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Scalable anti-Markovnikov hydrobromination of aliphatic and aromatic olefins†

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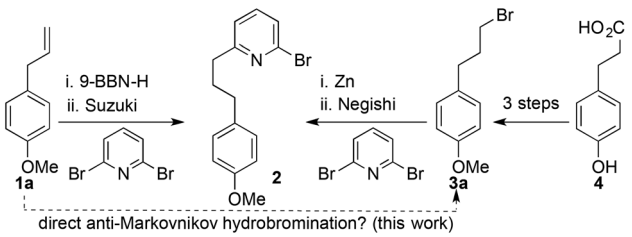
To improve access to a key synthetic intermediate we targeted a direct hydrobromination-Negishi route. Unsurprisingly, the anti-Markovnikov addition of HBr to estragole in the presence of AIBN proved successful. However, even in the absence of an added initiator, anti-Markovnikov addition was observed. Re-examination of early reports revealed that selective Markovnikov addition, often simply termed "normal" addition, is not always observed with HBr unless air is excluded, leading to the rediscovery of a reproducible and scalable initiator-free protocol.

Terminal alkenes are readily converted into valuable synthetic intermediates for metal-mediated cross-coupling reactions by hydro-metallation to give organo-boron[1] and other organo-metallics.[2] These reactions typically proceed under steric control to give the primary organometallic, often designated as the "anti-Markovnikov" product, a term that refers back to seminal work done over 140 years ago by Victor Markovnikov on the analogous addition of HI to alkenes.[3,4]

We recently applied such a hydrometallation-Suzuki approach to the synthesis of bromopyridine **2**,[5a] a key intermediate in the synthesis of mechanically chiral rotaxanes, stabilised reactive organometallic species and interlocked catalysts;[5] hydroboration of commodity chemical estragole (**1a**) with 9-BBN-H followed by an *in situ* cross coupling with 2,6-dibromopyridine yielded **2** in a concise manner (Scheme 1). However, on scale up we encountered problems with purification due to the borinic acid by-product, which, in addition to the high cost of 9-BBN-H, led us to explore other routes to **2**. Accordingly, we explored a Negishi approach employing an organozinc species produced *in situ* from bromide **3a**,[6] itself accessed in three steps from cheap and readily available hydroxyphenyl propionic acid **4**.[7] However, although the Negishi coupling step is efficient and scalable, the three-step synthesis of bromide **3a** once again proved cumbersome on scale up.



Scheme 1 Reported[5a,7] and proposed routes to bromopyridine **2**.

These issues led us to consider the direct anti-Markovnikov hydrobromination of estragole to produce **3a** in order to combine the key advantages of both syntheses. This approach proved extremely successful giving rapid access to **3a** and thus **2** in multi-gram quantities. More importantly, as a result of these studies we made an initially surprising observation: even in the absence of added initiators the hydrobromination of **1a** proceeds in reasonable selectivity to give the anti-Markovnikov product.

Here we report how this observation led to the rediscovery of simple scalable conditions for synthesis of primary bromides under "initiator free" conditions from alkyl and aryl alkenes. Our results increase the availability of primary bromides directly from feedstock alkene substrates.

The hydrobromination of olefins is generally held to proceed through two competing pathways:[8] polar pathway **I** *via* the most stable carbocation typically resulting in the branched, Markovnikov product, and radical pathway **II** *via* the most stable radical, resulting in the linear, anti-Markovnikov product (Fig. 1). To favour pathway **II**, reactions are carried out in apolar solvents in the presence of radical initiators (the "peroxide effect")[9] or under irradiation.[10] The Markovnikov and anti-Markovnikov products are also often simply called the "normal" and "abnormal" products respectively.[11]

Surprisingly, direct synthesis of primary bromides from monosubstituted alkenes by reaction with HBr appears to be a

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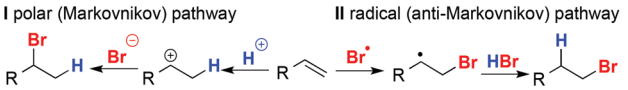
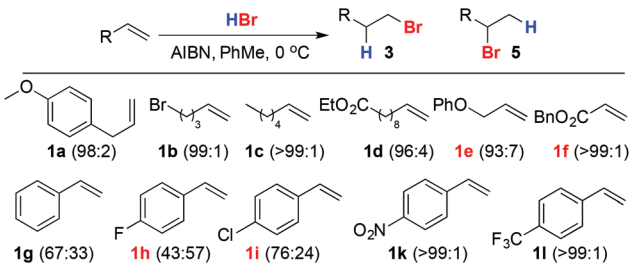


Fig. 1 Polar and radical pathways in the hydrobromination of alkenes.

relatively under-used reaction;[12] a simple search gave only 330 examples compared with the >48 000 such bromides reported.[13] We were also surprised to be unable to find anything recognisable as an organic methodological study in which a variety of substrates are screened under the same conditions, presumably because most work on the peroxide effect was carried out in the first half of the 20th century with each paper reporting only a few examples.[11] Thus, most recent reports of this transformation are confined to isolated examples as part of a larger synthetic campaign.

A brief screen of conditions[14,15] identified the use of HBr in PhMe in the presence of AIBN as appropriate, giving **3a** in excellent 97 : 3 selectivity (Scheme 2).[16] A minor drawback of this procedure on larger scales is the relatively high loading (13 mol%) of AIBN required. Unfortunately, attempts to reduce this led to erratic results (see below). However, the excess AIBN could be removed readily simply by filtering the reaction mixture through silica prior to evaporation and applying this procedure allowed us to reliably produce **3a** across a range of scales (1–200 mmol) in excellent yield (98%).

Moreover, these conditions proved general for representative monosubstituted aliphatic alkenes (**1b–f**). The slightly reduced selectivity in the case of allyl ether **1e** may be due to anchimeric assistance by the proximal O atom favouring the linear product. To our knowledge there are no previous reports of the direct addition of HBr to aromatic alkenes to give the primary bromide product in high selectivity,[17,18] presumably because the aromatic substituent can stabilise the cation formed in the Markovnikov pathway. In keeping with this, poor selectivity was observed in the case of styrene (**1g**) and this was reduced further in the case of a weakly electron donating *p*-fluoro substituent (**1h**). Conversely, a weakly electron-withdrawing *p*-chloro substituent (**1i**) led to higher selectivity and strongly electron-withdrawing substituents (**1k**, **1l**) gave excellent selectivity for the linear product.[17]



Scheme 2 Addition of HBr in PhMe to alkenes. Figures in parentheses refer to the selectivity **3** : **5**. Reagents and conditions: HBr in PhMe (sat.), AIBN (13 mol%), 0 °C, 2 h.

Based on these results the reaction of HBr in toluene with AIBN appears general for aliphatic alkenes but only applicable to electron styrenes bearing strongly electron withdrawing substituents. However, during our attempts to reduce the AIBN loading we made an unexpected observation: on small scales (1 mmol), even when no external initiator was added a significant selectivity for primary bromide **3a** was still observed, albeit with poor reproducibility. Based on the received wisdom of undergraduate chemistry this result is superficially surprising as, in the absence of added initiators or irradiation, the Markovnikov product is predicted in systems that lack significant electronic bias.[19]

In order to understand this observation we returned to the early publications in the field, in particular an excellent contemporary review from Walling.[11] This revealed a number of interesting points often omitted in recent discussions. Firstly, many of the early investigations of the addition of HBr to alkenes were conducted using the neat alkene, rather than under dilute conditions where the polar pathway is dramatically retarded. Secondly, in order to observe the Markovnikov product, great care was always taken to use extremely pure alkene substrates and exclude oxygen and other adventitious oxidants because, although Markovnikov addition is the rule for HCl and HI, the case of HBr is far more nuanced; even in the presence of vanishingly small quantities of oxidants, anti-Markovikov addition can compete and even dominate in the case of alkenes that are not activated to Markivnikov addition.

Thus our surprise observation was in fact common knowledge when the peroxide effect was first discovered. Perhaps unhelpfully, although Markovnikov's rule is often discussed in the context of hydrobromination, HBr is the only hydrohalous acid in which this outcome is sometimes hard to observe experimentally as anti-Markovnikov addition often competes due to the presence of adventitious oxidants. Indeed, the terms "normal" and "abnormal" addition actually seem to have originally referred to the reactions of HI and HCl in which no peroxide effect is observed and thus the abnormal addition actually refers to the contrast with these products, rather than with that observed in the case of HBr "normally".

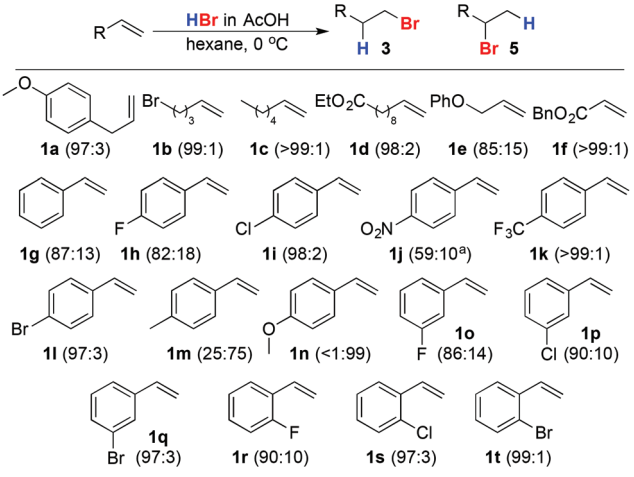
During our literature search, one of the early examples of initiator-free hydrobromination caught our attention. Sherrill and co-workers reported in 1934 that HBr added as a solution in AcOH gave reliable anti-Markovnikov addition to pent-1-ene and hept-1-ene in hexane.[20] Sherrill's conditions have been applied only twice in synthesis and the origin of the unusual reaction outcome was not commented upon.[21,19a,b] These conditions are particularly attractive as the use of a commercially available solution of HBr in AcOH is operationally simpler than using HBr gas to produce an HBr solution.

Under Sherrill's original conditions, aliphatic alkenes **1a–f**, with the exception of allyl ether **1e**, were hydrobrominated in excellent selectivity, comparable to that observed in toluene in the presence of AIBN. Furthermore, these conditions deliver improved selectivity (>80%) for the primary bromide product in the case of styrene itself (**1g**) and *p*-fluoro-styrene (**1h**). Furthermore, even weakly (**1i**, **1l**) electron withdrawing *para* sub-

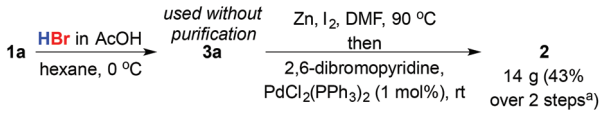
stituents led to excellent (>95%) selectivity for the primary bromide. Surprisingly, the reaction of *p*-NO_2 styrene (**1k**) failed to reach completion and gave poor selectivity for reasons that are currently unclear. Styrenes bearing a *p*-electron donating substituent (**1m**, **1n**) led unsurprisingly predominantly to Markovnikov addition. The reaction is not limited to *para*-substituted styrenes; *meta*- (**1o–1q**) and *ortho*-halo styrenes (**1r–1t**) were hydrobrominated in good to excellent selectivity (Scheme 3).

The anti-Markovnikov hydrobromination reaction in hexane under Sherril's conditions is operationally far simpler than those commonly employed in synthesis; the substrate is simply dissolved and the HBr added directly as a commercially available solution in AcOH, removing the need to saturate the reaction solvent with HBr gas or the addition of supplementary initiators, the bi-products of which must be removed after the reaction. The only requirement for the reaction to be reproduced reliably across a range of scales was for air to be passed through a solution of the alkene in hexane prior to the addition of AcOH–HBr. It is worth noting that the observation of spontaneous anti-Markovnikov addition in apolar solvents has previously led to Mahrouz and co-workers[22] and Sergeev *et al.*[23] to independently propose alternative mechanisms to the standard Markovnikov and anti-Markovnikov models (Fig. 1). Our results clearly support the peroxide effect orthodoxy; on larger scales, reactions in hexane–AcOH are enhanced when air is introduced intentionally, suggesting that O_2 initiates the process by oxidising HBr to produce Br radicals.

Finally, to demonstrate the advantage of the initiator-free hydrobromination process we returned to our original problem, the simple, rapid and concise synthesis of bromopyridine **2** (Scheme 4). Hydrobromination of **1a** gave 23 g (90%) of **3a**. Importantly no purification was required beyond simple aqueous workup. Subsequent formation of the primary organozinc of **3a** under Huo's conditions[6] and cross-coupling with 2,6-dibromopyridine yielded 14 g of key intermediate **2** (60% yield; 43% based on estragole over two steps), demonstrating that this approach to primary bromides from feedstock alkene substrates produces material in suitable purity for direct application in cross-coupling reactions.



Scheme 3 Addition of HBr in hexane–AcOH to alkenes. Figures in parentheses refer to the selectivity **3** : **5**. Reagents and conditions: **1**, HBr-AcOH (33% v/v, 2 equiv.), hexane, 0° C, 2 h. [a]The balance of material (~31%) is unreacted starting material.



Scheme 4 Synthesis of alkyl pyridine **2** from estragole. [a]Based on **1a**; 60% yield based on 2,6-dibromopyridine.

Conclusions

In conclusion, we have developed simple, scalable and high yielding conditions for the selective direct anti-Markovnikov hydrobromination of monosubstituted terminal aliphatic and, for the first time, aromatic alkenes. The omission of initiators such as AIBN or benzoylperoxide removes the need for purification of the products, allowing them to be taken forward directly in further synthetic manipulations. To be clear, we achieved this not by discovering new conditions but by investigating and generalising a previously reported but largely forgotten procedure from Sherrill and co-workers. That this procedure has remained largely ignored for so long is surprising given its synthetic utility and may be in part due to the counterintuitive nature of the conditions, in that no obvious initiator is added, combined with the lack of previous methodological investigations. The results presented here should increase the synthetic availability of primary bromides as synthetic intermediates derived from feedstock monosubstituted terminal alkenes.

Acknowledgements

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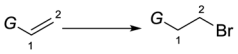

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