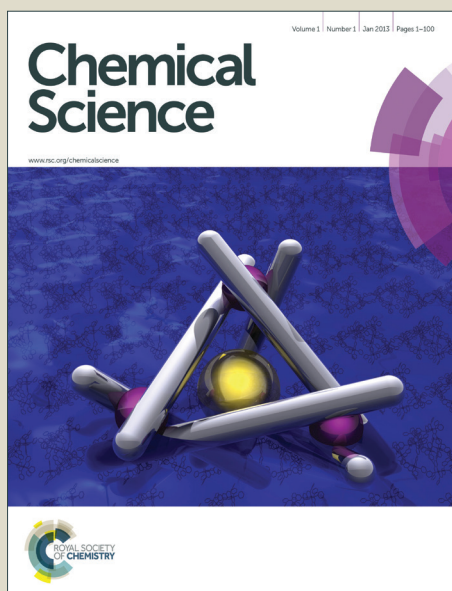


Chemical Science

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/chemicalscience

EDGE ARTICLE

Formal Asymmetric Hydrobromination of Styrenes via Copper-Catalyzed 1,3-Halogen Migration

Cite this: DOI:

10.1039/x0xx00000x

R. J. Van Hoveln, S. C. Schmid, M. Tretbar, C. T. Buttke, J. M. Schomaker^{*a}

Received 00th January 2012,

Accepted 00th January 2012

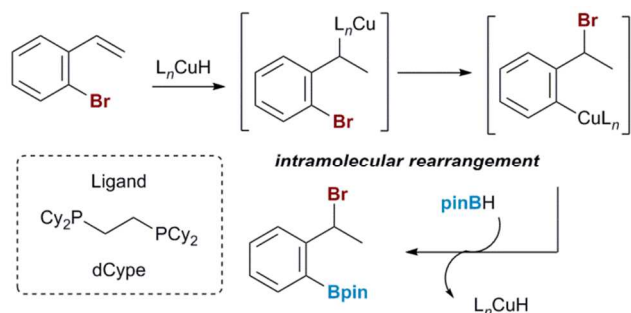
DOI: 10.1039/x0xx00000x

www.rsc.org/

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 rearrangements⁴ 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 migration⁸ 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.

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



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.

Table 1. Preliminary investigation of ligands for enantioselective 1,3-halogen migration.^a

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

^a See the SI for the remaining ligand structures.

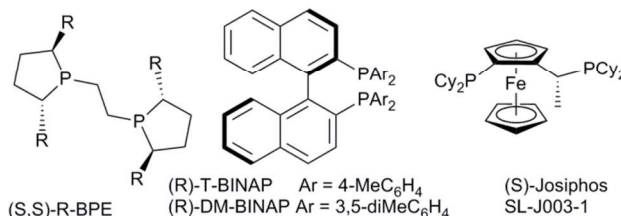
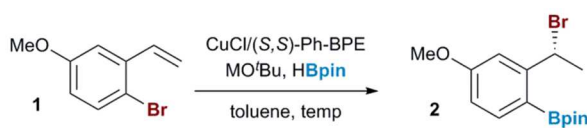
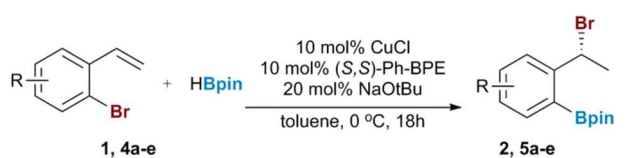


Table 2. Further optimization of the asymmetric 1,3-halogenation migration.^a


entry	temp (°C)	MOtBu	loading	[conc]	1 ^a	2	<i>er</i>
1	25	KOtBu	5%	0.5 M	16	46	93:7
2	25	KOtBu	5%	0.1 M	52	34	91:9
3	25	KOtBu	10%	0.1 M	41	38	92:8
4	25	NaOtBu	10%	0.1 M	13	75	87:13
5	0	NaOtBu	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.

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 KOtBu to NaOtBu increased the yield to 75% at the expense of *er*.

Table 3. Selected substrate scope.


entry	substrate	yield	<i>er</i>	entry	substrate	yield	<i>er</i>
1		73%	98:2	4		28%	92:8 ^b
2		53%	>99:1	5		40%	95:5 ^c
3		71% ^a	83:17	6		38%	92:8

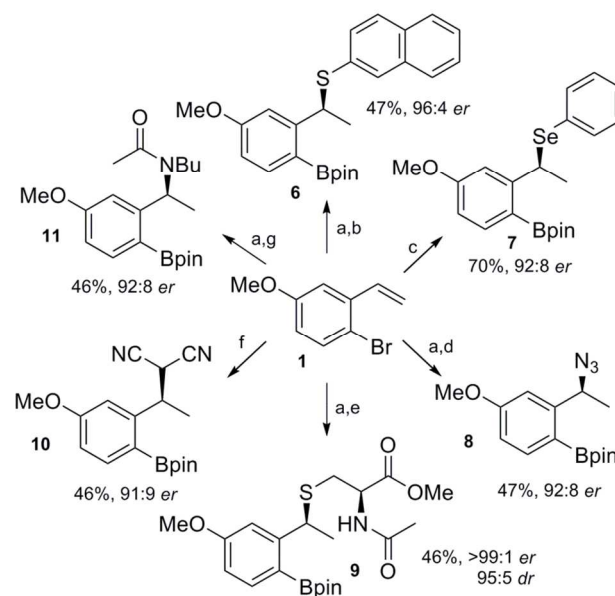
^a Trapped with LiSePh before isolation. ^b *er* determined after trapping with 2-naphthalenethiol. ^c *er* determined after trapping with LiSePh.

(entries 3, 4). The best results were obtained by lowering the reaction temperature to 0 °C in the presence of NaOtBu 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 OPr 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 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

Scheme 2. Functionalizations of chiral benzyl bromides.

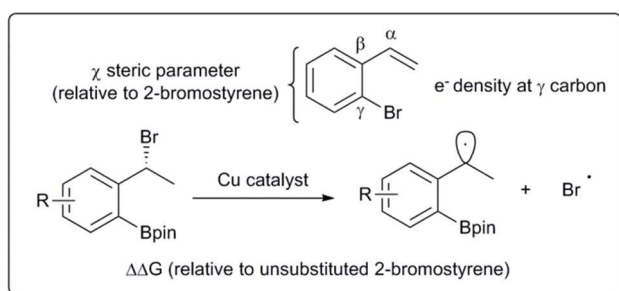
(a) Standard asymmetric halogen migration conditions was followed by solvent removal. (b) 1.5 equiv 2-naphthalenethiol, 2.5 equiv K₂CO₃, DMF, 1 h, rt. (c) Standard asymmetric halogen migration conditions and then 3 equiv of LiSePh in THF was added. (d) 3.0 equiv NaN₃, DMSO, 40 °C, 1 h. (e) 1.5 equiv *N*-acetyl cysteine methyl ester, 2.5 equiv K₂CO₃, DMSO, 40 °C, 3 h. (f) Standard asymmetric conditions and then 3.0 equiv lithium malononitrile in THF was added. (g) 3 equiv butylamine, 5 equiv K₂CO₃, DMF, 40 °C, 1 h then 5 equiv Ac₂O, 40 °C, 1 h.

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 SI for details).

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 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 , Figure 1) would promote the 1,3-halogen migration reaction. The major ATRP side reaction

Figure 1. Factors impacting yield.



was proposed to be favored by factors that promote or stabilize the formation of a benzyl radical (represented by $\Delta\Delta G$). Finally,

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 ^t 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-pyrrolyl	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

^aNMR yields determined using 1,1,1,2-tetrachloroethane as the internal standard.

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 equation 1 (Table 4). For the 10 substrates used to create equation 1, the calculated yield matched the experimental yield to within $\pm 10\%$, though many matched much more closely. Given the simplicity of our analysis and the tendency for some error in NMR yields¹⁵ if the parameters are not carefully

optimized to give quantitative integration, 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

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

parameters we chose are indeed the major factors impacting yield. For the substrates used in generating equation 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 09¹⁸ and NBO¹⁸ (see the SI for details).

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 equation 1 was then tested on a variety of 2-bromostyrene substrates that were not used in the generation of equation 1 (Table 5). Equation 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).

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 yields 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.

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 5-6) might be expected to reduce the predictive power of equation 1, since none of the substrates used to create the equation have steric bulk *ortho* to a reactive site. Indeed, even though equation 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.

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.

Acknowledgements

The authors would like to thank Sigma-Aldrich and Strem Chemicals for their generous help in procuring chiral ligands. Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for partial support of this research. We would also like to thank Professors Robert Bergman and Sam Gellman for their valuable feedback on this manuscript. Desiree Bates is thanked for many helpful conversations and Gabriel Le Gros for his assistance with substrate synthesis.

Notes and references

^a Department of Chemistry, University of Wisconsin, 1101 University Ave. Madison, Wisconsin 53706, United States.

Funding Sources

This research was supported by start-up funds provided by the University of Wisconsin-Madison. The NMR facilities at UW-Madison are funded by the NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01). The computational cluster is funded by NSF Grant CHE-0840494.

Electronic Supplementary Information (ESI) available: Experimental procedures and characterization for new compounds are provided in the Supporting Information. See DOI: 10.1039/b000000x/

- For recent reviews on enantioselective halogenations see: (a) A. Castellanos, S. P. Fletcher, *Chem. Eur. J.* 2011, **17**, 5766-5776; (b) U. Hennecke, *Chem. Asian J.* 2012, **7**, 456-465; (c) S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem. Int. Ed.* 2012, **51**, 10938-10953; (d) A. M. R. Smith, K. K. Hii, *Chem. Rev.* 2011, **111**, 1637-1656.
- (a) M. Oestreich, *Angew. Chem. Int. Ed.* 2005, **44**, 2324-2327; (b) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* 2011, **133**, 3339-3341; (c) H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury, T. Lectka, *J. Am. Chem. Soc.* 2001, **123**, 1531-1532; (d) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemansa, *Angew. Chem. Int. Ed.* 2005, **117**, 4276-4279 (e) J. Douglas, K. B. Ling, C. Concellon, G. Churchill, A. M. Z. Slawin, A. D. Smith, *Eur. J. Org. Chem.* 2010, **30**, 5863-5869; (f) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* 2005, **127**, 16406-16407; (g) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* 2010, **132**, 2860-2861.
- (a) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* 2010, **49**, 6160-6164; (b) X. Xu, R. S. S. Kotti, J. F. Cannon, A. D. Headley, G. Li, *Org. Lett.* 2004, **6**, 4881-4884; (c) A. Alix, C. Lalli, P. Retailleau, G. Masson, *J. Am. Chem. Soc.* 2012, **134**, 10389-10392.
- (a) H. Li, F.-M. Zhang, Y.-Q. Tu, Q.-W. Zhang, Z.-M. Chen, Z.-H. Chen, J. Li, *Chem. Sci.* 2011, **2**, 1839-1841; (b) Z.-M. Chen, Q.-W. Zhang, Z.-H. Chen, H. Li, Y.-Q. Tu, F.-M. Zhang, J.-M. Tian, *J. Am. Chem. Soc.* 2011, **133**, 8818-8821.
- (a) A. Jaganathan, R. J. Staples, B. Borhan, *J. Am. Chem. Soc.* 2013, **135**, 14806-14813; (b) R. Yousefi, K. D. Ashtekar, D. C. Whitehead, J. E. Jackson, B. Borhan, *J. Am. Chem. Soc.* 2013, **135**, 14524-14527; (c) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* 2010, **132**, 3664-3665; (d) W. Zhang, N. Liu, C. M. Schienebeck, K. Decloux, S. Zheng, J. B. Werness, W. Tang, *Chem. Eur. J.* 2012, **18**, 7296-7305; (e) G. Chen, S. Ma, *Angew. Chem. Int. Ed.* 2010, **49**, 8306-8308; (f) K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.* 2012, **14**, 6016-6019.
- For a recent example of catalytic enantioselective dichlorination of allylic alcohols see: (a) K. C. Nicolaou, L. N. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* 2011, **133**, 8134-8137; To the best of our knowledge, there are only two reports of enantioselective dibromination: (b) D. X. Hu, G. M. Shibuya, N. Z. Burns, *J. Am. Chem. Soc.* 2013, **135**, 12960-12963; (c) A. K. El-Qisairi, H. A. Qaseer, G. Katsigras, P. Lorenzi, U. Trivedi, S. Tracz, A. Hartman, J. A. Miller, P. M. Henry, *Org. Lett.* 2003, **5**, 439-441.
- For other examples of activating group recycling see: (a) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* 2011, **133**, 1778-1780; (b) J. F. Hooper, A. B. Chaplin, C. Gonzalez-Rodriguez, A. L. Thompson, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc.* 2012, **134**, 2906-2909.
- For examples of copper-catalyzed 1,3-migration see: (a) B. Alcaide, P. Almdros, J. M. Alonso, S. Cembellin, I. Fernandez, T. Martinez del Campo, M. R. Torres, *Chem. Commun.* 2013, **49**, 7779-7781; (b) Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* 2014, <http://dx.doi.org/10.1002/anie.201402449>
- R. D. Grigg, R. Van Hoveln, J. M. Schomaker, *J. Am. Chem. Soc.* 2012, **134**, 16131-16134.
- J. M. Schomaker, R. D. Grigg, *Synlett.* 2013, **24**, 401-407.
- For selected examples of the addition of Cu-H species across alkenes, see: (a) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* 2008, **108**, 2916-2927; For examples of asymmetric addition of copper-hydrides to olefins see: (b) S. Zhu, N. Niljianskul, S. L. Buchwald, *J.*

- Am. Chem. Soc.* 2013, **135**, 15746-15749; (c) D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* 1999, **121**, 9473-9474; (d) V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* 2002, **124**, 2892-2893; (e) D. Noh, H. Chea, J. Ju, J. Yun, *Angew. Chem. Int. Ed.* 2009, **48**, 6062-6064. (f) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* 2014, **16**, 1498-1501. (g) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* 2013, **52**, 10830-10834.
- 12 (a) K. Matyjaszewski, J. Xia, *Chem. Rev.* 2001, **101**, 2921-2990; (b) J.-S. Wang, K. Matyjaszewski, *Macromolecules*, 1995, **28**, 7901-7910.
- 13 Hammett parameters are often invoked to rationalize an electronic trend; for a helpful review of Hammett parameters see: (a) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* 1991, **91**, 165-195; For a useful resource on A values, see: (b) E. L. Eliel, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
- 14 P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.* 2013, **135**, 14052-14055.
- 15 H. J. Reich, Integration of Proton NMR Spectra, <http://www.chem.wisc.edu/areas/reich/nmr/05-hmr-01-integration.htm>, (accessed July 2014).
- 16 A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648-5652.
- 16 (a) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* 1980, **72**, 5639-5648; (b) K. Raghavachari, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* 1980, **72**, 650-654; (c) R. C. Binning, L. A. Curtiss, *J. Comp. Chem.* 1990, **11**, 1206-1216; (d) M. P. McGarh, L. Radom, *J. Chem. Phys.* 1991, **94**, 511-516; (e) L. A. Curtiss, M. P. McGarh, J.-P. Blaudeau, N. E. Davis, R. C. Binning Jr., L. Radom, *J. Chem. Phys.* 1995, **103**, 6104-6113.
- 17 Gaussian 09, Revision D.01, Frisch, M.J. *et. al.* (see the SI for the complete reference).
- 18 NBO 6.0. E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, and F. Weinhold (Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, 2013); <http://nbo6.chem.wisc.edu/>