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Formal asymmetric hydrobromination of styrenes *via* copper-catalyzed 1,3-halogen migration†

R. J. Van Hoveln, S. C. Schmid, M. Tretbar, C. T. Buttke and J. M. Schomaker*

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An enantioselective Cu(I)-catalyzed 1,3-halogen migration reaction accomplishes a formal hydrobromination by transferring a bromine activating group from a sp2 carbon to a benzylic carbon in good er and with concomitant borylation of the Ar–Br bond. Computational modelling aids in understanding the reaction outcome and suggests future directions to improve the formal asymmetric hydrobromination. The benzyl bromide can be displaced with a variety of nucleophiles to produce a wide array of functionalized products.

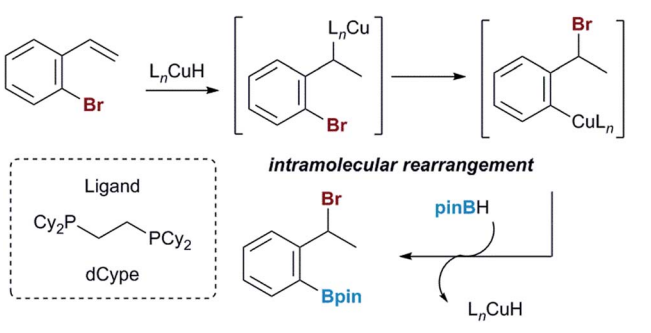
The enantioselective halogenation of olefins remains a challenging goal in organic synthesis.[1] Although recent strides have been made in asymmetric α-halogenation of carbonyls,[2] olefin aminohalogenations,[3] semi-pinacol rearrangements[4] and halocyclizations,[5] to the best of our knowledge, catalytic, enantioselective hydrohalogenations of olefins have not been reported.[6]

Our group has recently described the 'recycling'[7] of an activating group through a Cu-catalyzed 1,3-halogen migration[8] that combines a formal styrene hydrobromination with an arene borylation (Scheme 1).[9,10] This converts readily available halostyrenes into compounds bearing two differentiated functional groups that can be further transformed at each site in an orthogonal manner.[9] Crossover experiments established that the bromine transfer occurs in an intramolecular fashion, which led us to postulate that the halogen migration could be achieved in an enantioselective fashion. Our experimental efforts in this area, combined with DFT calculations, have provided: (1) a highly enantioselective hydrohalogenation method for a variety of substituted halostyrenes, and (2) a model for predicting the behavior of a broad range of substrates in this challenging transformation.

Studies were initiated by exploring a series of chiral bidentate phosphine ligands with CuCl (Table 1).[11] While three ligands (entries 2, 4 and 14) gave er's greater than 80 : 20 at 50 °C, (*S*,*S*)-Ph-BPE (entry 14) gave the best combination of yield and er while producing none of the benzyl boronic ester **3**, prompting its use in further investigations.

Further reaction optimization probed the reaction dependence on temperature, concentration and base (Table 2). While the yield decreased at rt, the er improved compared to running the reaction at 50 °C (entry 1). Decreasing the concentration from 0.5 M to 0.1 M significantly improved the mass balance by decreasing the rate of atom transfer radical polymerization (ATRP, entry 2), a major side reaction.[12] Higher catalyst loadings did not increase conversion, but switching the base from KO^{t}Bu to NaO^{t}Bu increased the yield to 75% at the expense of er (entries 3 and 4). The best results were obtained by lowering the reaction temperature to 0 °C in the presence of NaO^{t}Bu as the base (entry 5). Under these conditions, the enantioenriched benzyl bromide was produced in 73% yield and 98 : 2 er.

After significant optimization efforts, the scope of the enantioselective reaction exhibited generally good er (Table 3). Changing the OMe group to a bulkier O^{i}Pr group resulted in a lower yield but excellent er (entry 2). Substitution of the bromine activating group with iodine diminished the er to 83 : 17 (entry 3) due to the sensitive nature of the benzyl iodide product. The parent 2-bromostyrene still exhibited good er (entry 4), but the yield was significantly lower compared to the 94% obtained using the achiral version of the catalyst, which is supported by a 1,2-bis(dicyclohexylphosphino)ethane ligand, presumably due to ATRP competition.[9] Substitution at the

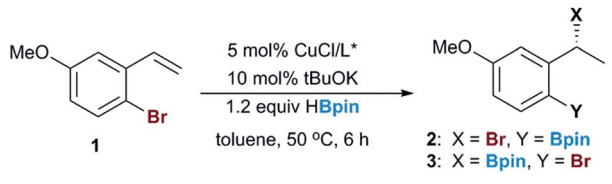


Scheme 1 Tandem 1,3-halogen migration/borylation catalyzed by a Cu(I) complex.

Department of Chemistry, University of Wisconsin, 1101 University Ave., Madison, Wisconsin 53706, USA. E-mail: schomakerj@chem.wisc.edu

† Electronic supplementary information (ESI) available: Experimental procedures and characterization for new compounds are provided. CCDC 985120. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc02040e

Table 1 Preliminary investigation of ligands for enantio-selective 1,3-halogen migration[a]



Entry	Ligand[a]	1	2	3	er
1	(*R*)-T-BINAP	23	17	0	77 : 23
2	(*R*)-DM-BINAP	18	33	0	83 : 17
3	SEGPHOS	12	29	0	65 : 35
4	DTBM-SegPhos	15	8	0	81 : 19
5	(*S*)-TunePhos	8	46	0	29 : 71
6	TangPhos	22	17	31	n.d.
7	DIPAMP	20	17	0	53 : 47
8	(*R*,*R*)-Me-DuPhos	8	23	0	61 : 39
9	(*S*,*S*)-^{i}Pr-DuPhos	23	0	0	n.d.
10	(*R*)-BenzP*	36	21	0	36 : 64
11	(*S*)-Josiphos SL-J003-1	0	82	0	68 : 32
12	(*S*,*S*)-Me-BPE	19	0	0	n.d.
13	(*R*,*R*)-^{i}Pr-BPE	13	17	0	45 : 55
14	(*S*,*S*)-Ph-BPE	14	34	0	89 : 11

[a] See the ESI for the remaining ligand structures.

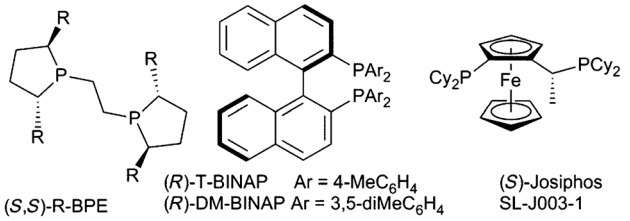
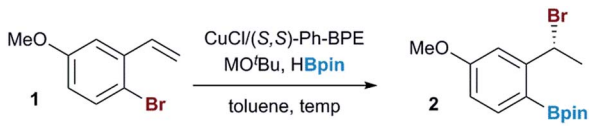


Table 2 Further optimization of the asymmetric 1,3-halogenation migration[a]



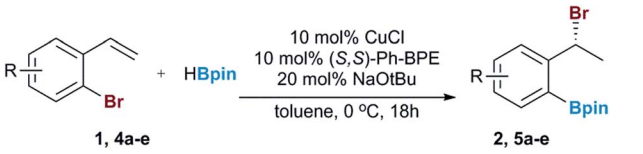
Entry	Temp (°C)	MO^{t}Bu	Loading	[Conc]	1[a]	2	er
1	25	KO^{t}Bu	5%	0.5 M	16	46	93 : 7
2	25	KO^{t}Bu	5%	0.1 M	52	34	91 : 9
3	25	KO^{t}Bu	10%	0.1 M	41	38	92 : 8
4	25	NaO^{t}Bu	10%	0.1 M	13	75	87 : 13
5	0	NaO^{t}Bu	10%	0.1 M	<10	73[b]	98 : 2

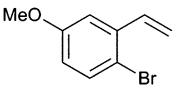
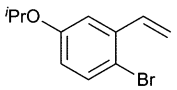
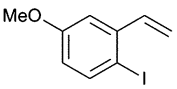
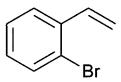
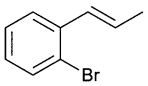
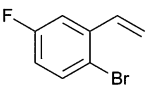
[a] NMR yields determined using 1,1,1,2-tetrachloroethane as the internal standard. [b] Isolated yield.

β-carbon of the styrene, as well as fluorine at C5, were tolerated (entry 5) and gave the benzyl bromide products in moderate er.

Recycling of the benzyl bromide was demonstrated by transforming **1** into a variety of benzyl-substituted aryl boronic esters, typically in one pot (Scheme 2). Asymmetric 1,3-halogen migration, followed by displacement of the bromide with sulfur nucleophiles to give compounds **6** and **9**, showed essentially no degradation in the er, while selenium, nitrogen, and carbon nucleophiles (**7**–**8**, **10**–**11**) resulted in slight loss in enantioenrichment. The use of chiral nucleophiles, such as the cysteine leading to **9**, did not lead to significant epimerization at the benzyl carbon (95 : 5 dr) and gave a product with >99 : 1 er. A derivative of **6** was employed to establish the absolute stereochemistry of the 1,3-halogen migration through X-ray crystallography (see ESI for details†).

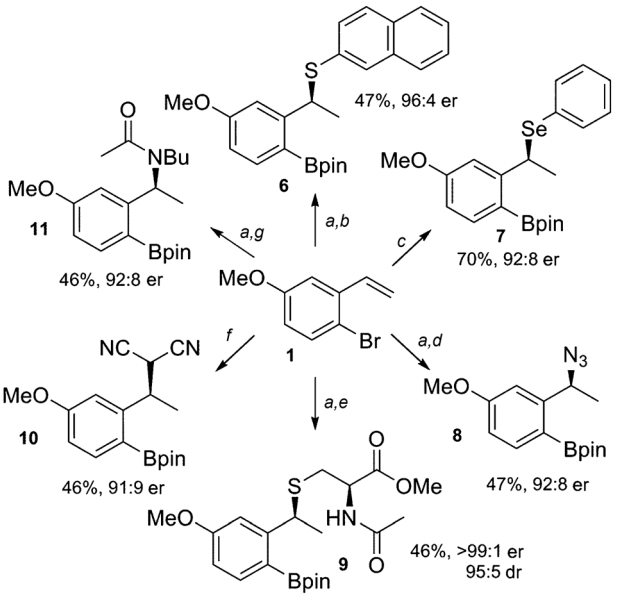
Table 3 Selected substrate scope



Entry	Substrate	Yield	er
1	 **1**	73% **2**	98 : 2
2	 **4a**	53% **5a**	>99 : 1
3	 **4b**	71%[a] **5b**	83 : 17
4	 **4c**	28% **5c**	92 : 8[b]
5	 **4d**	40% **5d**	95 : 5[c]
6	 **4e**	38% **5e**	92 : 8

[a] Trapped with LiSePh before isolation. [b] er determined after trapping with 2-naphthalenethiol. [c] er determined after trapping with LiSePh.

Often, qualitative observations concerning either the electronic or steric parameters of a particular system are used to rationalize reaction outcome.[13] However, our system did not seem to follow any particular pattern based on a qualitative analysis of electronic factors. To obtain a better understanding of the factors controlling the reactivity and provide insight into the types of bromostyrenes best suited for enantioselective 1,3-halogen migration, DFT calculations were carried out. Rather than modeling an overall reaction coordinate, three major



Scheme 2 Functionalizations of chiral benzyl bromides. (a) Standard asymmetric halogen migration conditions was followed by solvent removal. (b) 1.5 equiv. 2-naphthalenediol, 2.5 equiv. K_2CO_3, DMF, 1 h, rt. (c) Standard asymmetric halogen migration conditions and then 3 equiv. of LiSePh in ThF was added. (d) 3.0 equiv. NaN_3, DMSO, 40 °C, 1 h. (e) 1.5 equiv *N*-acetyl cysteine methyl ester, 2.5 equiv. K_2CO_3, DMSO, 40 °C, 3 h. (f) Standard asymmetric conditions and then 3.0 equiv. lithium malonitrile in THF was added. (g) 3 equiv. butylamine, 5 equiv. K_2CO_3, DMF, 40 °C, 1 h then 5 equiv. Ac_2O, 40 °C, 1 h.

features of the substrates were modeled with the goal of developing a straightforward, empirical equation capable of correlating substrate parameters with reaction yield for a range of substituted *o*-bromostyrenes in the asymmetric 1,3-halogen migration.[14] We hypothesized that greater electron density at the bromine-bearing carbon (carbon labelled γ, Fig. 1) would promote the 1,3-halogen migration reaction. The major ATRP side reaction was proposed to be favored by factors that promote or stabilize the formation of a benzyl radical (represented by $\Delta\Delta G$). Finally, the steric bulk of the (*S*,*S*)-Ph-BPE catalyst is significant, which could impact both the substrate scope and the yield; thus, a steric factor (the volume of the substrate relative to 2-bromostyrene) was also included in the computational studies (represented by χ).

Ten substrates were used as the "training set" to generate eqn (1) (Table 4). For the 10 substrates used to create eqn (1), the calculated yield matched the experimental yield to within ±10%, though many matched much more closely. Given the simplicity of our analysis and the tendency for some error in NMR yields[15], we felt that this was a sufficiently close fit to at least establish a trend in reactivity, if not the absolute yields. The close fit also indicates that the parameters we chose are indeed the major factors impacting yield. For the substrates used in generating eqn (1), χ and $\Delta\Delta G$ contributed nearly equally, whereas γ contributed approximately twice that of either χ or $\Delta\Delta G$. Each of these factors were parameterized from optimized structures (B3LYP/6-311++G(2d,p))[16,17] using Gaussian 09 [18] and NBO[19] (see the ESI for details†).

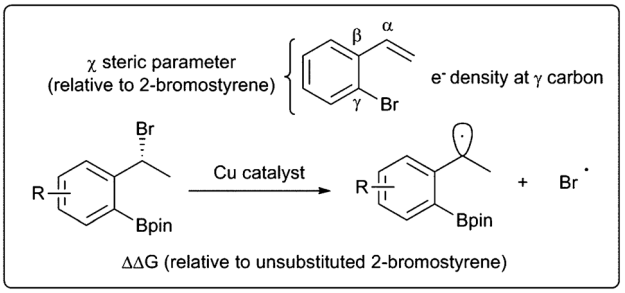
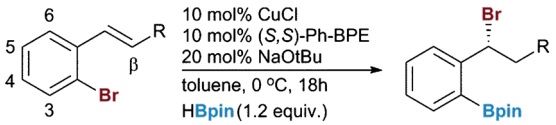


Fig. 1 Factors impacting yield.

Table 4 Training set of substrates to correlate calculated and experimental yields[a]



Entry	Substrate	Calc. yield	Exp. yield[a]	γ	$\Delta\Delta G$	χ
1	H	34	35	−0.069	0.00	0.00
2	5-OMe	65	73	−0.095	0.21	22.2
3	5-F	46	37	−0.087	−0.59	10.3
4	5-O^{i}Pr	56	54	−0.097	0.37	55.8
5	5-^{t}Bu	24	25	−0.075	0.16	48.9
6	4-^{t}Bu	13	4	−0.069	0.04	50.5
7	4-Ph	0.4	7	−0.072	−0.84	57.0
8	5-pyrryl	23	24	−0.081	−0.42	50.2
9	4-F	12	14	−0.057	−0.12	9.01
10	β-Me	39	40	−0.071	0.34	9.06

[a] NMR yield determined using 1,1,1,2-tetrachloroethane as the internal standard.

$$\text{Predicted yield} = -1415\gamma + 16.2(\Delta\Delta G) - 0.432\chi - 63.2 \quad (1)$$

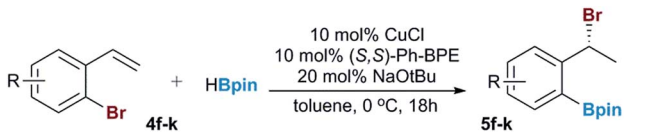
This straightforward equation indicates that, relative to 2-bromostyrene (Table 4, entry 1), increasing the electron density at the γ carbon results in increased yield (entry 2). However, if the $\Delta\Delta G$ of benzyl radical formation is negative compared to 2-bromostyrene (entry 3), the yield is adversely affected. Finally, the presence of remote, large R groups (entry 4) is also detrimental to the yield, presumably due to the bulkiness of the (*S*,*S*)-Ph-BPE ligand.

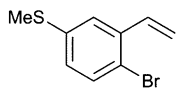
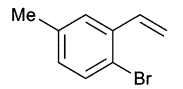
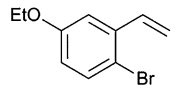
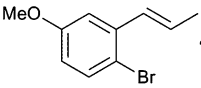
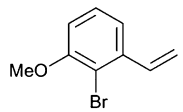
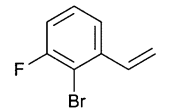
The predictive power of eqn (1) was then tested on a variety of 2-bromostyrene substrates that were not used in the generation of eqn (1) (Table 5). Eqn (1) predicted a poor yield when a -SMe group is placed *para* to the Br as in **4f**, and this was indeed the case due to the fact that sulfur participates in conjugation with the aromatic ring less effectively than oxygen, making the γ carbon relatively electron poor (Table 5, entry 1). Addition of a weakly donating group in the C5 position did not result in a significant improvement in yield (entry 2). Installation of an OEt group at the C5 position was predicted to give **5h** in 58% yield,

which was nearly identical to the observed yield of 57% (entry 3). Although substitution on the alkene resulted in slightly lower yields than expected, the observed and calculated yields were still comparable (entry 4). Placement of functional groups adjacent to the bromine (entries 5 and 6) might be expected to reduce the predictive power of eqn (1), since none of the substrates used to create the equation have steric bulk *ortho* to a reactive site. Indeed, even though eqn (1) predicted that placing OMe at C3 of **4i** would result in a quantitative yield, the actual yield of **5i** (entry 5) was only 50%. However, the model was useful for ascertaining the relative success of the 1,3-migration, as installing a F at C3 resulted in a good yield for the asymmetric 1,3-halogen migration (entry 6).

Establishing the relationship between various substrate parameters and reaction yield was a useful endeavor. The model enabled us to consider substrates that we would have not otherwise tried, both broadening the range of potential substrates and providing guidance for the development of new catalysts with improved substrate scope. Additionally, this multifaceted approach demonstrates the need to assess several reaction parameters that may act in concert, rather than focusing on a single factor as dictating the reaction outcome.

Table 5 Testing the predictive model for asymmetric 1,3-halogen migration



Entry	Substrate		Calculated yield	Yield	er
1		**4f**	10%	13%[a] **5f**	n.d.
2		**4g**	36%	30%[b] **5g**	92 : 8[c]
3		**4h**	58%	57%[b] **5h**	95 : 5[d]
4		**4i**	63%	50%[b] **5i**	97 : 3[d]
5		**4j**	Quant.	50%[b] **5j**	87 : 13
6		**4k**	Quant.	65%[a] **5k**	91 : 9[d]

[a] NMR yield determined using 1,1,1,2-tetrachloroethane as the internal standard. [b] Isolated yield. [c] er determined after trapping with LiSePh. [d] er determined after trapping with 2-naphthalenethiol.

Conclusions

A Cu(I) catalyst supported by a (*S*,*S*)-Ph-BPE ligand promotes an asymmetric cascade 1,3-halogen migration/borylation reaction that proceeds under mild conditions and results in a formal enantioselective addition of HBr across a carbon–carbon double bond. In-depth experimental and computational studies have allowed us to successfully correlate yields with features of both the substrate and the product, including electron density at the bromine-bearing carbon, the steric bulk of the substrate and the propensity of the product to form promiscuous radicals. A computational and experimental study of the mechanism is currently being conducted which will elaborate on the enantio-determining step and help extend the utility of 1,3-migration to incorporate a number of other functional groups.

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