Accepted Article

Authors: Joseph M. Ready, Bo Chen, Cheng Fang, and Peng Liu

WILEY-VCH

WILEY-VCH

COMMUNICATION

Rhodium-Catalyzed Enantioselective Radical Addition of CX$_4$ Reagents to Olefins

Bo Chen, Cheng Fang, Peng Liu* Joseph M. Ready*

Abstract: *We describe an enantioselective addition of Br-CX$_3$ (X = Cl or Br) to terminal olefins that introduces a trihalomethyl group and generates optically active secondary bromides. Computational and experimental evidence supports an asymmetric atom transfer radical addition (ATRA) mechanism in which the stereodetermining step involves outer-sphere bromine abstraction from a (bisphosphine)Rh(II)BrCl complex by a benzylic radical intermediate. Beyond the synthetic utility, this mechanism appears unprecedented in asymmetric catalysis.*

Radical additions to olefins provide effective methods to increase molecular complexity. For example, in 1945 Kharasch described the addition of CX$_4$ across terminal olefins to form a new C-C bond, introduce a new CX$_3$ group and generate a new C-X bond (Figure 1a).[1] This addition generally occurs with high Markovnikov selectivity and good functional group tolerance.[2] More broadly, free radicals are prized intermediates in organic synthesis because they possess exceptional reactivity, although controlling that reactivity remains difficult.[3] In this context, the development of an enantio-selective Kharasch addition reaction appeared valuable for both practical and fundamental reasons. It would provide optically active alkyl halides,[4] and the trihalomethyl group finds utility as a metabolically stable replacement for –CH$_3$ groups. Finally, an asymmetric platform for the Kharasch addition reaction could potentially be expanded to other C-X (X = halide) and X-Y (Y = SR, NR$_2$) reagents.

Kharasch noted, "Strange as the reactions cited may appear, the explanation of their mechanisms is not too difficult."[1] These atom-transfer radical additions proceed through addition of the CX$_3$ radical to an olefin, followed by abstraction of bromine radical to form the secondary C-Br bond (Figure 1B). Transition metals, heat or peroxides can initiate the reaction by generating the CX$_3$ radical. Importantly, in this scenario the initiator *does not participate in the stereodetermining step*, which involves abstraction of X radical from CX$_4$ to complete the propagation cycle (see **TS-A**).[3],[5] Accordingly, asymmetric induction is impossible with this mode of initiation.[6]

We hypothesized that radical abstraction of a halide from CX$_4$ by a metal catalyst (M^n) would generate the CX$_3$ radical and an M$^{(n+1)}$-X species. Radical addition to the terminal olefin would generate the secondary radical as in the radical propagation mechanism. In the key step, abstraction of X from the M-X

species would form the new C-X bond. Thus, the *metal catalyst would be present in the stereodetermining step,* offering the possibility to induce asymmetry with chiral ligands on the metal (see **TS-B**)
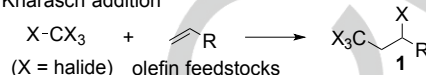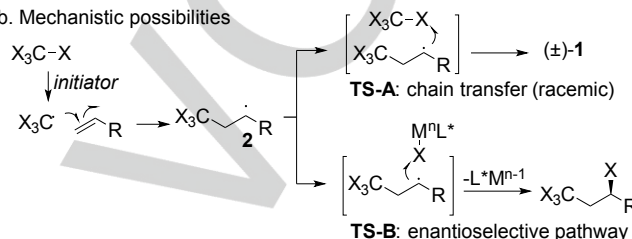

Figure 1. Addition of CX$_4$ reagents to olefins.

While the transition state envisioned in **TS-B** could lead to an enantioselective reaction, it appears largely unprecedented. More generally, asymmetric radical reactions of any type are rare, although notable successes have been achieved recently.[7] Most existing asymmetric radical reactions fall into one of three mechanistic classes. Most commonly, a radical adds to an olefin that is associated with a chiral metal complex (**3**, Figure 2A). Examples include the addition of nucleophilic radicals,[8] aminomethyl radicals,[9] and photolytically generated alkyl radicals[10] to α,β-unsaturated carbonyl compounds. Additionally, enolates coordinated to a chiral-at-metal Ir complex can combine with electrophilic trichloromethyl radicals[11] and electron-poor benzylic radicals.[12],[13]

A second mechanistic platform for asymmetric radical reactions features organocatalysts (Figure 2B). Chiral enamines **4** can undergo single electron transfer to generate a chiral radical species that then combines with a radical electrophile, as described by the Sibi[14] and MacMillan[15] laboratories.[16,17]

A third mechanism for enantioselective catalysis involving radical intermediates relies on inner-sphere bond formation from organometallic intermediates (Figure 2C). The Fu group defined a Ni-catalyzed cross-coupling of racemic alkyl bromides with a variety of electrophiles.[18] In these transformations a secondary radical likely combines with an alkyl metal species to provide a dialkyl metal species **6**. Reductive elimination generates the optically active cross-coupled product (**7**).[19] More recently Liu and Stahl reported a related Cu-catalyzed benzylic cyanation.[20,21] Cu-catalyzed α-amination of amides[22] and difunctionalization of olefins[23] likely operate through similar inner-sphere mechanisms, although complete mechanistic details are not available.

[a]   Dr. B. Chen, Prof. R. Joseph
        Department of Biochemistry, UT Southwestern Medical Center,
        5323 Harry Hines Blvd, Dallas, Texas 75390-9038 USA.
        E-mail: Joseph.ready@utsouthwestern.edu
[b]   C. Fang, Prof. P. Liu
        Department of Chemistry University of Pittsburgh, Pittsburgh, PA
        15260 USA
        E-mail: pengliu@pitt.edu
[c]   C. Fang
        Computational Modeling & Simulation Program University of
        Pittsburgh, Pittsburgh, PA 15260 USA
        Supporting information for this article is given via a link at the end of
        the document.

COMMUNICATION

active transition metals including Fe, Mn, Ni, Rh, Ru, Ir and Cu
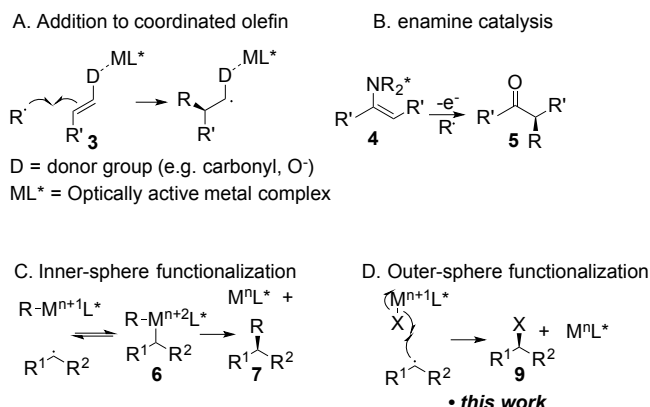

Figure 2. Mechanisms of asymmetric radical reactions. A. Radical addition to metal-coordinated substrate. B. Oxidation of chiral enamine intermediates followed by radical trapping. C. Metal capture of radical intermediates follwed by reductive elimination. D. Outer-sphere ligand abstraction by pro-chiral radical.

In contrast to the three mechanistic classes described above, a fourth potential mechanism remains essentially unexplored. Specifically, we wondered if it might be possible to effect an enantioselective outer-sphere bromine abstraction from an optically active metal bromide (Figure 2D). We are aware of only three examples of asymmetric Kharash addition reactions: The addition of CCl_3Br to acrylates and styrene in up to 22% ee[24] and 30% ee, respectively.[25] Alternatively, $ArSO_2Cl$ added to styrene in up to 40% ee.[26] More generally, we are aware of no asymmetric reactions that have been shown to involve outer-sphere abstraction of one of the ligands (halide in our case) by a radical, although the Jacobsen epoxidation likely involves radical addition to a metal oxo species.[27] Accordingly, the development of an enantioselective Kharasch addition could solve a long-standing challenge in asymmetric synthesis and provide a new mechanistic platform for the development of a variety of enantioselective reactions.

We initiated our investigations by evaluating the addition of $BrCCl_3$ to styrene (Figure 3). We evaluated a variety of redox-
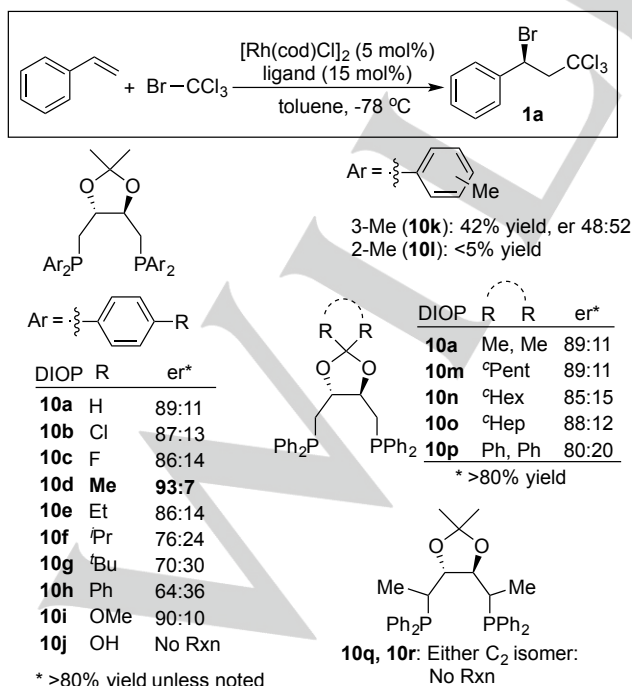

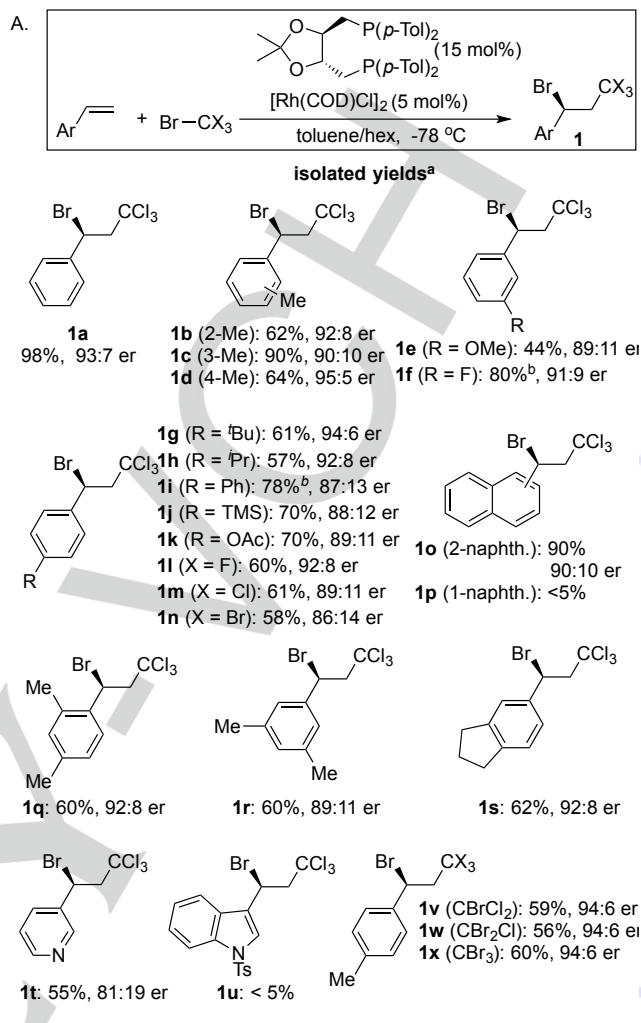**Figure 3.** Discovery of an enantioselective Kharasch reaction

Figure 4. A. Substrate scope for the addition of tetrahalomethanes to vinyl arenes. [a]Reactions carried out with 0.25 mmol olefin, 0.5 mmol CX_4, in 2.5 mL toluene/hexanes (1:1 v/v). Er's determined by HPLC. [b]toluene solvent. B. Derivitization of secondary bromide **1a**.

in our initial survey, and discovered that Rh(I) complexes promoted the reaction at room temperature and below. Therefore, we combined $[Rh(COD)Cl]_2$ with a variety of monodentate and bidentate ligands and evaluated the ability of the resulting complexes to catalyze the Kharash reaction at -78 °C. Monodentate phosphines and phosphoramidites did not yield active catalysts. Likewise, the complexes derived from BINAP, DuPhos and Trost's ligand[28] proved largely inactive. By contrast, chelating phosphines of the form Ph_2P-$(CH_2)_n$-PPh_2 proved more promising. Interestingly, we noticed a profound impact on bite angle such that bis(diphenylphosphino)butane generated the racemic product in quantitative yield whereas bis-phosphines with longer or shorter linkers were markedly less effective. DIOP features a similar 4-carbon bridge between phosphines, and it is also a diaryl, alkyl phosphine. We were therefore gratified to discover that the complex derived from DIOP (**10a**) and a Rh(I)

COMMUNICATION

source provided the secondary bromide in 89:11 er. *p*-Tol-DIOP (**10d**) emerged as the optimal ligand. In detail, small electron-donating groups (Me, OMe) at the 4-position of the phenyl ring improved er's while larger (Me > Et > ^{i}Pr > ^{t}Bu) alkyl groups or halogens decreased enantioselectivity. Substitution on the 2 or 3 position had deleterious effects on reactivity and selectivity (**10k**, **10l**). The ketal substitution on DIOP had little impact on reactivity or selectivity (**10a**, **10m** – **10p**). However, the reaction appears very sensitive to steric effects on the ligand because methyl substitution adjacent to the phosphine totally inhibited the reaction (**10q**, **10r**). Finally, we observed modest increases in enantioselectivity (depending on substrate) when the reaction was carried out in a 1:1 mixture of hexane and toluene. Other modifications to the reaction conditions did not improve selectivity including lower or higher temperatures, alternative Rh(I) sources, or different solvent mixtures.[29]

The addition of BrCCl₃ to vinyl arenes tolerates functional groups such as alkyl, halides, ester, methoxy, and TMS groups (Fig 4, **1b**-**1n**). The substituents on the aromatic ring could be in the ortho, meta, or para position (**1b**-**1d**). The addition is relatively insensitive to sterics at the para-position, and electron-donating and modestly electron withdrawing groups are suitable. In contrast, strongly electron-withdrawing groups (CN, CF₃) lead to poor enantioselectivity. Multiply- substituted styrenes are also suitable substrates for this reaction (**1q**-**1s**). 3-Vinyl pyridine afforded the adduct in moderate yield and ee (**1t**), while vinyl indole generated an unstable product (**1u**). Similarly, 2-vinyl naphthalene was an excellent substrate (**1o**), but the product derived from 1-vinyl naphthalene (**1p**) could not be isolated.

Other polyhalomethanes could react to give similar Kharasch Thus, a –CCl₃, –CBrCl₂, –CBr₂Cl and a –CBr₃ group could all be introduced with similar selectivity and yield (**1v**-**1x**). With bromo-chloro-methanes, exclusive formation of the benzylic bromide was observed, and we have not isolated any benzylic chloride products when the reaction is performed at -78 °C.

Benzylic bromides are synthetically valuable as substrates for stereospecific SN2 substitutions. We have performed preliminary experiments to evaluate the range of suitable nucleophiles for substitution reactions. Specifically, the C-Br bond can be transformed into a C-N (**11**) and C-S (**12**) bond with high stereochemical fidelity and moderate yield. Currently, attempted substitution with carbon nucleophiles (cyanide, enolates) leads to elimination.

Two general mechanisms for the asymmetric ATRA appeared reasonable, one closed shell and one radical in nature. Shown in Figure 5A is a Rh(I)-Rh(III) cycle featuring oxidative addition to Br-CX₃ to give a Rh(III) complex **13**. Stereospecific and enantioselective olefin insertion would generate a benzylic Rh species **14**. Final reductive elimination would provide the observed product **1**. Alternatively, bromine radical abstraction could generate the CX₃ radial and a Rh(II)BrCl species **16**; addition to styrene could then yield the benzylic radical **2** (Figure 5A, bottom). Radical **2** could recombine with Rh(II) to provide the Rh(III) intermediate **14**, which could again undergo reductive elimination to product. Alternatively, it could directly abstract bromine from the Rh(II)BrCl species in an outer-sphere mechanism to give the observed product **1** (see **17**).

Existing data implicates radical intermediates (Figure 5B). In particular, when styrene was exposed to CCl₄ and CBr₄ in the presence of ClRh(DIOP), we obtained the cross-over product **1a** along with the expected product **1x** (eq 1). At cryogenic temperatures, benzyl chloride formation is not observed, but the generation of **1a** suggests that CCl₃ radical was generated. After addition to styrene, the corresponding benzylic radical abstracted a bromine from a Rh(II)Br species, which was generated from CBr₄.[30] The low yields even at high Rh loadings are likely because the (DIOP)RhCl₂ formed from CCl₄ is

A. Potential mechanisms for the asymmetric Kharasch addition.
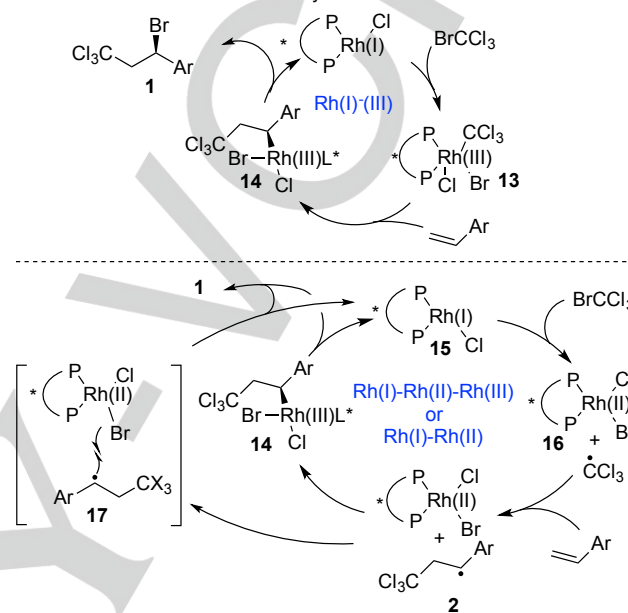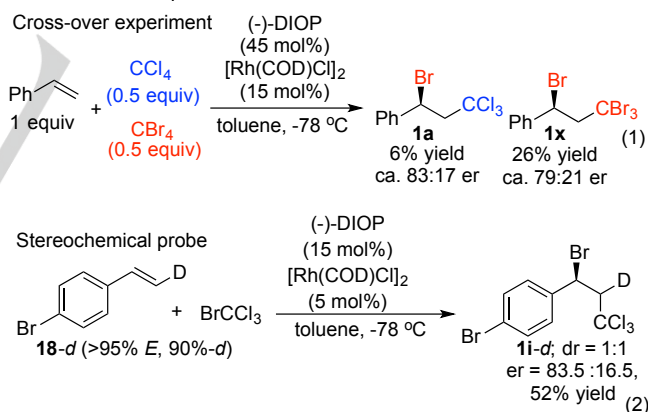

B. Mechanistic Experiments

Figure 5. A. Potential Rh(I)-Rh(III) catalytic cycle (top) and two catalytic cycles involving radical intermediates (bottom). B. Experiments to probe the mechanism of the addition reaction.

catalytically inactive. Similarly, stereochemically pure deuterated styrene **18**-*d* reacted with Br-CCl₃ to yield **1i**-*d* as a 1:1 mixture of diastereomers (eq 2). This result rules out the Rh(I)-Rh(III) mechanism because olefin insertion would proceed stereospecifically. By contrast, radical addition to styrene **18**-*d* is expected to yield a mixture of diastereomers, as observed.
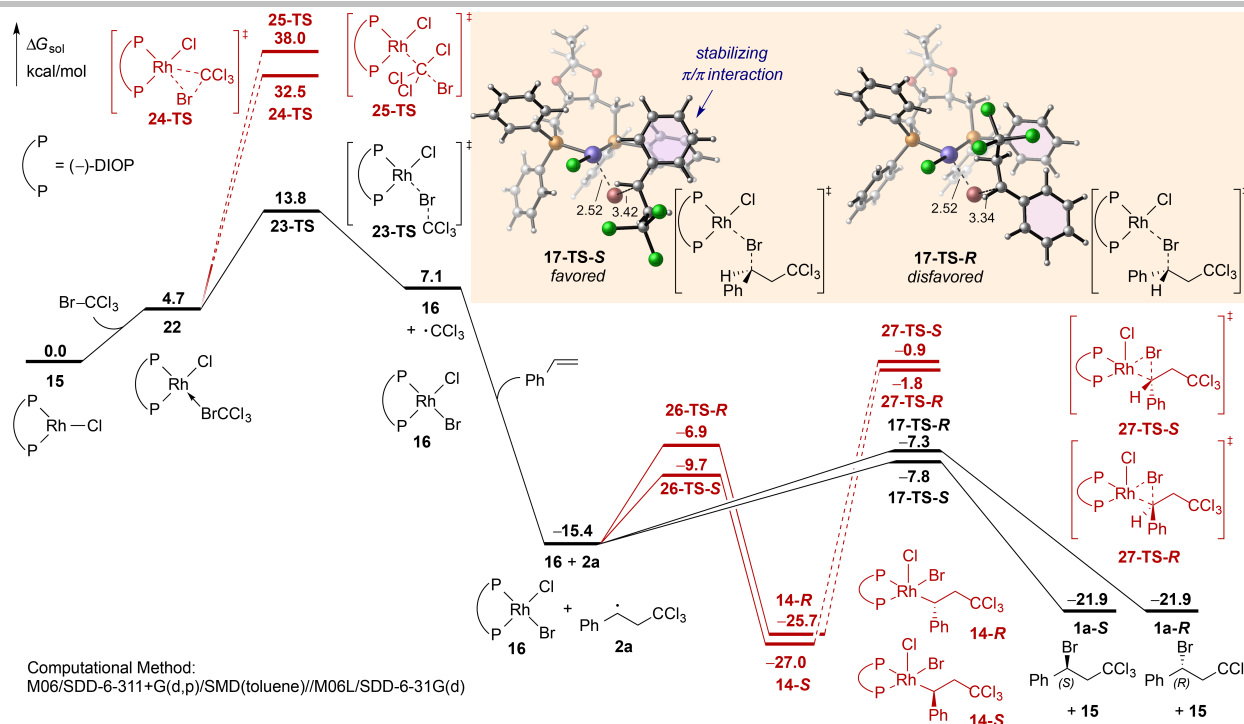
COMMUNICATION   WILEY-VCH

Figure 6. Computed reaction energy profiles of radical (in black) and closed-shell (in red) pathways of (DIOP)RhCl-catalyzed bromination of styrene.

We have used experimental[29] and DFT methods to explore the enantioselective bromination of styrene using [(−)-DIOP]RhCl as the catalyst (Figure 6). The closed-shell Br−CCl$_3$ oxidative addition via either a three-centered TS[31] (**24-TS**) or an S$_N$2-type linear TS[32,33] (**25-TS**) both require high activation free energies (32.5 and 38.0 kcal/mol, respectively). In contrast, the radical pathway involving bromine atom abstraction by the Rh(I) catalyst (**23-TS**) is much more favorable. The resulting CCl$_3$ radical adds to styrene to form the benzylic radical **2a**, which then abstracts the bromine atom from the Rh(II) complex **16** (via **17-TS**) to form the bromination product (**1a**) and regenerate the Rh(I) catalyst **15**. The Br atom abstraction again requires a very low barrier, 7.6 and 8.1 kcal/mol with respect to **16** and **2a** for the formation of (*S*)- and (*R*)-**1a**, respectively. The closed-shell reductive elimination from the Rh(III) intermediate **14** (via **27-TS**) and the chain transfer reaction of **2a** with BrCCl$_3$ ($\Delta G^{\ddagger}$ = 20.2 kcal/mol with respect to **2a**, see SI for details) both require much higher barriers. Thus, the DFT calculations suggested a Rh(I)/Rh(II) catalytic cycle with two Br atom abstraction steps. The closed-shell transition states (**24-TS**, **25-TS**, and **27-TS**) are all destabilized due to the unfavorable steric repulsions between the Rh center and the CCl$_3$ or benzyl group in the oxidative addition/reductive elimination transition states.

An interesting feature of the Br atom abstraction transition states (**23-TS** and **17-TS**) is that the Rh−Br−C bond angles are bent (85~105°) rather than linear, as expected in radical abstraction TSs involving two organic radicals. The bent geometry leads to much stronger interactions between the chiral bisphosphine ligand and the substrate in **17-TS**, and thus is critical to the chiral induction by the Rh catalyst. As shown in Figure 6, the preferred Br abstraction transition state **17-TS-*S*** is stabilized by a π/π interaction between the Ph on the benzylic radical and one of the Ph groups on the DIOP ligand, while in the disfavored transition state, **17-TS-*R***, the Ph on the benzylic radical is pointing away from the ligand.

The results described herein establish the first example of a highly enantioselective addition of CX$_4$ reagents to olefins. The addition appears to operate through a mechanism that has not been exploited previously in asymmetric catalysis. Looking forward, it appears likely that the principles outlined here will prove applicable to other enantioselective ATRA reactions.

Acknowledgements

Conflict of interest

The authors declare no conflicts of interest.

[1]   M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* **1945**, *102*, 128.

[2]   a) T. Pintauer, *Eur. J. Inorg. Chem.* **2010**, *2010*, 2449. b) O. Reiser, *Acc. Chem. Res.* **2016**, *49*, 1990. c) T. Courant, G. Masson, *J. Org. Chem.* **2016**, *81*, 6945.

[3]   A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58; *Angew. Chem.* **2016**, *128*, 58.

[4]   For alternative approaches to asymmetric halogenation, see: A. J. Cresswell, S. T. C. Eey, S. E. Denmark, *Angew. Chem., Int. Ed.* **2015**, *54*, 15642; *Angew. Chem.* **2015**, *127*, 15866.

[5]   J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160.

[6]   Atom-transfer polymerization presents another obstacle. See: K. Matyjaszewski, J. Xia, *Chem. Rev.* **2001**, *101*, 2921.

COMMUNICATION

[7]   a) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2003**, *103*, 3263. b) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692. c) H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2007**, *13*, 7280.

[8]   M. P. Sibi, J. Ji, J. H. Wu, S. Gurtler, N. A. Porter, *J. Am. Chem. Soc.* **1996**, *118*, 9200.

[9]   L. Ruiz Espelt, I. S. McPherson, E. M. Wiensch, T. P. Yoon, *J. Am. Chem. Soc.* **2015**, *137*, 2452.

[10]   H. Huo, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 6936.

[11]   H. Huo, C. Wang, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2015**, *137*, 9551.

[12]   H. Huo, X. Shen, C. Wang, L. Zhang, P. Rose, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100.

[13]   A. T. Herrmann, L. L. Smith, A. Zakarian, *J. Am. Chem. Soc.* **2012**, *134*, 6976.

[14]   M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124.

[15]   T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582.

[16]   D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875.

[17]   Y. Zhang, Y. Du, Z. Huang, J. Xu, X. Wu, Y. Wang, M. Wang, S. Yang, R. D. Webster, Y. R. Chi, *J. Am. Chem. Soc.* **2015**, *137*, 2416.

[18]   a) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003. b) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2015**, *137*, 9523. c) Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832. d) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265.

[19]   O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896.

[20]   W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014.

[21]   F. Wang, D. Wang, X. Wan, L. Wu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 15547.

[22]   Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681.

[23]   (a) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 8069. (b) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357-9360. (c) J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen, X.-Y. Liu, *Nat. Commun.* **2017**, *8*, 14841.

[24]   Y. Iizuka, Z. Li, K. Satoh, M. Kamigaito, Y. Okamoto, J.-i. Ito, H. Nishiyama, *Eur. J. Org. Chem.* **2007**, *2007*, 782.

[25]   S. Murai, R. Sugise, N. Sonoda, *Angew. Chem. Int. Ed.* **1981**, *20*, 475; *Angew. Chem*. **1981**, *93*, 481.

[26]   M. Kameyama, N. Kamigata, M. Kobayashi, *J. Org. Chem.* **1987**, *52*, 3312.

[27]   M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Güler, T. Ishida, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 948.

[28]   (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-*N*,*N'*-bis(2-diphenylphosphino-1-naphthoyl).

[29]   See supporting information.

[30]   Little halogen exchange occurred on Rh under the reaction conditions.

[31]   Y. Jiao, W. W. Brennessel, W. D. Jones, *Organometallics*, **2015**, *34,* 1552.

[32]   T. R. Griffin, D. B. Cook, A. Haynes, J. M. Pearson, D. Monti, G. E. Morris, *J. Am. Chem. Soc.* **1996**, *118*, 3029.

[33]   M. Feliz, Z. Freixa, P. W. N. M. van Leeuwen, C. Bo, *Organometallics*, **2005**, *24,* 5718.
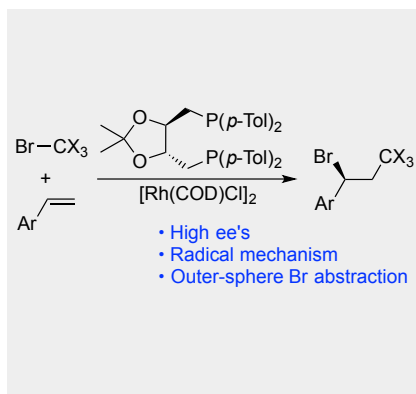
COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

- High ee's
- Radical mechanism
- Outer-sphere Br abstraction

Bo Chen, Cheng Fang, Peng Liu*
Joseph M. Ready*

Page No. – Page No.

Rhodium-Catalyzed Enantioselective Radical Addition of CX_4 Reagents to Olefins. The first highly enantioselective Kharasch addition reaction involves CX_3 radical addition to olefins followed by outer-sphere bromine abstraction from a Rh(II)Br complex. The reaction provides benzylic bromides in enantioenriched form and high yields.

Layout 2:

COMMUNICATION

((Insert TOC Graphic here))

Page No. – Page No.

Title

Text for Table of Contents