CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Title: Iron-Catalyzed Aminative Cyclization/Intermolecular Homolytic Aromatic Substitution Using Oxime Esters and Simple Arenes

Authors: Takuya Shimbayashi, Kazuhiro Okamoto, and Kouichi Ohe

To be cited as: *Chem. Asian J.* 10.1002/asia.201701634

Link to VoR: http://dx.doi.org/10.1002/asia.201701634

A Journal of
ACES
Asian Chemical Editorial Society

A sister journal of **Angewandte Chemie** and **Chemistry – A European Journal**

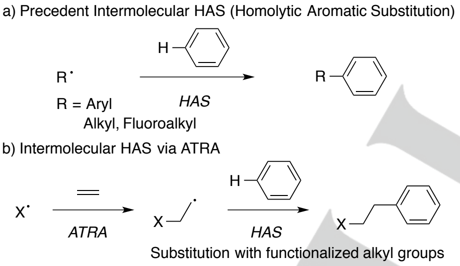
WILEY-VCH

Iron-Catalyzed Aminative Cyclization/Intermolecular Homolytic Aromatic Substitution Using Oxime Esters and Simple Arenes

Takuya Shimbayashi, Kazuhiro Okamoto* and Kouichi Ohe*[a]

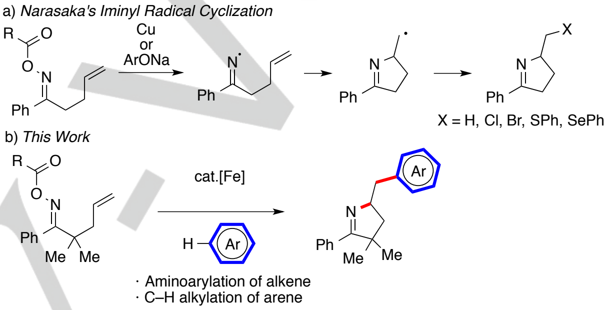
Abstract: Intermolecular C–H alkylation of simple arenes in the presence of an iron catalyst has been achieved in a cascade manner with an aminative cyclization triggered by N–O bond cleavage of an alkene-tethered oxime ester. Various arenes, including electron-rich and electron-poor arenes, and heteroarenes can be employed in the reaction system. Regioselectivity and radical trapping experiments support the involvement of alkyl radical species, which undergo a homolytic aromatic substitution (HAS) to afford the arylation products.

Radical-based aromatic C–H functionalization such as homolytic aromatic substitution (HAS) reactions has emerged as an atom-efficient and direct route to substituted arenes because less functionalized starting materials can be employed.[1] HAS reactions often involve intramolecular reactions because the slow rate of radical addition to simple arenes, in particular with alkyl radicals,[2] means that radical quenching is difficult to avoid. In contrast to the intramolecular reactions, the number of intermolecular variants of HAS that take advantage of electron transfer induced by strong base, transition-metal catalysts, and photoredox catalysts, has grown significantly,[3] and many successful examples, such as biaryl coupling,[4] fluoroalkylation,[5] or alkylation[5b,6] have been developed (Scheme 1a). However, these alkylation reactions are typically limited to heteroarenes. Furthermore, intermolecular HAS reactions involving an alkyl radical generated through atom transfer radical addition (ATRA) to alkenes in a cascade manner are scarce (Scheme 1b).[7]



Scheme 1. C–H Functionalization via HAS.

The iminyl radical, which is a highly reactive N-centered radical, has been applied to the synthesis of N-containing heterocycles.[8] Reductive cleavage of an N–O bond in oxime esters or ethers with transition metals or photoredox catalysts has been applied to the generation of iminyl radicals and radical cascade with tethered unsaturated bonds[9,10] since Narasaka's pioneering work (Scheme 2a).[11] Most recently, much attention in this area has focused on iron catalysis.[12]



Scheme 2. Aminative transformation involving iminyl radicals.

Our research interests have focused on N–O bond cleavage of oxime derivatives with a variety of transition metals for new transformations involving reactive species, such as nitrene or ketimido complexes, and catalytic synthesis of N-containing heterocycles[13] and isolation of Rh(III)-imine and Ru(IV)-ketimido complexes[14] have been described. The Ru(IV)-ketimido complex would be a key intermediate for aminochlorination of tethered alkenes or alkynes,[14b] which prompted us to explore their catalytic aminative transformation. In the course of many trials, we found that oxime esters undergo N–O bond cleavage with a cationic Fe(II)-bipyridine complex followed by 5-exo-trig cyclization with a tethered alkene to give an intermediate[12c] that is applicable to the intermolecular HAS reactions (Scheme 2b). Here, we report catalyst screening, substrate scope, and mechanistic insight on this transformation.

During our development of an aminative transformation reaction of oxime ester **1a**-*t*-Bu in benzene solvent under $Fe(OTf)_2$ catalysis (Table 1), we were surprised to observe the formation of phenylated product **3aa** together with a small amount of hydrogen atom adduct **4a** and acyloxylated product **5a**-*t*-Bu (entry 1). Intense efforts were then made to optimize the conditions for the phenylation reaction. Various ligands for the iron catalyst were examined.[15] The use of bipyridyl ligands slightly improved the yield of **3aa** (entries 2–4). Among the ligands tested, **L1** was found to give the best result (entry 2). Raising the reaction temperature to 120 °C gave **3aa** in the highest yield (entry 5). The reaction was also catalyzed by $Fe(OTf)_3$, albeit in lower yield (entry 6). The substituent R on the carboxyl group had a significant effect on the results. When acetyl ester (**1a**-Me) was used, the yield of **3aa** decreased (entry 7). The use of picolinoyl ester (**1a**-2-Py) afforded **3aa** in an

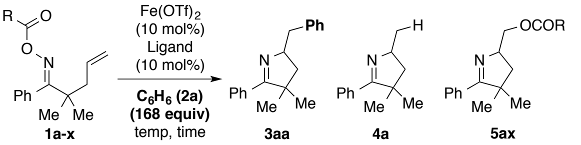
---

[a] T. Shimbayashi, Dr. K. Okamoto, Prof. Dr. K. Ohe
Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University
Nishikyo-ku, Kyoto 615-8510 (Japan)
E-mail: kokamoto@scl.kyoto-u.ac.jp
ohe@scl.kyoto-u.ac.jp

Supportinginformation and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.xxxxxxxxx.

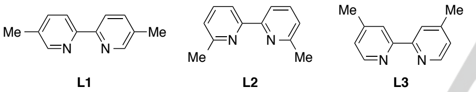
identical yield to that obtained with a *t*-butyl group (**1a**-*t*-Bu) without forming acyloxylated product **5a**-2-Py (entry 8). Interestingly, pentafluorobenzoyl ester (**1a**-C_6F_5), having an electron-withdrawing nature, prohibited the formation of **3aa**, affording acyloxylated product **5a**-C_6F_5 in high yield (entry 9).[16]

Table 1. Optimization of reaction conditions.[a]

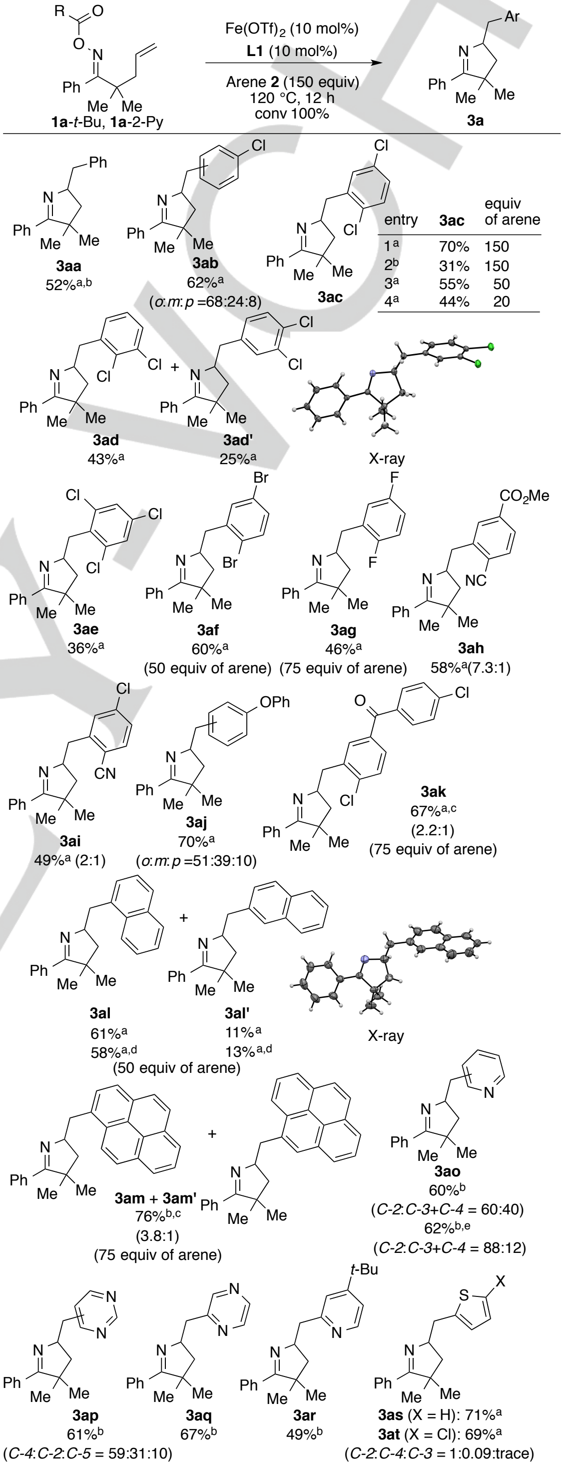


Entry	Ligand	R	Temp (°C)	Time (h)	**3aa** (%)	**4a** (%)	**5ax** (%)
1	none	*t*-Bu (**1a**-*t*-Bu)	100	20	38	11	14
2	**L1**	*t*-Bu	100	20	51	12	10
3	**L2**	*t*-Bu	100	20	45	9	17
4	**L3**	*t*-Bu	100	20	47	11	13
5	**L1**	*t*-Bu	120	12	54(52)[b]	11	11
6[c]	**L1**	*t*-Bu	120	12	33	11	10
7	**L1**	Me (**1a**-Me)	120	12	30	6	45
8	**L1**	2-Py (**1a**-2-Py)	120	12	54(52)[b]	13	0
9	**L1**	C_6F_5 (**1a**-C_6F_5)	100	20	9	0	79(68)[b]

[a] Reaction conditions: **1a**-x (0.20 mmol), $Fe(OTf)_2$ (0.020 mmol), ligand (0.020 mmol), C_6H_6 (3.0 mL, 33.7 mmol). Yields were determined by ^1H NMR. [b] Isolated yield. [c] $Fe(OTf)_3$ was used instead of $Fe(OTf)_2$.



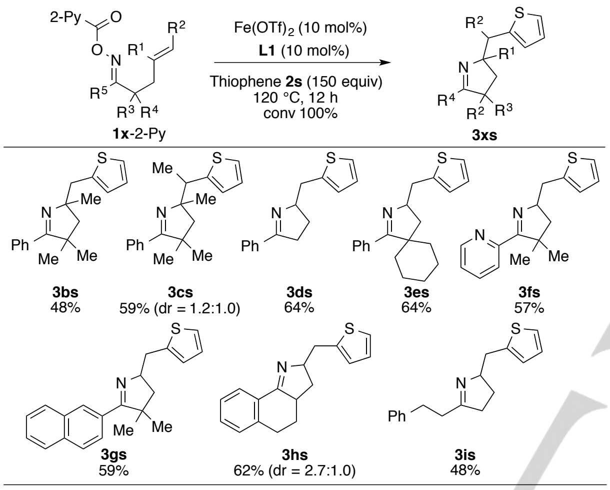
With the optimized reaction conditions in hand, the scope of the reaction with various arenes was explored (Scheme 3). For substituted arenes, picolinoyl ester (**1a**-2-Py) provided better results than pivaloyl ester (**1a**-*t*-Bu). Reaction with chlorobenzene **2b** afforded the product **3ab** in good yield, albeit with low regioselectivity (*o*/*m*/*p* = 68:24:8) which is in good accordance with other HAS-type reactions.[4g] The reaction with *p*-dichlorobenzene **2c** also afforded the product **3ac** in good yield. The amount of **2c** could be reduced to 50 or 20 equivalents, although the yield of **3ac** was decreased. *o*-Dichlorobenzene **2d** also showed good reactivity, affording **3ad** and **3ad'** in 43% and 25% yield, respectively.[16] 1,3,5-Trichlorobenzene **2e** was also applicable despite its steric hindrance. Other haloarenes such as *p*-dibromobenzene (**2f**) and *p*-difluorobenzene (**2g**) could also be used. Various functional groups such as nitrile (**3ah** and **3ai**), ester (**3ah**), ether (**3aj**), and ketone (**3ak**) were tolerated under the present reaction system. Major structures are shown for **3ah**, **3ai**, and **3ak**. The reaction with ketone **2k** required a higher reaction temperature because of its high melting point. It is noted that the reactions were applicable to both electron-rich and electron-poor arenes. Polycyclic aromatic compounds such as naphthalene **2l** and pyrene **2m** showed high reactivity in the reaction system.[16] The reaction with **2l** could be performed at larger scale (1.5 mmol). Nitrogen- or sulfur-containing heteroarenes **2o**–**t** also worked well, affording products in good yield. High C-2 selectivity in the reaction with pyridine **2o** was observed with addition of trifluoroacetic acid, probably because of protonation of the nitrogen atom of pyridine. Thiophenes **2s** or **2t** afforded **3as** or **3at**, respectively, in good yield with high C-2 selectivity.



entry	**3ac**	equiv of arene
1[a]	70%	150
2[b]	31%	150
3[a]	55%	50
4[a]	44%	20

Scheme 3. Scope of arenes. Reaction conditions: **1a**-*t*-Bu or **1a**-2-Py (0.20 mmol), $Fe(OTf)_2$ (0.020 mmol), **L1** (0.020 mmol), arene (30 mmol). Isolated yields are shown. Major regioisomer were shown. The ratio were shown in parentheses. [a] **1a**-2-Py was used. [b] **1a**-*t*-Bu was used. [c] Reaction at 150 °C. [d] Reaction at 1.5 mmol scale. [e] Trifluoroacetic acid (1.8 mmol) was added.

Based on the scope of the reaction with respect to arenes, the substituent effect on oxime esters **1** was then examined using thiophene as a reaction partner because of its high reactivity and regioselectivity (Scheme 4). Oxime esters bearing sterically hindered alkene moieties (**1b**-2-Py, **1c**-2-Py) were applicable to the reaction system, giving **3bs** and **3cs** in good yields. It is noteworthy that arylation on the secondary carbon was possible (**3cs**). Substituents such as R^3 or R^4 at the α-position to the oxime were not necessary for the reaction to occur, with **3ds** being obtained. Spirocyclic product **3es** was also successfully obtained. The substituent R^5 was altered to other aromatic groups such as 2-pyridyl (**3fs**) and 2-naphthyl group (**3gs**). Tricyclic compound **3hs** could also be obtained. The reaction was also applicable to oxime ester **1i**-2-Py, having an alkyl substituent at R^5, to afford the product **3is**.

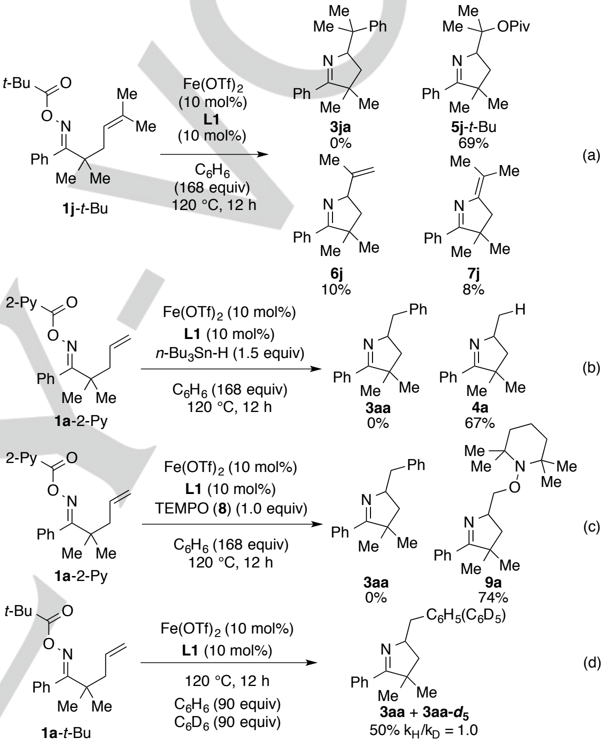


Scheme 4. Scope of oxime esters. Reaction conditions: **1x**-2-Py (0.20 mmol), $Fe(OTf)_2$ (0.020 mmol), **L1** (0.020 mmol), thiophen (30 mmol). Isolated yields are shown. dr = diastereomer ratio. Diastereomer ratio was determined by ^1H NMR.

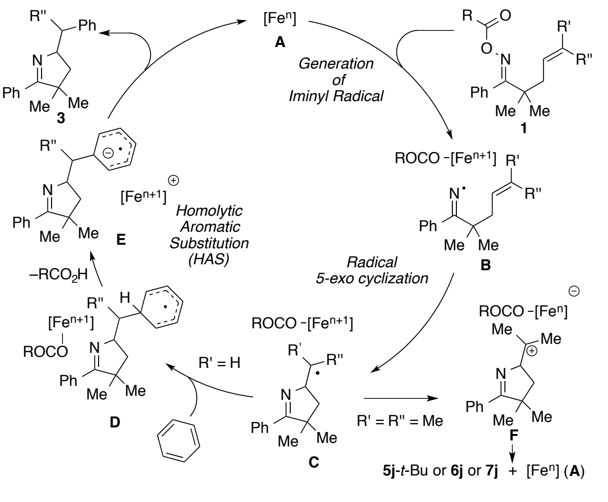
Preliminary experiments also provided some mechanistic insights into the reaction. The reaction of terminally disubstituted alkene **1j**-*t*-Bu with benzene gave no phenylated product **3ja**; alternatively, pivaloxylated product **5j**-*t*-Bu was obtained in good yield together with small amounts of dehydropivaloxylation products **6j** and **7j** (Scheme 5a). The addition of *n*-Bu_3SnH resulted in complete inhibition of arylation and gave the hydrogen atom adduct (Scheme 5b). The addition of radical scavenger (TEMPO) also prevented arylation completely, giving TEMPO adduct **9a** (Scheme 5c). These results imply the involvement of a radical intermediate. Deuterium labeling experiments using an equimolar amount of benzene and benzene-d_6 showed no kinetic isotope effect (Scheme 5d). This result is consistent with the general HAS reaction in which C–H bond cleavage should proceed through deprotonation.[1b,c]

Based on these observations, a plausible mechanism is shown in Scheme 6.[17] First, an iminyl radical or iron-ketimido is generated by N–O bond cleavage of oxime ester **1** induced by iron catalyst **A**. Intermediate **B** then undergoes 5-exo-trig cyclization to give intermediate **C**.[12c] When the latter does not have a tertiary alkyl center (R' = H), the reactive center of **C** adds to arenes to give arenyl radical **D**, which readily undergoes deprotonation to form arene-radical anion **E**. Finally, back electron transfer from radical anion **E** to iron releases product **3**, thereby regenerating iron catalyst **A**.

On the other hand, when **C** has a tertiary center (R' = R'' = Me), addition of **C** to arenes become slower compared with the other reaction pathway. Instead, **C** may undergo one-electron oxidation to form stable cation intermediate **F**, which affords either the pivaloxylated product **5j**-*t*-Bu or deprotonated olefinic product **6j** and **7j** (Scheme 5a).



Scheme 5. Preliminary mechanistic studies.



Scheme 6. Aminative transformation involving iminyl radicals.

In summary, we have demonstrated the iron-catalyzed direct alkylation of unactivated arenes, which takes place through HAS in a cascade manner with aminative cyclization of alkene-tethered oxime esters. C–H alkylation of both electron-rich and electron-poor arenes has been achieved, albeit with the requirement for an excess amount of arene. Mechanistic studies support the involvement of radical intermediates. The present transformation involving intermolecular HAS reaction will find synthetic application in the construction of intricate molecules when combined with atom transfer radical addition.

Acknowledgements

This study has been financially supported by Grant-in-aid for JSPS Research Fellow (T. Shimbayashi) (Grant No. 17J09627), Kansai Research Foundation for technology promotion (K. Okamoto), and JSPS KAKENHI (a Scientific Research (C); Grant No. 17K05861).

Conflict of interest

The authors declare no conflict of interest.

Keywords: Iron • Aromatic substitution • Radical reaction • Amination • Cyclization

[1] For reviews, see: a) W. R. Bowma, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803; b) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2011**, *50*, 5018; c) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765; d) M. Gurry, F. Aldabbagh, *Org. Biomol. Chem.* **2016**, *14*, 3849.

[2] A. Citterio, F. Minisci, O. Porta, G. Sesana, *J. Am. Chem. Soc.* **1977**, *99*, 7960.

[3] For reviews, see: a) E. Shirakawa, T. Hayashi, *Chem. Lett.* **2012**, *41*, 130; b) T. L. Chan, Y. Wu, P. Y. Choy, F. Y. Kwong, *Chem.— Eur. J.* **2013**, *19*, 15802; c) J. Hofmann, M. R. Heinrich, *Tetrahedron Lett.* **2016**, *57*, 4334; d) P. Gao, Y.-R. Gu, X.-H. Duan, *Synthesis* **2017**, *49*, 3407.

[4] a) S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673; b) F. Vallée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1514; c) W. Liu, H. Cao, A. Lei, *Angew. Chem. Int. Ed.* **2010**, *49*, 2004; d) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nat. Chem.* **2010**, *2*, 1044; e) E. Shirakawa, K.-I. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 15537; f) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 16737; g) N. Uchiyama, E. Shirakawa, R. Nishikawa, T. Hayashi, *Chem. Commun.* **2011**, *47*, 11671; h) Y. Cheng, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 2664; i) A. Dewanji, S. Murarka, D. P. Curran, A. Studer, *Org. Lett.* **2013**, *15*, 6102; j) J. Cuthbertson, V. J. Gray, J. D. Wilden, *Chem. Commun.* **2014**, *50*, 2575; k) T. Kawamoto, A. Sato, I. Ryu, *Org. Lett.* **2014**, *16*, 2111; l) H. Yang, L. Zhang, L. Jiao, *Chem.—Eur. J.* **2017**, *23*, 65.

[5] a) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; b) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95; c) Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, X. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958; d) L. Wang, W.-J. Wei, W.-L. Jia, J.-J. Zhong, L.-Z. Wu, Q. Liu, *Org. Lett.* **2014**, *16*, 5842; e) L. He, K. Natte, J. Rabeah, C. Taeschler, H. Neumann, A. Brückner, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 4320; f) W. J. Choi, S. Choi, K. Ohkubo, S. Fukuzumi, E. J. Cho, Y. You, *Chem. Sci.* **2015**, *6*, 1454; g) P. Liu, W. Liu, C.-J. Li, *J. Am. Chem. Soc.* **2017**, *139*, 14315.

[6] a) L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 3104; b) A. Nakatani, K. Hirano, T. Satoh, M. Miura, *Chem.—Eur. J.* **2013**, *19*, 7691; c) X. Wu, J. W. T. See, H. Hirao, J. Roger, J.-C. Hierso, J. S. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 13573; d) E. C. Swift, T. M. Williams, C. R. J. Stephenson, *Synlett* **2016**, *27*, 754; e) T. McCallum, L. Barriault, *Chem. Sci.* **2016**, *7*, 4754; f) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 2484; g) C. Theunissen, J. Wang, G. Evano, *Chem. Sci.* **2017**, *8*, 3465.

[7] Such transformation may involve in copper catalysis, see: T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 2020.

[8] For reviews, see: a) S. Z. Zard, *Synlett* **1996**, *12*, 1148; b)S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603; c) M. M. Jackman, Y. Cai, S. L. Castle, *Synthesis* **2017**, *49*, 1785.

[9] For reviews, see: a) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505; b) M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 539; c) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155; d) N. J. Race, I. R. Hazelden, A. Faulkner, J. F. Bower, *Chem. Sci.* **2017**, *8*, 5248.

[10] For selected examples, see: a) T. Nishimura, T. Yoshinaka, Y. Nishiguchi, Y. Maeda, S. Uemura, *Org. Lett.* **2005**, *7*, 2425; b) S. Liu, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2007**, 9, 1947; c) Z.-H. Ren, Z.-Y. Zhang, B.-Q. Yang, Y.-Y. Wang, Z.-H. Guan, *Org. Lett.* **2011**, *13*, 5394; d) A. Faulkner, N. J. Race, J. S. Scott, J. F. Bower, *Chem. Sci.* **2014**, *5*, 2416; e) W. Du, M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Chem. Commun.* **2014**, *50*, 7437; f) A. Faulkner, J. S. Scott, J. F. Bower, *J. Am. Chem. Soc.* **2015**, *137*, 7244; g) J. Davies, S. G. Booth, S. Essafi, R. A. W. Dryfe, D. Leonori, *Angew. Chem. Int. Ed.* **2015**, *54*, 14017; h) N. J. Race, A. Faulkner, M. H. Shaw, J. F. Bower, *Chem. Sci.* **2016**, *7*, 1508; i) S.-H. Cai, J.-H. Xie, S. Song, L. Ye, C. Feng, T.-P. Loh, *ACS Catal.* **2016**, *6*, 5571; j) X. Bao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9577; k) H. Jiang, A. Studer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12273.

[11] a) K. Uchiyama, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1998**, *27*, 1261; b) K. Uchiyama, Y. Hayashi, K. Narasaka, *Tetrahedron* **1999**, *55*, 8915; c) Y. Koganemaru, M. Kitamura, K. Narasaka, *Chem. Lett.* **2002**, *31*, 784.

[12] a) M.-N. Zhao, Z.-H. Ren, L. Yu, Y.-Y. Wang, Z.-H. Guan, *Org. Lett.* **2016**, *18*, 1194; b) Z. Zhu, X. Tang, J. Li, X. Li, W. Wu, G. Deng, H. Jiang, *Org. Lett.* **2017**, *19*, 1370; c) H.-B. Yang, N. Selander, *Chem.—Eur. J.* **2017**, *23*, 1779.

[13] a) K. Okamoto, T. Oda, S. Kohigashi, K. Ohe, *Angew. Chem. Int. Ed.* **2011**, *50*, 11470; b) K. Okamoto, T. Shimbayashi, E. Tamura, K. Ohe, *Chem.—Eur. J.* **2014**, *20*, 1490; c) T. Shimbayashi, K. Okamoto, K. Ohe, *Synlett* **2014**, *25*, 1916; d) K. Okamoto, T. Shimbayashi, M. Yoshida, A. Nanya, K. Ohe, *Angew. Chem. Int. Ed.* **2016**, *55*, 7199; e) K. Okamoto, K. Sasakura, T. Shimbayashi, K. Ohe, *Chem. Lett.* **2016**, *45*, 988.

[14] a) T. Shimbayashi, K. Okamoto, K. Ohe, *Organometallics* **2016**, *35*, 2026; b) T. Shimbayashi, K. Okamoto, K. Ohe, *Chem.—Eur. J.* doi:10.1002/chem.2017040102.

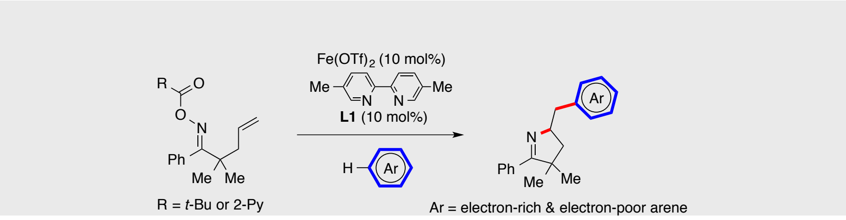
[15] See supporting information for detail.

[16] CCDC 1579269 (**5a**-C_6F_5), 1579270 (**3ad'**) and 1579271 (**3al'**) contains the supplementary crystallographic data.

[17] In the catalytic cycle, there may be equilibrium between free radical species and corresponding iron adduct. Such equilibrium is proposed to be involved in iron-catalyzed cross coupling or borylation of aryl chloride, see: a) T. Hatakeyama, T. Hashimoto, K. K. A. D. S. Kathriarachchi, T. Zenmyo, H. Seike, M. Nakamura, *Angew. Chem. Int. Ed.* **2012**, *51*, 8834; b) L. Adak, S. Kawamura, G. Toma, T. Takenaka, K. Isozaki, H. Takaya, A. Orita, H. C. Li, T. K. M. Shing, M. Nakamura, *J. Am. Chem. Soc.* **2017**, *139*, 10693; c) T. Yoshida, L. Ilies, E. Nakamura, *ACS Catal.* **2017**, *7*, 3199.

Entry for the Table of Contents

COMMUNICATION



Directly come in!: Iron-catalyzed intermolecular homolytic aromatic substitution (HAS) employing simple arenes was achieved in cascade manner with aminative cyclization of alkene-tethered oxime esters ignited by N–O bond cleavage. This system will open a path to application of intermolecular HAS reaction into construction of intricate molecules.

T. Shimbayashi, K. Okamoto, K. Ohe**

Page No. – Page No.

Iron-Catalyzed Aminative Cyclization/Intermolecular Homolytic Aromatic Substitution Using Oxime Esters and Simple Arenes