Communication

Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals

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Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals

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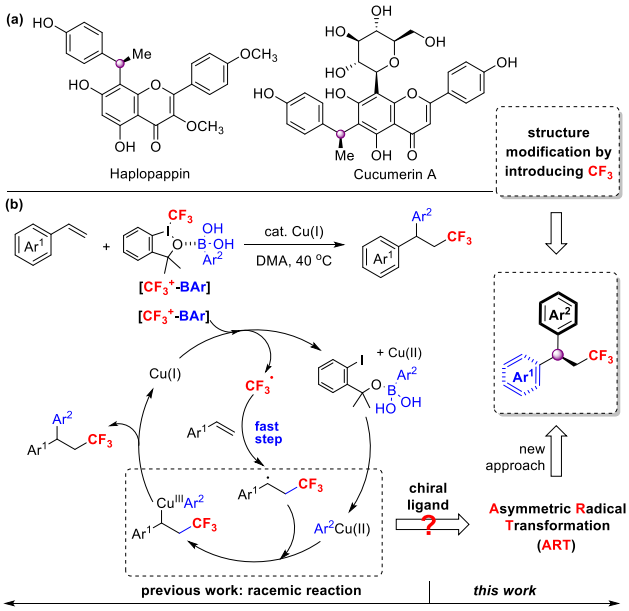
Supporting Information

ABSTRACT: A novel asymmetric radical trifluoromethyl-arylation of alkenes has been developed, which provides an efficient approach to access chiral CF_3-containing 1,1-diarylmethane derivatives with good to excellent enantioselectivity. Various vinyl arenes and aryl boronic acids are compatible with these conditions. The utility of the method is demonstrated by accessing modified bioactive molecules.

Tertiary stereocenters with two aryl substituents are important core structures in natural products and bioactive compounds, such as Haplopappin and Cucumerin A (Scheme 1a).[1] Thus, many efforts have made toward the enantioselective synthesis of 1,1-diarylalkanes, including asymmetric hydrogenation,[2] nucleophilic addition of activated alkenes,[3] and cross-coupling reactions with chiral benzylic electrophiles or nucleophiles.[4] Recently, Fu and coworkers reported an elegant Ni-catalyzed asymmetric radical transformation (ART), which enabled the synthesis of optically active 1,1-diarylalkanes from achiral benzylic electrophiles and aryl zinc reagents.[5]

Given the prevalence of CF_3 groups in pharmaceuticals, materials, and agriculture chemicals, introducing trifluoromethyl groups into 1,1-diarylalkanes should provide a chance to adjust its bioactivity.[6] Recent studies demonstrated that trifluoro-methylation of alkenes represented one of the most efficient methods to generate CF_3-substituted alkane derivatives,[7,8] and we recently reported a copper-catalyzed intermolecular trifluoromethyl-arylation of styrenes, in which a variety of CF_3-substituted 1,1-diarylalkanes could be efficiently synthesized (Scheme 1b, left).[9] In this transformation, a benzylic radical species was proved as a key intermediate. The reaction of an activated CF_3^+ reagent and the Cu(I) catalyst generated a CF_3 radical via a single electron transfer (SET) process, which attacked the olefin to generate a benzylic radical. The benzylic radical species was trapped by aryl-Cu(II), which was formed by transmetallation of the Cu(II) species and activated aryl boronic acid, to give a Cu(III) species, followed by its reductive elimination to account for the final C-C bond formation.[10] In this scenario, we speculated that introducing a chiral environment around copper center would allow the enantioselective trapping of the benzylic radical by the copper catalyst. This intermediate may



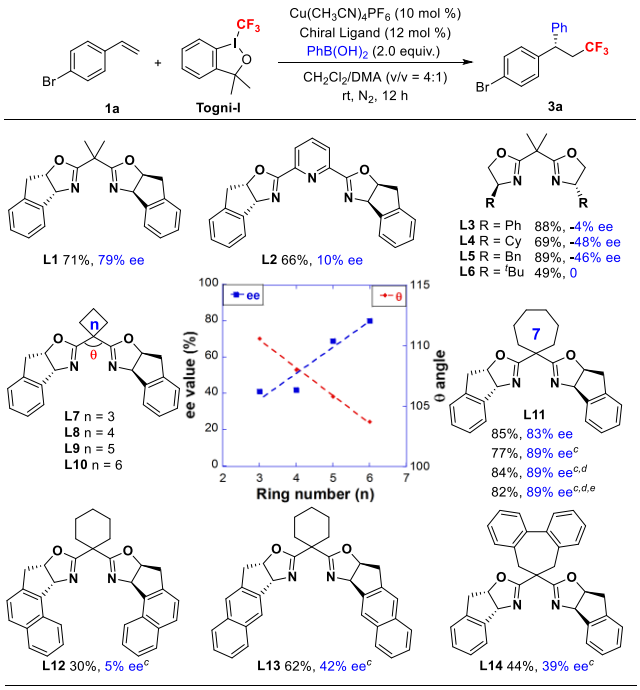
Scheme 1. Proposed ART reaction for the synthesis of chiral CF_3-substituted 1,1-diarylalkanes.

produce optically active CF_3-sbustituted 1,1-diarylalkanes (Scheme 1b, right). Although a few examples of the catalytic, asymmetric control of benzylic radicals by Cu(II) species exist, such as oxygenation,[11] amination,[12] and cyanation[13], the related enantioselective arylation of benzylic radical species with copper catalysts is still unknown.[14] Herein, we report the intermolecular trifluoromethylarylation of styrenes in the presence of chiral bisoxazoline/copper catalysts to provide a variety of β-CF_3 substituted 1,1-diaryl compounds with excellent enantioselectivity (up to 94% ee).

Bisoxazoline (Box) was demonstrated as a privileged ligand in the copper-catalyzed asymmetric benzylic C-H bond cyanation[13a] and trifluoromethylcyanation of styrenes.[13b] Thus, a series of Box ligands were applied, and the initial study was focused on the reaction of 4-bromostyrene (**1a**), $PhB(OH)_2$ (**2a**) and Togni **I** [CF_3^+] reagent with catalytic amount of Box **L1** and $[Cu(MeCN)_4]PF_6$ in *N*,*N*-dimethylacetamide (DMA). Compared

to previous racemic reaction, however, poor reactivity was observed in pure DMA. While good yield was obtained in a mixture of CH_2Cl_2 and DMA (see SI). Interestingly, a promising enantiomeric excess (79%) was observed in this case (Table 1). In contrast, Py-Box type ligand **L2** gave very low ee (10%). Further ligand screening revealed that Box ligands **L4** and **L5** bearing a gem-dimethyl linkage exhibited moderate enantioselectivity, but almost no enantioselective control was observed in the cases of **L3** and **L6**. Subsequent investigations focused on ligands **L7**-**L10**, which featured an indane group. We were delighted to find that increasing the ring size is beneficial to the enantioselectivity (chart in Table 1). Ligand **L10** (n = 6), with a small bite-angle, provided 80% ee, but **L7** (n = 3), with large bite-angle, gave 40% ee.[15] Following this logic, ligand **L11** (n = 7) was evaluated, which provided a higher enantiomeric excess (83%). Further optimizing the reaction conditions showed that decreasing temperature to 0 °C could improve ee to 89% but with slightly lower yield (77%). Addition of EtOH (2.0 equivalents) could accelerate the reaction[16] and provide good yield (84%) without affecting the entantioselectivity. Further modifications to the ligand skeleton failed to improve enantioselectivity. For instance, introducing greater steric hindrance (**L12** and **L13**) or modifying the cyclic ring linkage (**L14**) resulted in a marked decrease in enantioselectivity.

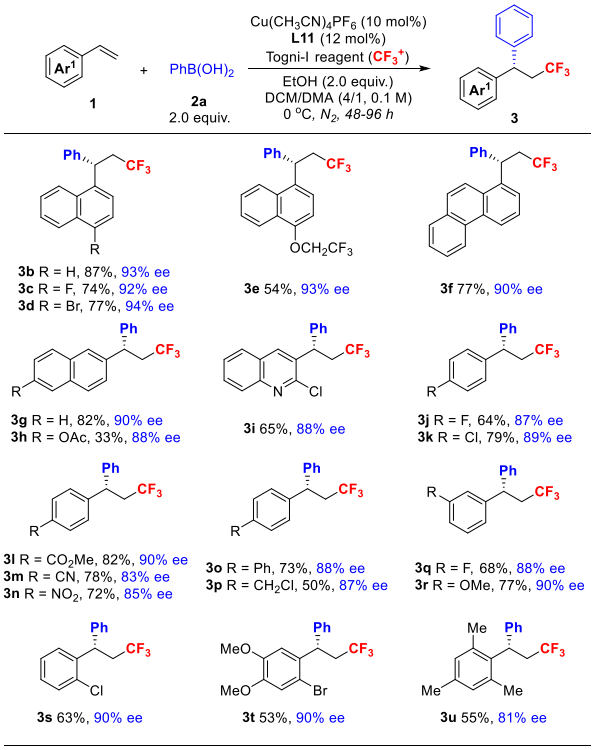
Table 1. Optimization of the Conditions for Trifluoromethylation of **1a**.[a,b]



[a]All reactions were conducted on 0.1 mmol scale. [b]Yield was determined by ^{19}F-NMR with CF_3-DMA as internal standard. Enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase. [c]Reactions were conducted at 0 °C. [d]EtOH (2.0 equiv.) was added. [e] Substrate: 0.2 mmol, isolated yield.

With the optimized reaction conditions in hand, the substrate scope of the alkenes was then investigated. As shown in Table 2, a variety of α-vinyl naphthalenes were proven to be suitable substrates, furnishing the corresponding products **3b**-**3e** in good to excellent yields (54-87%) with excellent ee (92-94%). The α-vinyl anthracene, with more extensive conjugation, also afforded product **3f** in 77% yield and 90% ee, absent of trifluoromethylation on the aryl ring. Furthermore, β-vinyl naphthalenes were also good for this transformation, giving **3g** in 82% yield and 90% ee, however, 6-acetoxy-2-vinyl naphthalene gave **3h** in low yield (33%) but with good ee (88%). Interestingly, the reaction of heterocyclic substrate, 2-chloro-3-vinyl quinoline, proceeded smoothly to give **3i** in satisfactory yield (65%) and 88% ee.

Table 2. Scope of Alkenes.[a,b]



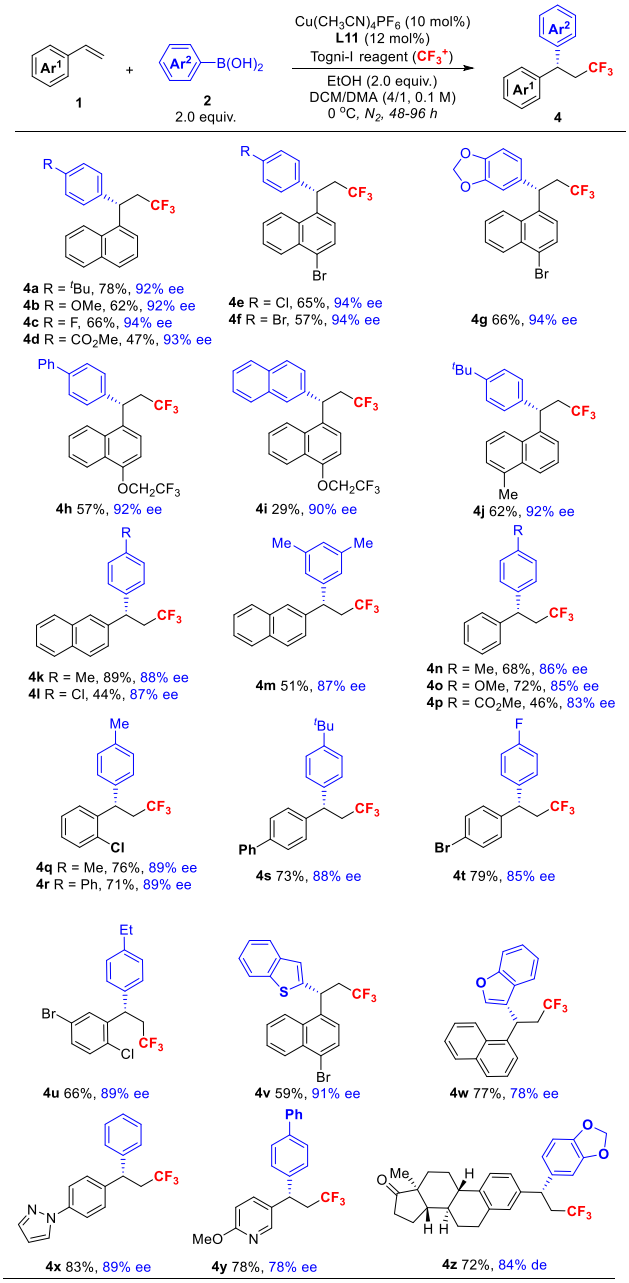
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Togni I (0.3 mmol), $Cu(CH_3CN)_4PF_6$ (0.02 mmol, 10 mol %), **L11** (0.024 mmol, 12 mol %), EtOH (0.4 mmol), DCM/DMA (v/v 4/1, 2.0 mL) at 0 °C. [b]Isolated yield, and enantiomeric excess (ee) were determined by HPLC or SFC on a chiral stationary phase.

In addition to vinyl naphthalenes, related vinyl benezenes were effective for this transformation with good to excellent enantioselectivities. Various styrenes with *para*-, *meta*-, and *ortho*-substituents afforded the corresponding products **3j**-**3s** in moderate to good yields (50-82%) and good to excellent enantioselectivities (83-90% ee). A variety of functional groups could be tolerated under the reaction conditions, such as halides, ethers, esters, nitriles, nitro, and others. For the styrenes with multiple substitutents on the aryl ring, the reactions also proceeded smoothly. Product **3t** was obtained in moderate yield (53%) and excellent ee (90%), while **3u** was generated in 55% yield with 81% ee from vinyl mesitylene.

Inspired by the above results, we turned our attention to the substrate scope of aryl boronic acids. As illustrated in Table 3, a wide range of aryl boronic acids were coupled with various α-vinyl naphthalenes to give the corresponding products **4a**-**4j** with excellent enantioselectivities (>90% ee). Various functional groups on the aryl boronic acid, such as ether, halides, acetal, and

ester, were tolerated under the reaction conditions. Notably, product **4i**, containing two similar naphthyl groups which are extremely difficult to differentiate via asymmetric hydrogenation, was obtained in excellent enantioselectivity (90% ee), albeit in low yield (29%). Again, various functionalized aryl boronic acids

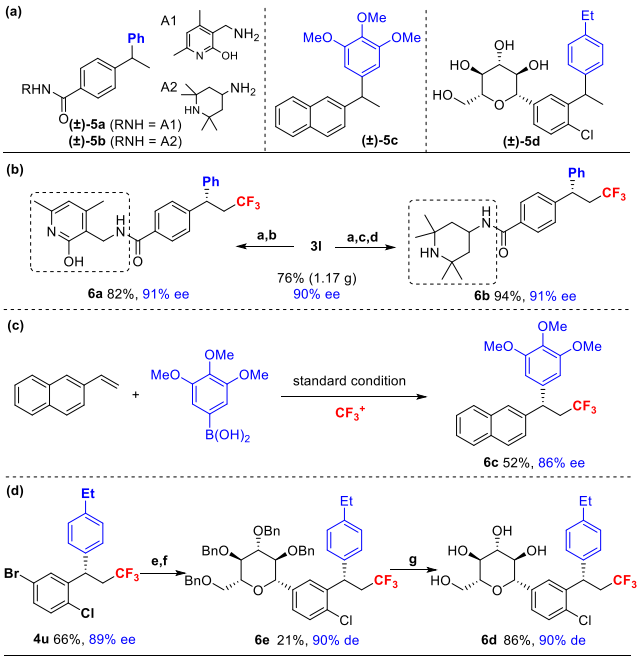
Table 3. Scope of Aryl Boronic Acids.[a,b]



[a]Reaction conditions: substrate **1** (0.2 mmol), **2** (0.4 mmol), Togni I (0.3 mmol), $Cu(CH_3CN)_4PF_6$ (0.02 mmol, 10 mol %), **L11** (0.024 mmol, 12 mol %), EtOH (0.4 mmol), DCM/DMA (v/v 4/1, 2.0 mL) at 0 °C. [b]Isolated yield, and enantiomeric excess (ee) was determined by HPLC or SFC on a chiral stationary phase.

could also react with β-vinyl naphthylenes and vinyl benzenes to give products **4k**-**4u** in good yields (44-89%) and good enantioselectivities (85-89% ee). Meanwhile, (hetero)aryl boronic acids, such as benzothienyl boronic acid and benzofuran boronic acid, were also compatible and provided **4v** and **4w** in modest yields. The former exhibited higher enantioselectivity than the latter, showing 91% ee and 78% ee, respectively. Moreover, vinyl (hetero)arenes were also suitable to the reaction to give **4x** and **4y** with 89% ee and 78% ee, respectively. Finally, styrenes bearing a complex estrone moiety could be employed to deliver product **4z** in 72% yield and 92:8 diastereomeric excess (de).[17]

As we mentioned in the introduction, the 1,1-diarylalkane moiety exists in a wide variety of natural products and bioactive compounds. For example, compounds (±)-**5a** and (±)-**5b** act as EZH2 inhibitors, [18] (±)-**5c** is an anti-tubulin polymerization agent,[19] and (±)-**5d** is an SGLT2 inhibitor (Scheme 2a).[20] In order to modify the bioactivity of these compounds, we synthesized their optical analogues **6a**-**6d** by introducing CF_3 groups with our current method. As described in Scheme 2b, the reaction of methyl 4-vinylbenzoate could be performed on gram scale to give product **3l** in 76% yield and 90% ee. Sequential ester hydrolysis and condensation with amines gave the optically active CF_3-containing amides **6a** and **6b** in good yields with retention of ee. Furthermore, compound **6c** could be directly obtained from the reaction of β-vinyl naphthalene and 3,4,5-trimethoxylphenyl boronic acid in 52% yield and 86% ee (Scheme 2c). Utilizing this asymmetric radical process, optically active product **4u** could be easily obtained in 66% yield and 89% ee, which was transformed into CF_3 analogue **6d** (90% de) through the unmodified literature procedure,[21] albeit with low yields (Scheme 2d).



Scheme 2. Reaction conditions: (a) NaOH (aq, 2N), MeOH, 75 °C, 4 h; (b) amine A1, EDC, HOAt, NMM, DMSO, rt, 30 h; (c) $(COCl)_2$, DMF/DCM, 0 °C-rt, 8 h; (d) aminie A2, Et_3N, DCM, 0 °C-rt, 6 h; (e) n-BuLi, THF/toluene, -78 °C, 1 h; then benzylate D-glucono-1,5-lactone, -78 °C, 5 h; (f) DCM, Et_3SiH, BF_3Et_2O, -15 °C, 5 h; (g) 10% Pd-C, MeOH/THF, H_2 (0.1 MPa), 25 °C, 7 h.

In summary, we have developed a copper-catalyzed enantioselective trifluoromethylarylation of alkenes. The present process serves as a versatile, efficient, and convenient approach for the rapid access of chiral CF_3-containing diarylalkane derivatives. A broad range of substrates with various functional

groups exhibit good to excellent enantioselectivity. Future efforts will focus on the exploring mechanistic details [22] and new asymmetric radical transformations based on this chemistry.

Supporting Information

Synthetic procedures, characterization, mechanistic study data, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, 55, 813. (b) Silva, D. H. S.; Davino, S. C.; de Moraes Barros, S. B.; Yoshida, M. *J. Nat. Prod.* **1999**, *62*, 1475. (c) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother*. **2001**, *2*, 883. (d) Tschesche, R.; Delhvi, M. S.; Sepulveda-Boza, S.; Zilliken, F.; Kirfel, A.; Will, G. *Liebigs Ann. Chem.* **1985**, 2465. (e) McNally, D. J.; Wurms, K. V.; Labbe, C.; Quideau, S.; Belanger, R. R. *J. Nat. Prod.* **2003**, *66*, 1280.

(2) (a) Wang, Z.; Ai, F.; Wang, Z.; Zhao, W.; Zhu, G.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 383. (b) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855. (b) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912.

(3) (a) Yasukawa, T.; Suzuki, A.; Miyamura, H.; Nishino, K.; Kobayashi, S.; *J. Am. Chem. Soc.* **2015**, *137*, 6616. (b) Paquin, J.−F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.

(4) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280. (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (d) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

(5) For the reaction with achiral benzylic electrophiles, see: (a) Do, H.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288. For the selected reaction with achiral alkyl electrophiles, see: (b) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003. (c) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102. (d) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794. (e) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966. (f) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (g) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.;Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 17662. (h) Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128. (i) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681. (j) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832.

(6) (a) Smart, B. E. *Chem. Rev*. **1996**, *96*, 1555. (b) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. (c) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishman, S., Eds.; Wiley: New York, 1991. (d) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart,B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994.

(7) For some recent examples, see, (a) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577. (b) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem. Eur. J.* **2012**, *18*, 8583. (c) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (d) Li, Y.; Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8221. (e) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 9567. (f) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (g) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458. (h) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheeelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505. (i) Wu, X.; Chu, L.; Qing, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (j) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841. (k) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12414. (l) Ilchenko, N. O.; Janson, P. G.; Szabó, K. J. *Chem. Commun.* **2013**, *49*, 6614. (m) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504. (n) Yang, F.; Klumphu, P.; Liang, Y.-M.; Lipshutz, B. H. *Chem. Commun.* **2014**, *50*, 936. (o) Kawamura, S.; Egami, H.; Sodeoka, M. *J. Am. Chem. Soc.* **2015**, *137*, 4865.

(8) Some examples from our group, see: (a) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881. (b) Liang, Z.; Wang, F.; Chen, P.; Liu, G. *J. Fluorine. Chem.* **2014**, *167*, 55. (c) Liang, Z.; Wang, F.; Chen, P.; Liu, G. *Org. Lett.* **2015**, *17*, 2438.

(9) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202.

(10) For the studies on the reductive elimination of Cu(III) species, see: (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) Wang, Z.-L.; Zhao, L.; Wang, M.-X. *Chem. Commun.* **2012**, *48*, 9418.

(11) (a) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 8069.

(12) Lin, J.-S.; Dong, X.-Y.; Li, T.-T.; Jiang, N.-C.; Tan, B.; Liu, X.-Y. *J. Am. Chem. Soc.* **2016**, *138*, 9357.

(13) (a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014. (b) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2016**, *138*, 15547.

(14) For the enantioselective coupling of benzylic radical and aryl reagent using Ni catalyst, see ref. 5a.

(15) Generally, when ring size of Box ligands become larger (from n = 3 to 6), the bite angel (ʘ) decreased. For details, see: (a) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753. (b) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233.

(16) Addition of alcohol could accelerate transmetallation step. This observation has been reported in the previous racemic reaction (ref. 9).

(17) Similar to the trifluoromethylcyanation reaction (see ref. 13b), terminal alkenes with alkyl substituent provided poor enantioselectivity (See SI).

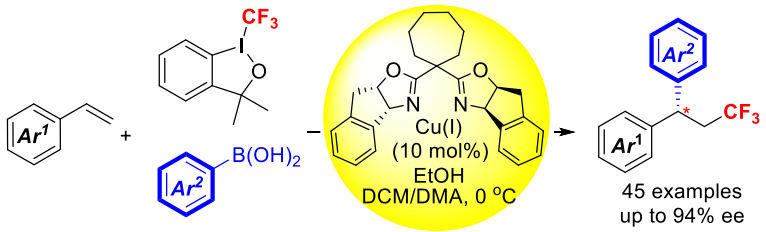
(18) (a) Albrecht, B. K.; Audia, J. E.; Cook, A. S.; Gagnon, A.; Harmange, J. C.; Nasveschuk, C. G. Patent: US9206128 B2, 2015. (b) Nasveschuk, C. G.; Gagnon, A.; Garapaty, R. S.; Balasubramanian, S.; Campbell, R.; Lee, C.; Zhao, F.; Bergeron, L.; Cummings, R.; Trojer, P.; Audia, J. E.; Albrecht, B. K.; Harmange, J. C. *ACS Med. Chem. Lett.* **2014**, *5*, 378.

(19) Alami, M.; Messaoudi, S.; Hamze, A.; Provot, O.; Brion, J.-D.; Liu, J.-M.; Bignon, J.; Bakala, J. Patent WO/2009/147217 A1, 2009.

(20) Zhao, G.; Shao, H.; Xu, W.; Liu, W.; Wang, Y.; Tang, L.; Tan, C.; Liu, B.; Zhang, S. Patent: US2013/23486 A1, 2013.

(21) (a) Pan, X.; Huan, Y.; Shen, Z.; Liu, Z. *Eur. J. Med Chem.* **2016**, 114, 89. (b) Czernecki, S.; Ville, G. *J. Org Chem.* **1989**, *54*, 610.

(22) As the same as our previous racemic reaction, the addition of TEMPO could significantly inhibit the reaction. The related trapping products of benzylic and CF_3 radicals by TMPEO were obtained, indicating a radical pathway involved in the catalytic cycle.



Highly enantioselective Aryltrifluoromethylation via radical relay