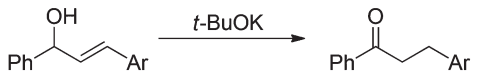
Although known for over 100 years, base mediated variants of this reaction are much less common with relatively few reported examples.[7] Dimmel demonstrated the use of butyl lithium and Na/K to isomerise phenyl substituted allylic alcohols which was proposed to proceed *via* a double anion with both the alcohol and the allylic C–H being deprotonated followed by reprotonation to form the more conjugated product.[8] Borschberg reported an analogous isomerisation of a diaryl-substituted allylic alcohol under much milder reaction conditions using *t*-BuOK as base (eqn (2)).[9] Following deuterium labelling studies they proposed that following initial deprotonation of the alcohol, a competing [1,2] or [1,3]-hydride shift occurs as deuterium is observed at both of these positions in the product. 2-Pyridyl substituted allylic alcohols have also been shown to isomerise both thermally and under sodium hydride mediated conditions.[10,11] To our knowledge there have been no reports of base mediated isomerisations of 1,3-disubstituted allylic alcohols followed by electrophilic trapping. Herein we describe the base mediated isomerisation of 1,3-diaryl and 1-aryl-3-silyl propen-1-ols and subsequent trapping with an allylic bromide (eqn (3)).

Motherwell: Ni-catalyzed Isomerisation-Allylation (*Ref.6b*)



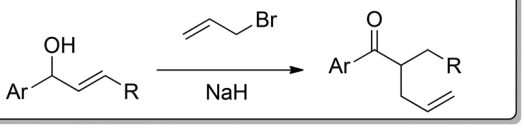
(1)

Borschberg: Base Mediated Isomerisation *(Ref.9)*



(2)

This Work: NaH mediated Isomerisation-Allylation



(3)

We discovered an unusual product during the course of an allylation reaction of silyl allylic alcohol **1** (Table 1).[12,13] When allylic alcohol was treated with sodium hydride and allyl bromide **2** in THF with heating the major product observed was not the expected allyl ether but ketone **3**.[14] The mass balance of the reaction was made up of unallylated ketone product and the expected bis-allyl ether. This was further optimised and found that lowering the equivalents of NaH increased the yield to 57%. When the sodium hydride content was lowered further, a reaction was still observed (at 1.05 equivalents) however *O*-allylation was the major product. Other bases such as *t*-BuOK gave decomposition and a solvent screen

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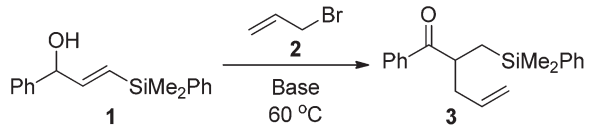
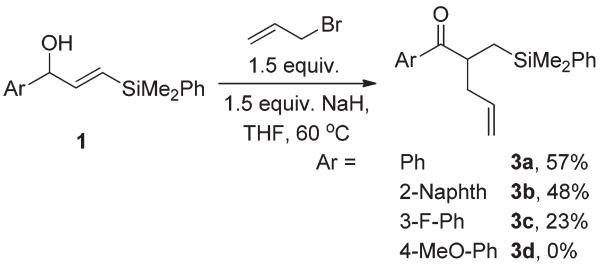
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob41857j

Table 1 Optimisation studies



Entry	Base	Solvent	Equiv. 2	Additive	Yield[a] (%)
1	NaH	THF	3	—	48
2	NaH	THF	1.5	—	57
3	NaH	THF	1.05	—	22
4	KO*t*-Bu	THF	1.5	—	Dec.
5	NaH	DMSO	1.5	—	40
6	NaH	DMF[b]	1.5	—	0[c]
7	NaH	THF	1.5	15-c-5	0[d]
8	NaH	THF	1.5	HMPA	43

[a] Isolated yield of **3**. [b] Reaction performed at 25 °C. [c] Only *O*-allylated product observed. [d] Only isomerised, unallylated product observed.



Scheme 1 Vinyl silane substrate scope.

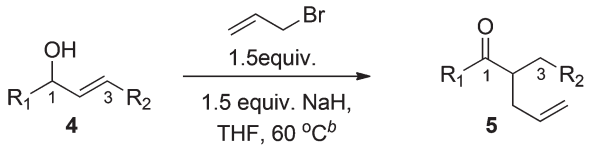
showed that THF was the optimal solvent. Interestingly, when DMF was used as solvent no ketone was observed with only *O*-allylation being observed. Finally, the use of additives was explored with 15-crown-5 giving no ketone and HMPA affording a slightly reduced yield with several unidentified by-products being formed.

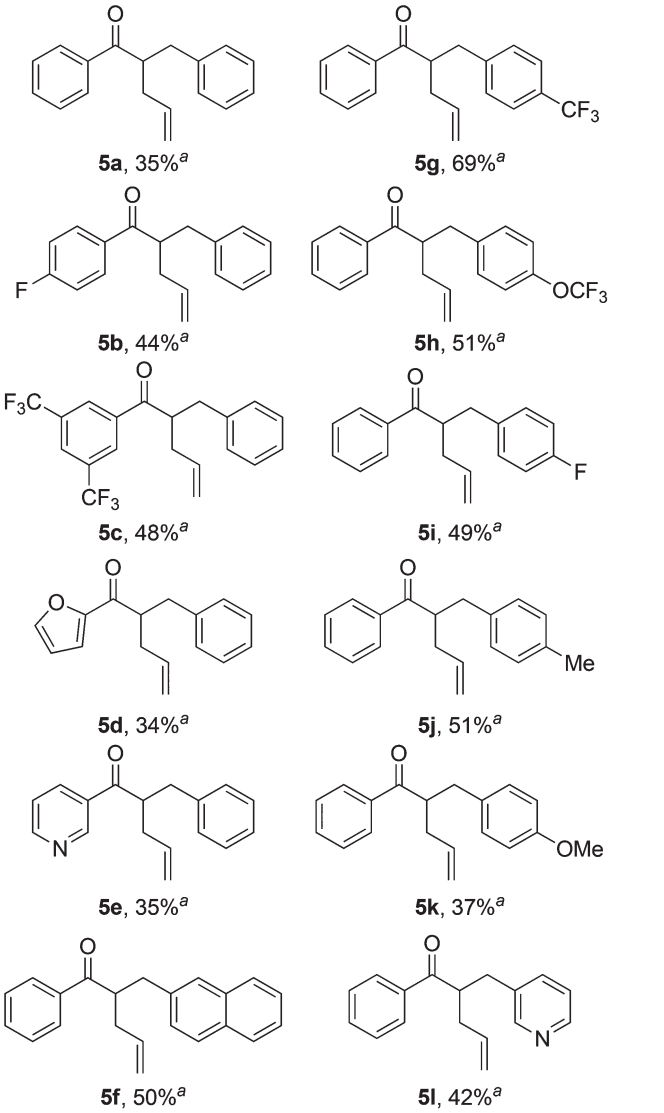
With the optimised conditions in hand, we then probed the substrate scope (Scheme 1). The reaction proceeded with both phenyl and naphthyl to afford α-allylated ketones **3a** and **3b**. When substitution was present on the aryl ring the reactivity was compromised with both electron withdrawing and donating groups. 3-Fluoro substituent **1c** afforded allylated product **3c** in low yield and 4-methoxy substituent **1d** afforded no isomerisation–allylation product with the majority of the mass balance made up of *O*-allylated product.

As the substrate scope of the vinyl silanes was limited, with only three examples providing any ketone product, we next turned our attention to 1,3-diaryl propen-1-ols **4** which are readily available using a number of methods (Table 2).[15] We first looked at commercially available 1,3-diphenyl propen-1-ol **4a** and found the same type of reaction occurred to afford ketone **5a** in a moderate yield.

We next examined the effect of changing the electronic nature of the aryl group at the 1-position. Adding electron withdrawing substituents such as 4-fluoro or 3,5-bis(trifluoromethyl) did increase the yield of the reaction affording **5b** and

Table 2 Biaryl substrate scope





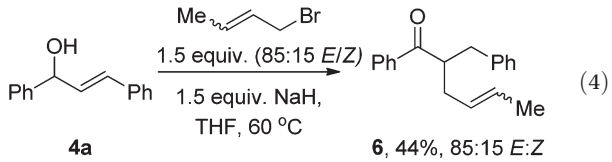
[a] Isolated yields. [b] Reaction conditions: 1.5 equiv. NaH, 1.5 equiv. allyl bromide, THF, 60 °C, 12 hours.

5c respectively. Heterocycles could be incorporated at the 1-position with little effect on reactivity. Both furyl **5d** and pyridyl **5e** proceeded in a similar manner to the parent phenyl compound.

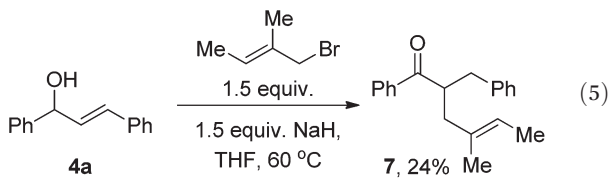
We also probed the effect the 3-aryl group had on reactivity and found that changing this showed a much larger effect than the 1-position. 2-Naphthyl substituent **4f** gave much improved reactivity affording **5f** in 50% yield. This could be further improved by the installation of a 4-trifluoromethyl group giving **5g** in good yield. Other substituents including

4-trifluoromethoxy **4h**, 4-methyl **4i** and 4-fluoro **4j** also provided isomerised-allylated products **5h–j** in around 50% yield. The installation of electron donating groups in the form of a 4-methoxy group **4k** resulted in a similar yield to the phenyl group and a pyridyl group could be tolerated in the 3-position forming **5l** in 42% yield. When no anion stabilising groups were present, such as alkyl substituents, no isomerisation was observed and only *O*-allylation was obtained.

Next we examined other substituted allyl bromides. When crotyl bromide was used a similar reaction was observed with the α-crotylated product **6** being produced in 44% yield in the same *E* : *Z* ratio as the electrophilic component (eqn (4)). This was further extended to 2,3-dimethylallyl bromide and again α-allylation was observed to form **7**, albeit in reduced yields (eqn (5)).

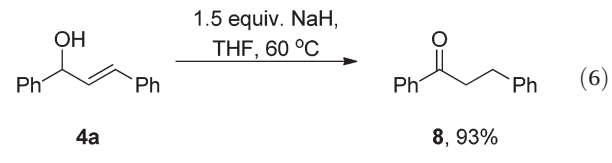


4a **6**, 44%, 85:15 *E*:*Z* (4)

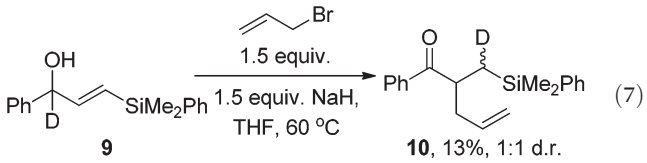


4a **7**, 24% (5)

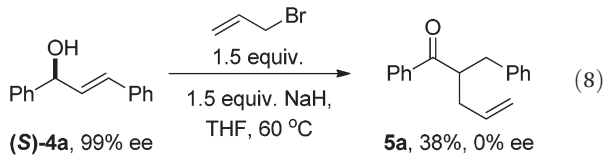
Several experiments were performed to probe the mechanism of these reactions. Firstly, in the absence of an electrophile, the allylic alcohol isomerises to the corresponding ketone **8** in excellent yield with no observed by-products (eqn (6)). Secondly, when deuterated compound **9** is used, the deuterium atom is removed from the 1-position by the base and this was observed at the 3-position in approximately 40% D-incorporation (eqn (7)). The majority of the product in this reaction was simple *O*-allylation product. When enantio-enriched compound (*S*)-**4a** was used,[16] the corresponding allylated product **5a** was produced as a racemic mixture thus indicating the intermediacy of a planar achiral intermediate (eqn (8)). Finally we took the allyl ether **11** and subjected this to the reaction conditions and no reaction was observed thus ruling out the intermediacy of allyl ether **11** (eqn (9)).



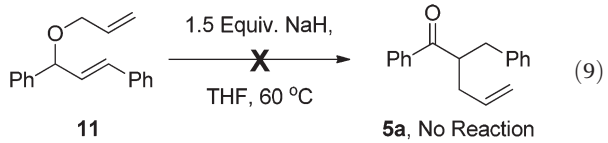
4a **8**, 93% (6)



9 **10**, 13%, 1:1 d.r. *40% D-Incorporation*, (7)



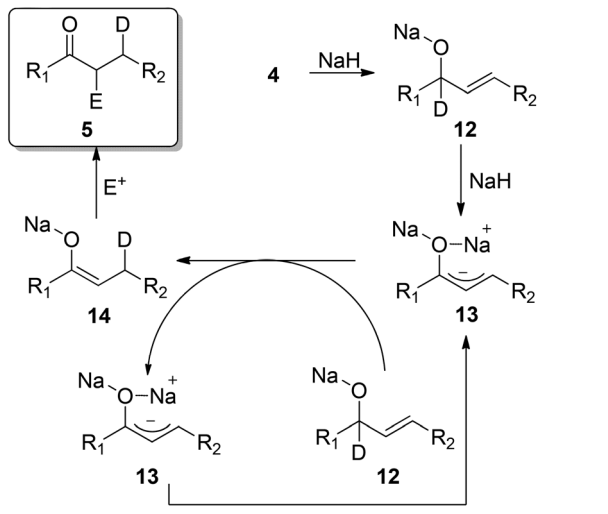
(*S*)-**4a**, 99% ee **5a**, 38%, 0% ee (8)



11 **5a**, No Reaction (9)

With the mechanistic data in hand we have proposed a mechanism that accounts for all observations (Scheme 2). Firstly the OH of allylic alcohol **4** is deprotonated to form the corresponding alkoxide **12**. This alkoxide can undergo a second deprotonation to form allylic anion **13**. The allylic anion **13** can deprotonate a second equivalent of alkoxide **12** to afford an enolate **14** incorporating deuterium in the 3-position and regenerating allylic anion **13**. Finally the enolate **14** is then allylated to afford the observed isomerisation allylation product **5**. As only 40%-deuterium incorporation is observed the deprotonation of **12** must be performed by both **13** and NaH at comparable rates. This indicates that the isomerisation is catalytic with respect to **13** and complete double deprotonation is not necessary before isomerisation can occur. In all cases no bis-allylated product was observed, a significant by-product in many of the other isomerisation–allylation protocols that have been reported. The position of the methyl groups when a substituted allyl bromide is used, S_N2 type substitution, also rules out possibility of an *O*-allylation-Claisen pathway.

Sodium hydride has been shown to isomerise *N*-acyl allylic amines to their corresponding enamines with high levels of *E*/*Z* control. Clayden demonstrated the use of allylic ureas in this pathway[17] and Smith used allylic acrylamides.[18,19] Both of these reactions give the corresponding enamine as a single *Z*



Scheme 2 Proposed mechanism.

isomer and they both propose a sodium chelate analogous to **13**. As deuterium is only observed at the 3-position, we can eliminate the possibility that a competing [1,2] and [1,3] shift is in operation as proposed by Borschberg.[9]

Conclusions

In conclusion, we have discovered and investigated the NaH catalyzed isomerization of allylic alcohols and α-allylation of the resultant enolate to form α-allylated ketones. We have discovered that both silyl and aryl substitution is tolerated at the γ-position. Several mechanistic probes and control reactions has shed light on the mechanism of this reaction.

We thank Queen's University Belfast for support. We are also grateful to the Department of Employment and Learning, Northern Ireland for a studentship (MGM). GlaxoSmithKline and AstraZeneca are also thanked for their generous donation of laboratory equipment. We also thank Professor Andrew Smith, University of St. Andrews for useful discussions.

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