Highly Stereoselective, Intermolecular Haloetherification and Haloesterification of Allyl Amides

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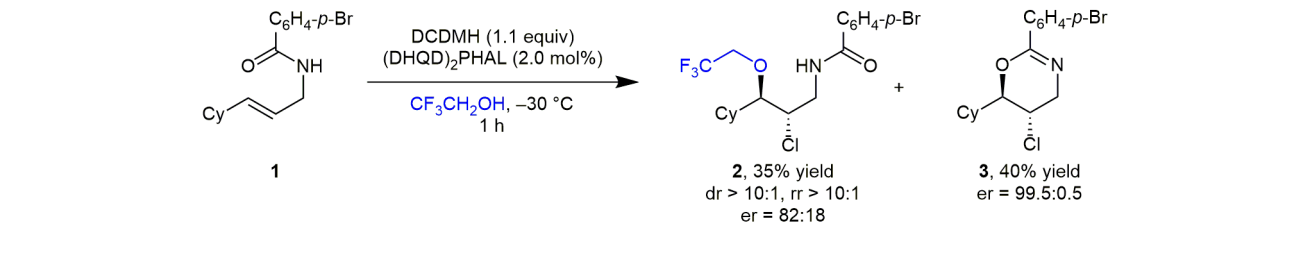
Asymmetric alkene halogenation is a powerful synthetic transformation that allows for a straightforward functionalization of readily available compounds into valuable chiral, halogenated building blocks. Although isolated reports of enantioselective variants appeared in the literature in the 1990s, the expansion of the scope and robustness of this transformation has only occurred since 2010, when the group of Professor Babak Borhan at Michigan State University (USA) published a report of a highly enantioselective chlorolactonization reaction. Since then, this research area has witnessed dramatic progress with respect to the scope of transformations and mechanistic understanding. Numerous reviews on this chemistry have already appeared in this short time (see the original *Angew. Chem. Int. Ed.* manuscript for these and other leading references).

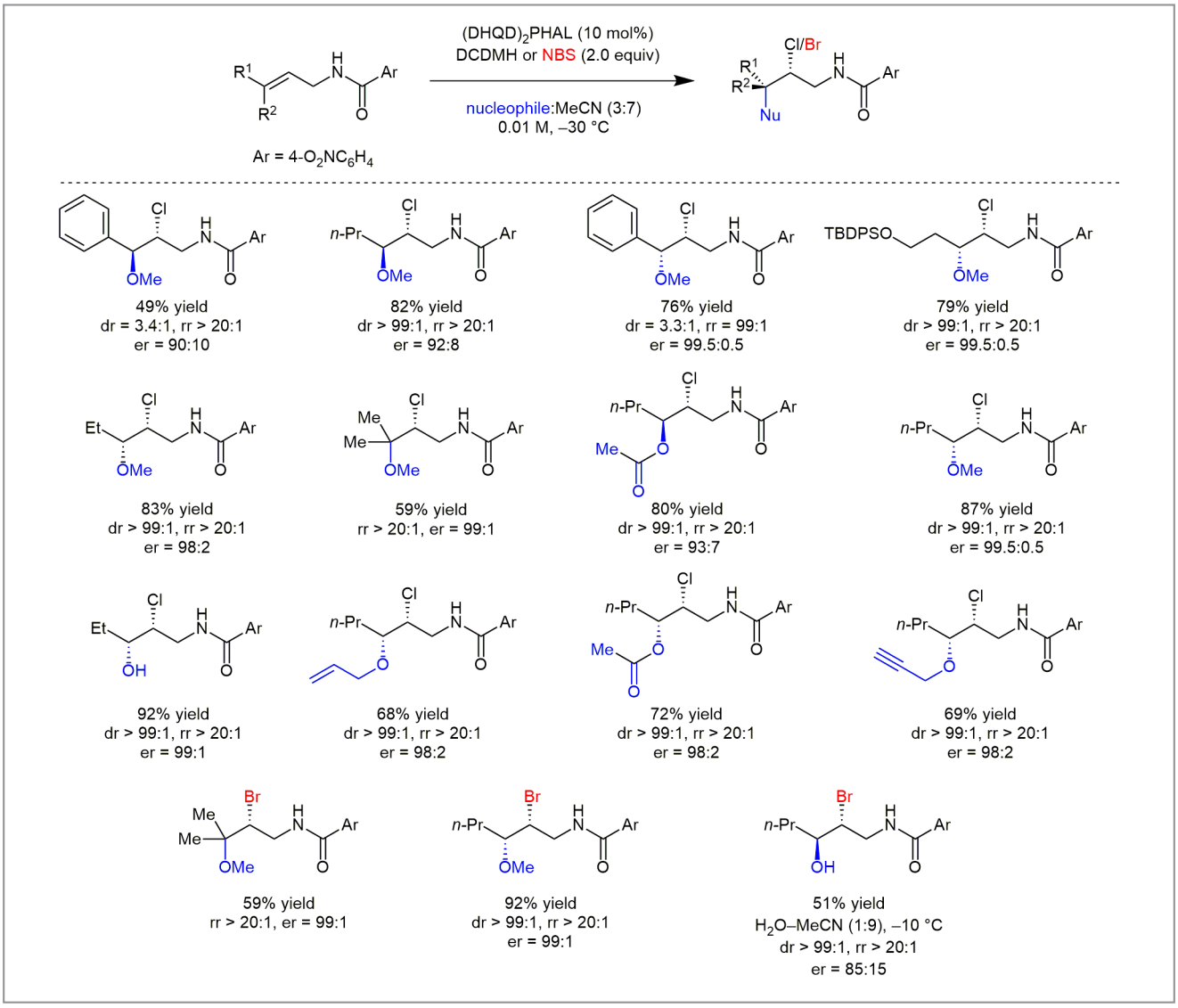
Recently, focus has shifted to the more challenging intermolecular halofunctionalization of alkenes. Although significant progress has been made in this area, some of the most readily available nucleophiles such as water and alcohols had yet to be demonstrated as viable nucleophiles for this chemistry. Professor Borhan explained: "At the outset of this project, the aim was to develop an intermolecular haloetherification reaction with a wide substrate scope and good stereoselectivities while using readily available catalysts and reagents." The group identified many challenges very early in the project – 1) Preventing or minimizing facile intramolecular nucleophilic capture by the pendant amide nucleophile (i.e. halocyclization) while promoting intermolecular nucleophilic capture of the intermediate by the weakly nucleophilic alcohols; 2) Addressing regioselectivity issues in substrates that do not have an intrinsic electronic bias for the site of nucleophilic capture; this latter requirement would enable the inclusion of aliphatic alkenes as compatible substrates; and 3) Discovering conditions that could be used with a variety of nucleophiles and halenium precursors with little or no modifications – this promiscuity has thus far been elusive in asymmetric alkene halogenation reactions, thereby necessitating the discovery of a unique catalyst/reagent system for different halenium source-nucleophile combinations.

Professor Borhan remarked: "The first evidence for the feasibility of an intermolecular chloroetherification reaction came (rather ironically!) while studying a halocyclization reaction (*Angew. Chem. Int. Ed.* **2011**, *50*, 2593)." While examining the asymmetric chlorocyclization of substrate **1** to give the dihydrooxazine **3** in CF_3CH_2OH (TFE), the undesired 'TFE-incorporated' product **2** was isolated in as high as 35% yield with moderate levels of enantioselectivity (er = 82:18) and exquisite regioselectivity (>10:1; see Scheme 1). Professor Borhan continued: "This result was encouraging to say the least, given the low nucleophilicity of TFE and no precedent for an intermolecular interception of the putative intermediate by an alcohol. Efforts were then directed towards coaxing this reaction to proceed exclusively via the intermolecular nucleophilic capture pathway by the judicious choice of reaction conditions."

Graduate student Bardia Soltanzadeh was able to demonstrate that numerous parameters such as the choice of the amide group, substrate concentration, solvent composition, temperature and catalyst loading could all be tweaked to promote intermolecular chloroetherification in preference to the



Scheme 1 Discovery of an asymmetric intermolecular chloroetherification of allyl amides

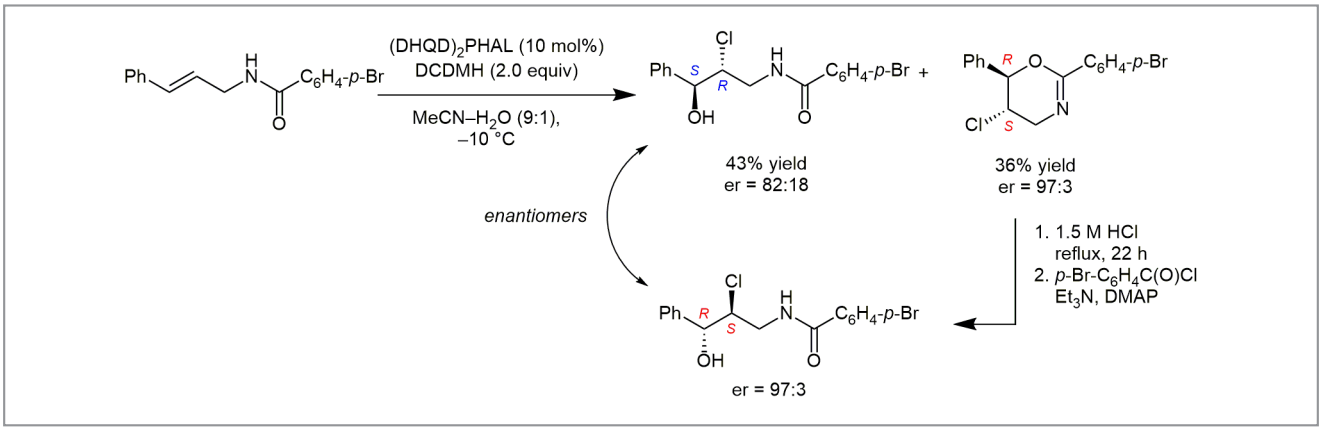


Scheme 2 Substrate scope for haloetherification and haloesterification of allyl amides

halocyclization reaction. More importantly, these reaction parameters also affected the regioselectivity and enantioselectivity for the transformation. Professor Borhan explained: "Eventually, conditions were identified that gave >20:1 rr, >99:1 dr and up to >99:1 er for a variety of substrates for the chloroetherification reaction with MeOH as the nucleophilic component (see Scheme 2). Aliphatic alkenes (*E*-, *Z*- and trisubstituted alkenes) were the best substrates for this chemistry, whereas *trans*-styryl substrates gave lower yields due to competing halocyclization that could not be suppressed completely."

In an effort to further showcase the generality of these conditions, other alcohols, water and carboxylic acids were evaluated as nucleophiles with both 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, as the Cl source) and *N*-bromosuccinimide (NBS, as the Br source). All these reactions proceeded with excellent stereoselectivities (selected results are highlighted in Scheme 2).

Professor Borhan remarked: "Noteworthy is the fact that the chiral catalyst is responsible not only for the high enantioselectivities but also for the exquisite regioselectivity for reactions employing aliphatic substrates (for example, noncatalyzed reactions gave rr values of ~4:1 at best for these



Scheme 3 Stereodivergence in the formation of halohydrin and dihydro-oxazine products

substrates). These results hint at extensive pre-organization of the substrate–nucleophile–catalyst ternary complex in addition to the halogen source catalyst H-bonded complex that we have previously established (*J. Am. Chem. Soc.* **2010**, *132*, 3298)."

According to Professor Borhan, the culmination of this work has addressed a well-known limitation in asymmetric alkene halogenation reactions. "Moreover, a fairly diverse substrate and nucleophile scope and the use of commercially available catalyst ($DHQD_2PHAL$) and halogenating reagents (DCDMH or NBS) should make this chemistry readily accessible to synthetic chemists," he said.

"Preliminary investigations also reveal intriguing nucleophile-dependent face selectivity in the alkene halogenation step. The halocyclization and the intermolecular haloetherification reactions exhibit complementary alkene face selectivity for the halenium capture despite the fact that they are formed in the same reaction! This was confirmed by derivatization studies (see Scheme 3, note the complementary absolute stereochemistry at the newly created stereocenters)," said Professor Borhan, who concluded: "These results have prompted a detailed investigation into the origins of the enantioselectivity for this class of reactions."

About the authors

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Bardia Soltanzadeh was born in Esfahan (Iran) in 1984. He obtained his B.Sc. from Shahid Beheshti University in Iran in 2007 and his M.Sc. from Sharif University of Technology (Iran) in 2009. He is currently a PhD student at Michigan State University (USA) and his research is mainly focused on the development of the enantioselective intermolecular halofunctionalization of alkenes.

Dr. A. Jaganathan

Arvind Jaganathan obtained his B.Sc. and M.Sc. degrees in organic chemistry (2005) from the University of Pune (India). After a short stint as a research assistant at CSIR-National Chemical Laboratory, Pune (2006), he commenced his graduate studies in Professor Borhan's group at Michigan State University (USA) in 2007. His PhD research was primarily focused on the development of novel asymmetric alkene halogenation reactions. Arvind is currently a senior chemist at The Dow Chemical Company (USA).

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Prof. B. Borhan

Babak Borhan received his PhD in 1995 from the University of California, Davis (USA), under the joint mentorship of Professors Mark Kurth and Bruce Hammock. He then joined Professor Koji Nakanishi's group at Columbia University (USA), focusing on research related to the isomerization events in the rhodopsin photocycle. In 1998, he started his independent career at Michigan State University (USA) and is currently a full professor in chemistry. His research spans areas of organic synthetic methodology, bioorganic chemistry, and circular dichroism spectroscopy.