

Hydroalkylation of styrenes with benzylamines by potassium hydride

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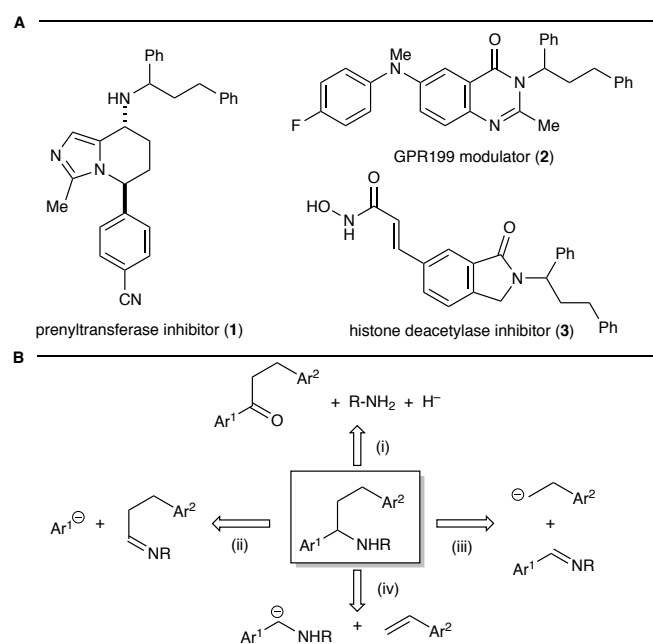
Dedicated to Professor E. Peter Kündig in celebration of his 75th birthday

A method for the synthesis of 1,3-diarylpropylamines via hydroalkylation of styrenes with benzylamines by potassium hydride has been developed. The protocol is initiated by solvothermal treatment of benzylamines with KH at 100 °C to generate deprotonated anionic species, which undergo selective C-alkylation with arylalkenes at 0 °C-ambient temperature to afford 1,3-diarylpropylamines as the major product.

Keywords: Hydroalkylation • benzylamines • arylalkenes • potassium hydride

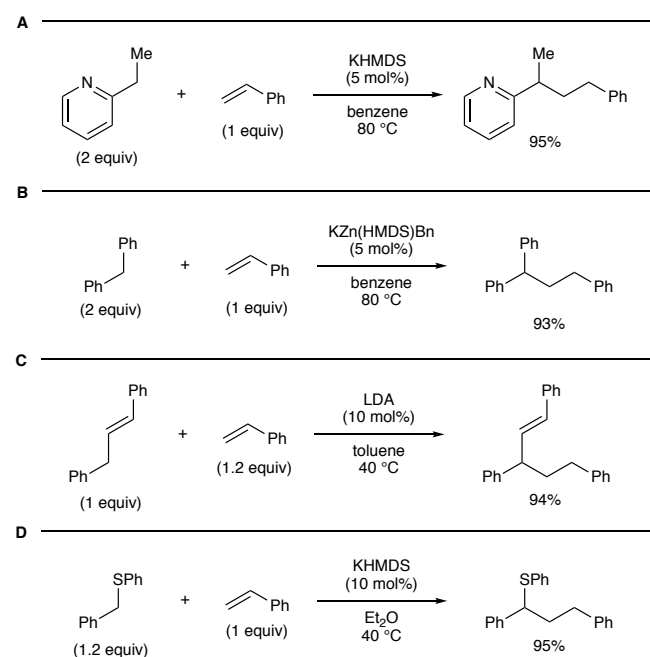
Introduction

The 1,3-diarylpropylamine motif is found as a key structural unit in various biologically active small molecules such as prenyltransferase inhibitor **1**,^[1] GPR199 modulator **2**,^[2] and histone deacetylase inhibitor **3**^[3] (Scheme 1A). Commonly, synthesis of 1,3-diarylpropylamines could be conceived through the reductive amination (Scheme 1B-i)^[4,5] or Mannich/Petasis type disconnection approaches^[6] either via a combination of arylanion nucleophiles and aldimine electrophiles (Scheme 1B-ii) or that of arylethyl anion nucleophiles and aldimine electrophiles (Scheme 1B-iii). Nonetheless, development of facile construction methods of the 1,3-diarylpropylamine scaffolds from readily available feedstocks would be of need to diversify their chemical synthesis. In this work, we explored an unusual disconnection approach that leverages α -amino benzylic carbanions and styrenes (Scheme 1B-iv).



Scheme 1. (A) Bioactive molecules having a 1,3-diarylpropylamine moiety. (B) Retrosynthetic approaches toward 1,3-diarylpropylamines.

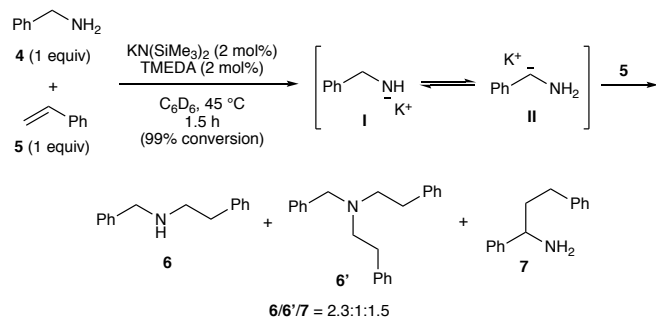
Generation of benzylic carbanions through deprotonation with strong bases and their ensuing regioselective addition onto styrenes enable efficient construction of 1,3-diarylpropane motifs.^[7] The method was pioneered by Pines,^[8-13] and more recently, Guan and Kobayashi advanced the state-of-the-art, where benzylic carbanions derived from alkyl(hetero)arenes (Scheme 2A),^[14,15] diarylmethanes (Scheme 2B),^[16,17] 1,3-diarylpropenes (Scheme 2C),^[18] benzyl sulfides (Scheme 2D)^[19] were utilized for the nucleophilic addition to styrenes.



Scheme 2. Addition of benzylic carbanion to styrenes.

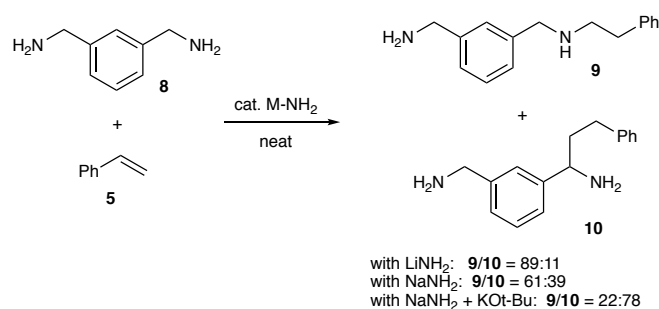
Despite these advances, engagement of benzylamines in their deprotonative benzylic alkylation with styrenes remains elusive. When primary and secondary amines are employed, the base-mediated deprotonation occurs on the amine site and the resulting amide anions show the propensity to undergo hydroamination.^[20-24] Interestingly, Hultsch observed that the reaction of benzylamine (**4**) and styrene (**5**) catalyzed by KN(SiMe₃)₂ and TMEDA affords not only hydroamination

products **6** and **6'**, but also 1,3-diphenylpropylamine (**7**) as a minor co-product through hydroalkylation of styrene (**5**) (Scheme 3). We hypothesized that there might be an equilibrium between the amide anion **I** and benzylic anion **II**. It should be noted that no formation of **7** was observed when $\text{LiN}(\text{SiMe}_3)_2$ was used, implicating that the counter alkali metal cation on the bases should impact the reaction course.



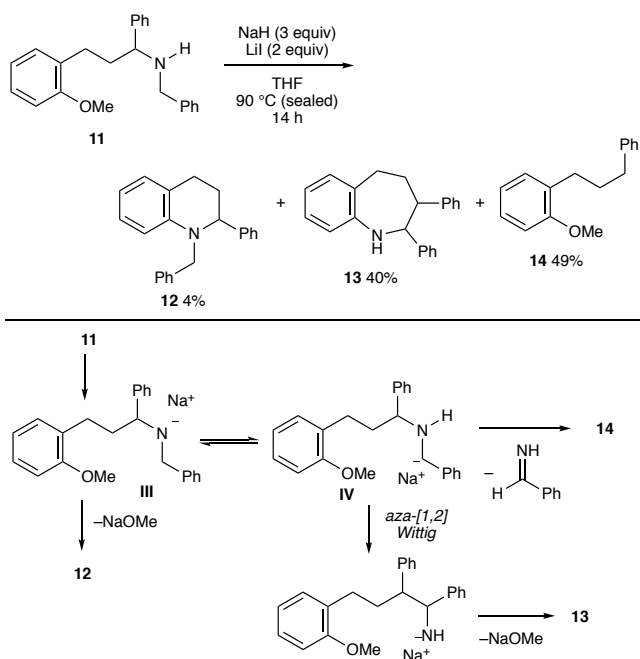
Scheme 3. Observation of hydroalkylation of styrene (**5**) with benzylamine (**4**).

The research team of the Mitsubishi Gas Chemical Company Inc. also observed a similar counter cation effect in hydroamination or hydroalkylation of styrene (**5**) with 1,3-phenylenedimethaneamine (**8**) (Scheme 4). Namely, use of LiNH_2 or NaNH_2 facilitates hydroamination to form **9** as the predominant pathway, whereas a combination of NaNH_2 and KOt-Bu switches the selectivity toward hydroalkylation to provide **10** as the major product.^[25]



Scheme 4. Counter cation effect in hydroamination/alkylation of styrene (**5**) with 1,3-phenylenedimethaneamine (**8**).

On the other hand, we recently discovered that sodium amide anions could be generated by the solvothermal deprotonation of aliphatic amines with sodium hydride (NaH) in the presence of dissolving iodide such as sodium iodide (NaI) or lithium iodide (LiI) and the resulting amide anions could undergo nucleophilic amination of methoxyarenes in both intra and intermolecular manners.^[26,27] During this study, we also observed the equilibrium between the amide anion and the in the reaction of substrate **11** (Scheme 5). Namely, the reaction of **11** with NaH and LiI in THF at 90°C provided a mixture of tetrahydroquinoline **12**, tetrahydro-1*H*-benzo[*b*]azepine **13**, and alkane **14**. Tetrahydroquinoline **12** was formed from amide anion **III** via intramolecular nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$), while tetrahydro-1*H*-benzo[*b*]azepine **13** and alkane **14** might be formed from benzylic anion **IV** via aza-[1,2]-Wittig rearrangement followed by intramolecular $\text{S}_{\text{N}}\text{Ar}$ and β -elimination of imine, respectively.



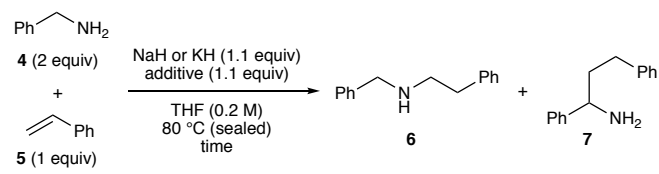
Scheme 5. Observation of equilibrium between sodium amide and benzylic anion species.

Based on these backgrounds, we wondered if anionic species generated by the treatment of benzylamines with alkali metal hydrides could drive hydroamination or hydroalkylation of styrenes. Herein, we report selective hydroalkylation of styrenes with benzylamines mediated by potassium hydride (KH) in THF, enabling facile synthesis of 1,3-diarylpropylamines.

Results and Discussion

We began our investigation using benzylamine (**4**) (2 equiv) and styrene (**5**) as the model substrates (Table 1). We observed that the treatment of a mixture of **4** and **5** with NaH (1.1 equiv) in THF at 80°C resulted in formation of the hydroamination product **6** and the hydroalkylation product **7** in 17% and 19% yields, respectively (entry 1). The use of lithium iodide (LiI) as an additive could not improve the overall mass-balance of the reaction (entry 2). We reasoned that the poor mass-balance should stem from anionic polymerization of styrene (**5**) and thus we examined use of larger counter alkali metal cations to prevent the propagation of the anionic polymerization. Interestingly, the use of cesium iodide (CsI) (entry 3) and cesium fluoride (CsF) (entry 4) could enhance the mass-balance and moreover, the reaction with CsF pushed the selectivity towards the formation of hydroalkylation product **7** (entry 4). We reasoned that the use of CsF would accelerate the counter ion metathesis between NaH and CsF due to the higher lattice energy of the resulting NaF (910 kJ mol^{-1}) than that of NaI (682 kJ mol^{-1}).^[28] We observed that increasing the amount of benzylamine (**4**) to 2.5 equiv further improved the mass-balance (entry 5). Curiously, employment of potassium hydride (KH) (1.1 equiv) instead of NaH drastically accelerated the consumption rate of styrene (**5**), completing the reaction within 0.5 h to afford **7** in 60% yield (entry 6). This observation with KH was consistent even if

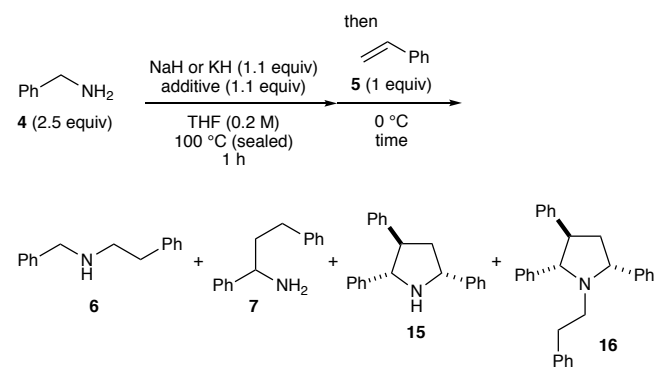
the reaction was conducted in the absence of CsF (entry 7). These observations stimulated us to tune the experimental protocol of the method using KH.

Table 1. Optimization of reaction conditions–1^[a]


Entry	NaH or KH	Additive (equiv)	Time (h)	Yield of 6 (%) ^[b]	Yield of 7 (%) ^[b]
1	NaH	none	3	17	19
2	NaH	Lil	3	11	16
3	NaH	CsI	3	40	21
4	NaH	CsF	3	5	59
5 ^[c]	NaH	CsF	3	11	74
6 ^[c]	KH	CsF	0.5	0	58
7 ^[c]	KH	none	0.5	0	57

[a] The reactions were conducted using 1 mmol of benzylamine (**4**) and 0.5 mmol of styrene (**5**) in the presence of NaH or KH (1.1 equiv) and additive (1.1 equiv) in THF (0.2 M) at 80 °C (in sealed tube). [b] ¹H NMR yields of isolated inseparable mixtures including **6** and **7** based on the internal standard. [c] The reactions were conducted using 1.25 mmol (2.5 equiv) of benzylamine (**4**).

We observed that solvothermal treatment of benzylamine (**4**) with KH and CsF at 100 °C could generate a reddish suspension, indicating the formation of anionic species.^[29] Subsequent addition of styrene (**2**) at 0 °C allowed for rapid trapping of styrene (**5**) to form **6** and **7** in 13% and 51% yields, respectively, within 0.3 h (Table 2, entry 1). Moreover, the pretreatment of **4** with KH in the absence of CsF followed by addition of styrene (**5**) resulted in better mass balance, providing **6** and **7** in 10% and 63% yields, respectively (entry 2). In these cases, pyrrolidines **15** and **16** could also be identified as minor co-products. We elucidated the reaction pathway for the formation of these co-products at the mechanistic discussion in Scheme 8. On the other hand, this protocol was not applicable for the use of NaH-CsF system (entry 3).

Table 2. Optimization of reaction conditions–2^[a]


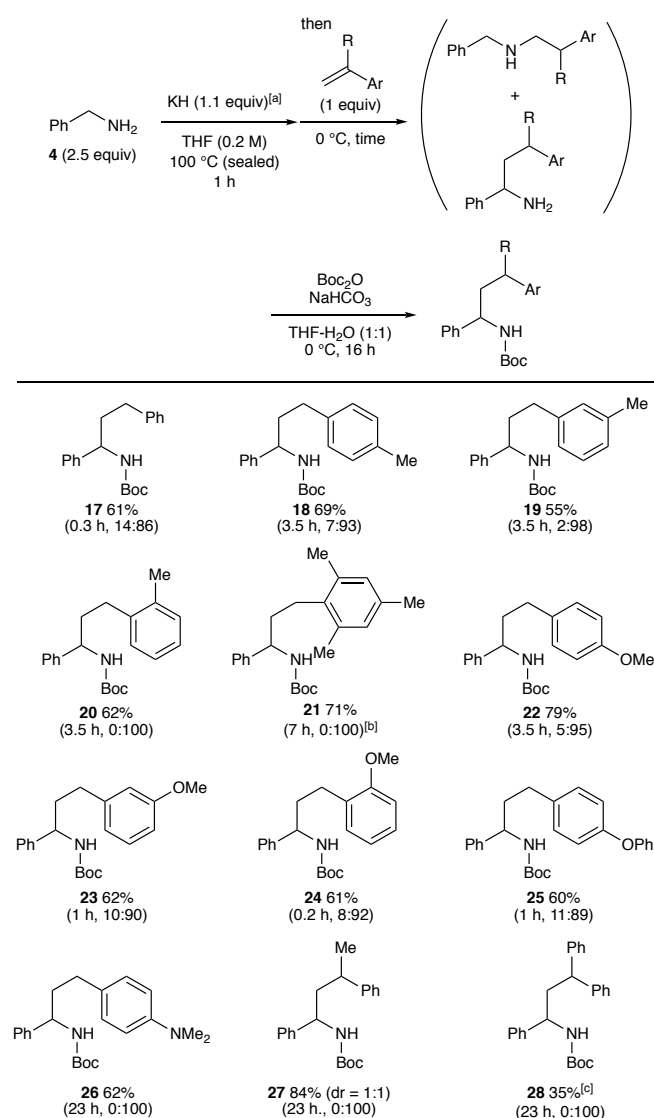
Entry	NaH or KH	Additive (equiv)	Time (h)	Yields (%) ^[b]			
				6	7	15	16
1	KH	CsF	0.3	12	45	5	5
2	KH	none	0.3	10	63	4	12
3	NaH	CsF	24	0	0	0	0

[a] The reactions were conducted using 1.25 mmol of benzylamine (**4**) in the presence of KH (1.1 equiv) and additive (1.1 equiv) in THF (0.2 M) at 100 °C (in sealed tube) for 1 h, followed by addition of styrene (**2**) (0.5 mmol) at 0 °C.

[b] ¹H NMR yields based on the internal standard.

Having optimized the reaction conditions for selective hydroalkylation of styrene (**5**) with benzylamine (**4**) (Table 2, entry 2), we next turned our attention to investigate the substrate scope with respect to styrenes for the synthesis of 1,3-diarylpropylamines (Scheme 6). We found that treatment of an inseparable mixture of **6** and **7** with di-*tert*-butyl dicarbonate (Boc₂O) allows for separation and isolation of 1,3-diarylpropylamine as an N-Boc adduct **17** in 61% yield. We set this as the standardized protocol to examine the reactivity of other styrenes. As for the substituents on the aryl group, the method allowed for installation of methyl groups to afford hydroalkylation products **18-21** in good yields regardless of their positions including sterically hindered 2-methylphenyl and 2,4,6-trimethylphenyl groups (for **20** and **21**). Moreover, introduction of electron-donating methoxy (for **22-24**), phenoxy (for **25**), and dimethylamino (for **26**) groups did not impact the productivity for the hydroalkylation process. Of worthy to note is the rate acceleration of the hydroalkylation step observed in the reaction with 2-methoxyphenyl substrate (for **24**), implicating the presence of the chelation between the methoxy group and potassium cation in the carbanion intermediate formed via the addition of the benzylic carbanion onto the alkene. It should be noted that the reactions with electron-deficient styrenes having halogen atoms or a trifluoromethyl group on the aryl group did not afford the desired hydroalkylation product at all. In these cases, we observed anionic polymerization of styrenes. Next, we examined the substituent effect on the alkene. The hydroalkylation of α -methylstyrene was found to proceed smoothly to give **27** in good yield, whereas that of 1,1-diphenylethylene resulted in the isolation of **28** in 35% yield, along with the formation of diphenylmethane (**28'**) and 1,1,3,3-tetraphenylpropane (**28''**) in 7%

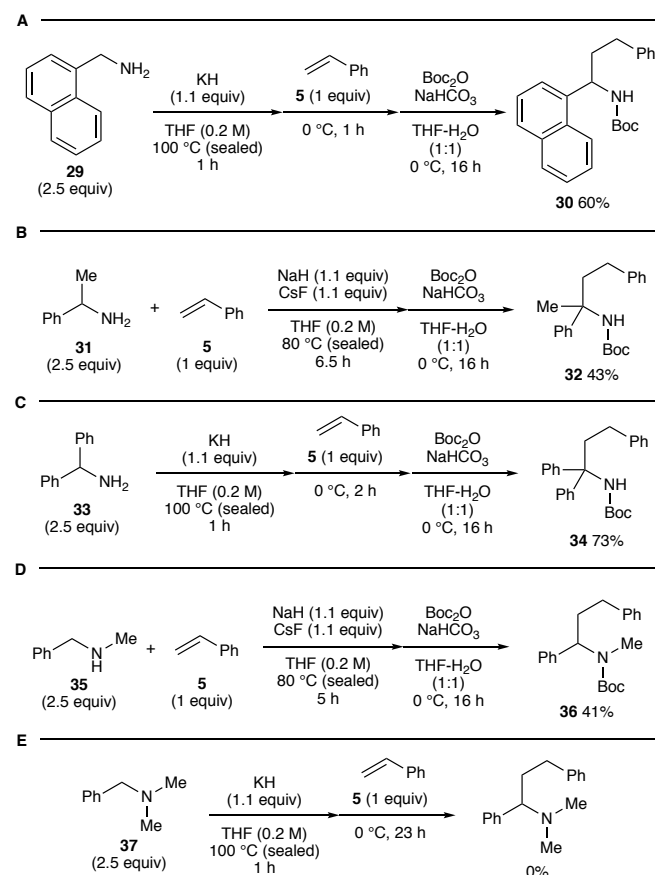
and 25% yields, respectively (see the Supporting Information for the proposed mechanism for the formation of **28'** and **28''**).



Scheme 6. Scope of styrenes. [a] Unless otherwise stated, the reactions were conducted using 1.25 mmol of benzylamine (**4**) in the presence of KH (1.1 equiv) in THF (0.2 M) at 100 °C (in sealed tube) for 1 h, followed by addition of styrenes (0.5 mmol) at 0 °C (the reaction times as well as the ratio of hydroamination/hydroalkylation products were noted in the parentheses). After separation by flash column chromatography, the resulting inseparable mixtures including amines were treated with Boc₂O and NaHCO₃ to isolate hydroalkylation products. The isolated yields were stated. [b] The reaction with styrene was conducted at 30 °C. [c] Diphenylmethane (**28'**) and (1,1,3,3-tetraphenylpropane (**28''**) were isolated in 7% and 25% yields, respectively, based on 1,1-diphenylethylene used (see the Supporting Information for details).

We then tested other benzylamines as the nucleophile for hydroalkylation of styrene (**5**) (Scheme 7). The hydroalkylation with 1-naphthylmethylamine (**29**) proceeded smoothly to afford **30** in 60% yield (Scheme 7A). Branched amines such as α -methylbenzylamine (**31**) and diphenylmethylamine (**33**) were found to be compatible for the hydroalkylation of styrene (**5**) (Scheme 7B and C). We observed that the protocol employing NaH and CsF (Table 1, entry 5) could work more efficiently in the reaction with α -methylbenzylamine (Scheme

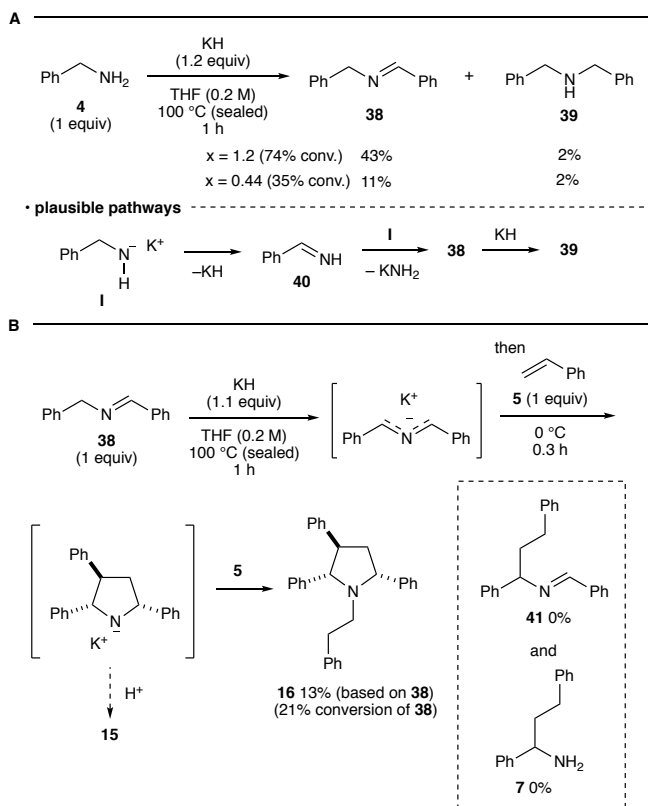
7B). We found that the presence of proton(s) on the nitrogen is essential for the productive hydroalkylation. Namely, *N*-methylbenzylamine (**35**) could be engaged in the hydroalkylation of styrene (**5**) under NaH-CsF system (Scheme 7D), whereas no reactivity was shown in the reaction of *N,N*-dimethylbenzylamine (**37**) (Scheme 7E).



Scheme 7. Scope of benzylamines.

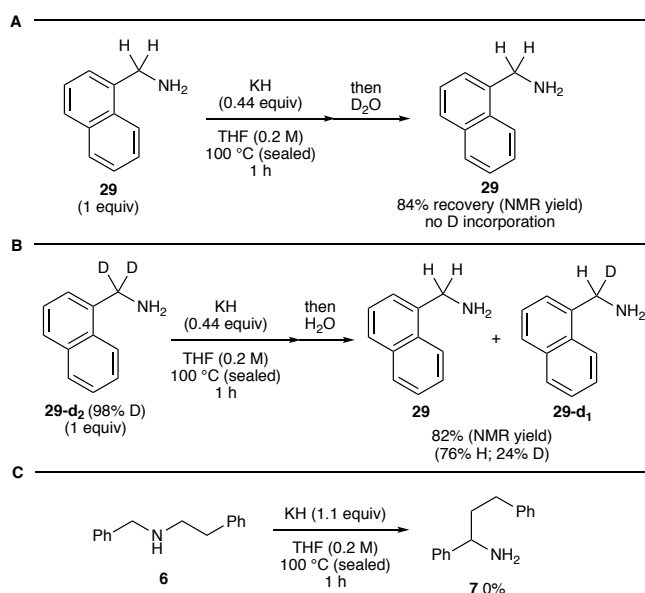
To obtain mechanistic insights on the present selective hydroalkylation process, we conducted several control experiments (Scheme 8). The optimization of the reaction conditions revealed that excess use (2.5 equiv) of benzylamines is optimal to realize the productive hydroalkylation. Indeed, treatment of benzylamine (**4**) with 1.2 equiv of KH converted benzylamine (**4**) to *N*-benzylimine **38** and dibenzylamine (**39**) in 43% and 2% yields, respectively. We assumed that *N*-benzylimine **38** is formed through condensation of benzylamine (**4**) and aldimine **40**, which is generated via β -hydride elimination of amide anion **1**,^[30] whereas dibenzylamine (**39**) is formed by hydride reduction of imine **38** with KH^[31-34] (Scheme 8A). On the other hand, treatment of benzylamine (**4**) with 0.44 equiv of KH, which is exactly the same stoichiometry with the optimized reaction conditions, could suppress the formation of **38** and **39** to around 13% combined yield. We also confirmed that the present hydroalkylation is not mediated via *N*-benzylimine **38**. Namely, the treatment of *N*-benzylimine **38** with KH followed by styrene (**5**) resulted in formation of pyrrolidine **16** in 13% yield via [3+2]-cycloaddition of a 2-azaallyl anion,^[35-37] which is derived from deprotonation of **38**, with styrene (**5**), followed by *N*-alkylation of

an anionic pyrrolidine intermediate with another styrene (**5**), while no formation of hydroalkylation products such as **41** and **7** was observed. It should be noted that pyrrolidine **15** observed in the reactions in Table 2 is formed via protonation of the anionic pyrrolidine intermediate.



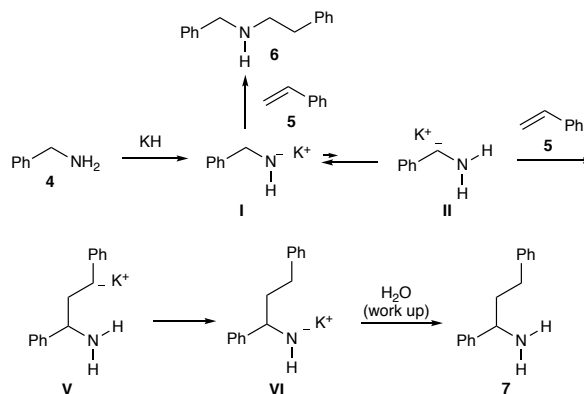
Scheme 8. Reactivity of benzylamine (**4**) and *N*-benzylimine **36** in the presence of KH.

Next, we examined deuterium labelling experiments (Schemes 9A and B). Treatment of 1-naphthylmethylamine (**29**) with 0.44 equiv of KH followed by aqueous workup with D₂O gave **29** back with no deuterium incorporation at the benzylic position (Scheme 9A). On the other hand, treatment of deuterated 1-naphthylmethylamine (**29-d₂**) with KH (0.44 equiv) followed by workup with H₂O resulted in 76% loss of deuterium from **29-d₂**, providing a mixture of **29** and **29-d₁** (Scheme 9B). These results indicated that there is an equilibrium between the amide anion and the benzylic carbanion, while this equilibrium is biased to the amide anion. Finally, we confirmed that a pathway from hydroamination product **6** to hydroalkylation product **7** via base-mediated aza-[1,2]-Wittig rearrangement^[38] is unlikely (Scheme 9C).



Scheme 9. Deuterium labelling experiments with **27** and reactivity of **6**.

Based on these observations, a proposed mechanism for KH-mediated hydroalkylation of styrene (**5**) with benzylamine (**4**) was described in Scheme 10. Pretreatment of benzylamine (**4**) with KH allows for generation of amide anion **I**, which should be under an equilibrium with benzylic carbanion **II**. Addition of styrene (**5**) to the anionic species triggers selective C-alkylation of **II** to generate another benzylic carbanion intermediate **V** over *N*-alkylation to form **6**. Subsequent H-transfer of **V** with the intramolecular primary amine moiety generates amide anion **VI**, which is finally protonated via aqueous work-up to furnish the hydroalkylation product **7**.

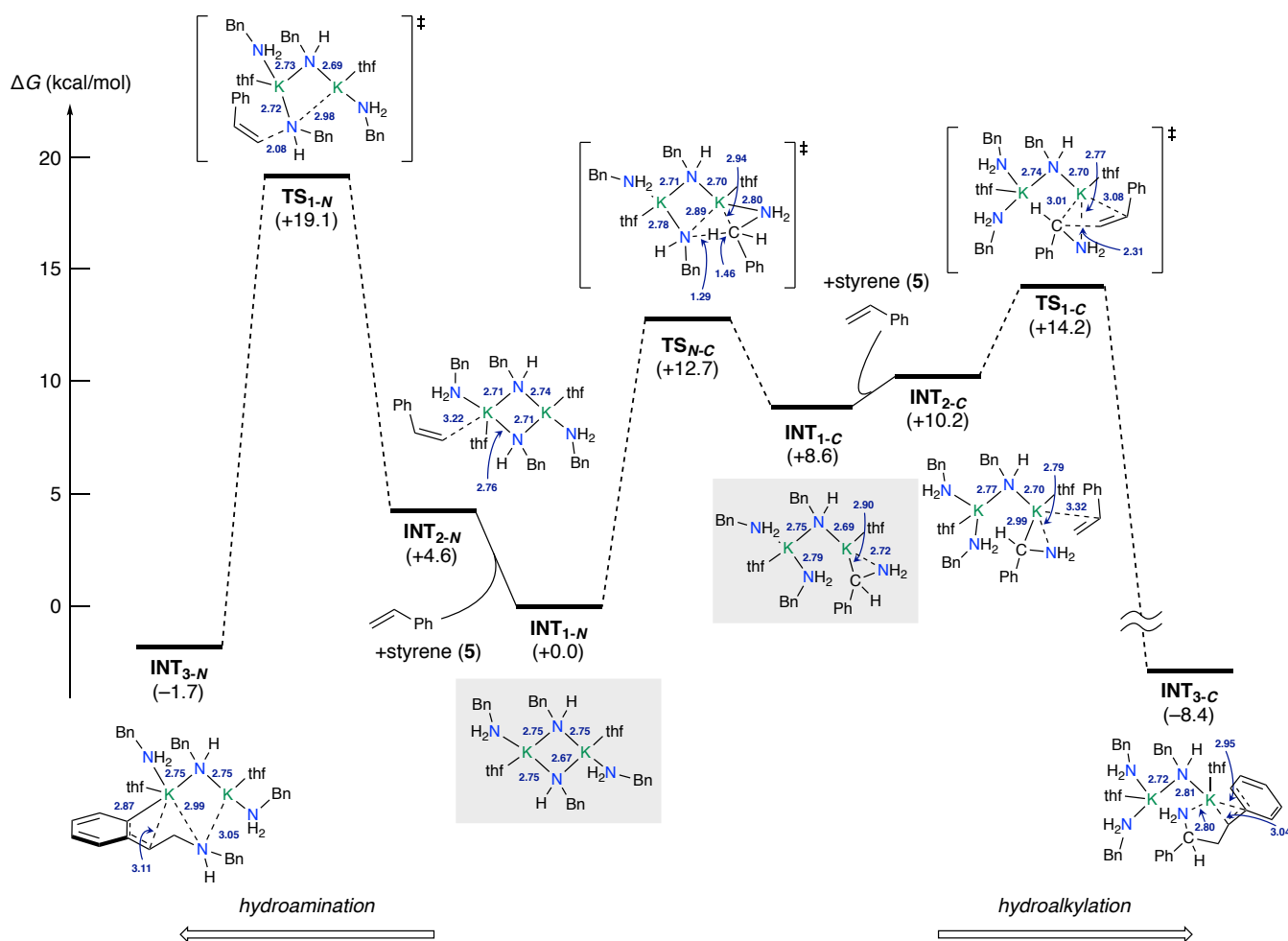


Scheme 10. Proposed mechanisms.

To further understand the present reactivity and selectivity for the hydroalkylation, we carried out the DFT calculations at the M06-2X/6-311++G*/SMD(THF)//M06-2X/6-31+G* level of theory. Based on the previous reports which revealed that potassium amides possess dimeric (or oligomeric) structures in THF solution,^[39-41] we adopted a dimeric structure as a model complex of the potassium amide. In addition, given that use of more than 2 equivalents of benzylamine (**4**) to KH was required to avoid the undesired side reactions (Scheme 8), we assumed that the coordination of benzylamine (**4**) should be involved in the potassium amide.^[18,24] We thus located the potassium

amide dimer **INT_{1-N}** having the coordination of benzylamine (**4**) and THF (Scheme 11). The possible pathway for the deprotonation of the benzylic proton of the coordinated proximal benzylamine (**4**) was first examined. The reasonable deprotonation pathway was elucidated with **TS_{N-C}** with a reasonable activation barrier ($\Delta G^\ddagger +12.7$ kcal/mol) to give carbanion **INT_{1-C}**, which is more unstable (+8.6 kcal/mol) than **INT_{1-N}**, yet kinetically accessible; these species can exist in an equilibrium under the reaction conditions. We also found that 1,2-H-shift from the potassium amide species for the formation of carbanion species necessitates a very high activation energy and thus this pathway is unlikely (for details, see the Supporting Information). Next, starting from the amide anion **INT_{1-N}** and the carbanion **INT_{1-C}**, the subsequent hydroamination and hydroalkylation processes with

styrene (**5**) were examined and the reaction pathways of the lowest energy barriers were presented in Scheme 11. The hydroamination (on the left side of Scheme 11) proceeds via the transition state **TS_{1-N}**, which is located at +19.1 kcal/mol. In the case of the hydroalkylation process (on the right side), the formation of the carbanion species **INT_{1-C}** makes the corresponding potassium cation less crowded and more accessible by styrene (**5**). The efficient coordination of styrene (**5**) promotes the C–C bond formation smoothly with more stable transition state **TS_{1-C}** (+14.2 kcal/mol) than **TS_{1-N}** for the hydroamination. These results corroborated the reactivity and selectivity observed in the present KH-mediated hydroalkylation process.



Scheme 11. DFT calculations on the hydroamination and hydroalkylation reactions of modeled dimeric species with styrene (**5**). Energy changes and bond lengths at the M06-2X/6-311++G*/SMD(THF)//M06-2X/6-31+G* level of theory are shown in kcal/mol and Å, respectively.

Conclusions

We have presented a new disconnection approach toward 1,3-diarylpropylamines based on base-mediated hydroalkylation of styrenes with benzylamines. Use of potassium hydride as the base is the key enabling the present unusual hydroalkylation selectively over the common hydroamination.

Supplementary Material

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/MS-number>.

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Author Contribution Statement

S.C. designed the studies. J.H.P. and B.W. performed the experiments. K.W. and R.T. conducted DFT calculations. J.H.P., R.T. and S.C. wrote the manuscript.

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