ORGANIC LETTERS

2013
Vol. 15, No. 9
2160–2163

Metal-Free Fluorination of C(sp^3)–H Bonds Using a Catalytic *N*-Oxyl Radical

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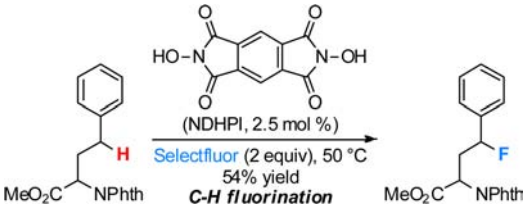
Received March 13, 2013

ABSTRACT



A direct conversion of C(sp^3)–H bonds to C(sp^3)–F bonds has been developed. In this process, a catalytic *N*-oxyl radical generated from *N,N*-dihydroxypyromellitimide abstracts hydrogen from the C(sp^3)–H bond and Selectfluor acts to trap the resulting carbon radical to form the C(sp^3)–F bond. This simple metal-free protocol enables the chemoselective introduction of a fluorine atom into various aromatic and aliphatic compounds and serves as a powerful tool for the efficient synthesis of fluorinated molecules.

Organofluorine compounds are widely used in many different applications, ranging from pharmaceuticals and agrochemicals to advanced materials and polymers.[1,2] Thirty to forty percent of agrochemicals and twenty percent of pharmaceuticals currently on the market contain at least one fluorine atom (e.g., CETP inhibitor[3] and fluticasone propionate[4] in Figure 1). It has been recognized that fluorine substitution can confer useful molecular properties, such as enhanced stability and hydrophobicity.[5] In addition, fluorine substitution of an sp^3-rich carboskeleton can modify the overall molecular shape by changing the conformational preference through dipole–dipole interactions or hyperconjugation.[6]

The one-step fluorination of C–H bonds at the sp^3-carbon centers dramatically simplifies the synthetic routes to such characteristic fluorinated carboskeletons in comparison to conventional methodologies.[7,8] However, only a limited number of direct fluorination methods have been developed, and those involving catalysis are especially

(1) (a) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Jeschke, P. *Pest Manag. Sci.* **2010**, *66*, 10. (d) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

(2) Thayer, A. M. *Chem. Eng. News* **2006**, *84* (23), 15.

(3) Paulsen, H.; Antons, S.; Brandes, A.; Lögers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuß, J. *Angew. Chem., Int, Ed.* **1999**, *38*, 3373.

(4) Phillipps, G. H.; Bailey, E. J.; Bain, B. M.; Borella, R. A.; Buckton, J. B.; Clark, J. C.; Doherty, A. E.; English, A. F.; Fazakerley, H.; Laing, S. B.; Lane-Allman, E.; Robinson, J. D.; Sandford, P. E.; Sharratt, P. J.; Steeples, I. P.; Stonehouse, R. D.; Williamson, C. *J. Med. Chem.* **1994**, *37*, 3717.

(5) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(6) Hunter, L. *Beilstein J. Org. Chem.* **2010**, DOI: 10.3762/bjoc.6.38.

(7) For recent reviews on synthesis of fluorinated compounds, see: (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (f) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867.

(8) For recent reviews on C–H transformations, see: (a) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vols. 1 and 2. (b) *Handbook of Reagents for Organic Synthesis: Reagents for Direct Functionalization of C–H Bonds*; Paquette, L. A., Fuchs, P. L., Eds.; Wiley: Chichester, 2007. (c) Special issue on "C–H Functionalizations in Organic Synthesis: *Chem. Soc. Rev.* **2011**, *40* (4). (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(9) For representative examples of catalytic C(sp^3)–H fluorination, see: (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094. (c) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580. (d) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (e) Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. *Org. Lett.* **2013**, *15*, 1722. For a recent account, see: (f) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570.

(10) F_2-induced direct fluorination of C(sp^3)–H bonds: (a) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307. (b) Chambers, R. D.; Kenwright, A. M.; Parsons, M.; Sandford, G.; Moilliet, J. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2190. (c) Sandford, G. *J. Fluorine Chem.* **2007**, *128*, 90.

10.1021/ol4006757
Published on Web 04/19/2013

rare.[9,10] Recently, Lectka's group described C(sp^3)–H fluorination employing a combination of Selectfluor, a copper(I) bisimine complex, an anionic phase-transfer catalyst and *N*-hydroxyphthalimide (NHPI).[9c] Herein, we report metal-free direct C(sp^3)–H fluorination using a catalytic system consisting of *N*,*N*-dihydroxypyromellitimide (NDHPI)[11] and Selectfluor[12] (Scheme 1). The present transformation is applicable to benzylic or aliphatic C(sp^3)–H bonds of **1** and generates the corresponding monofluorinated derivatives **2** under mild conditions in a highly chemoselective fashion.

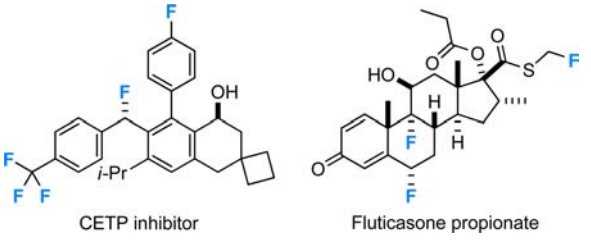
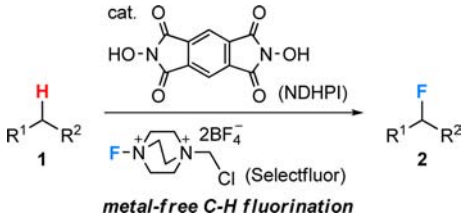


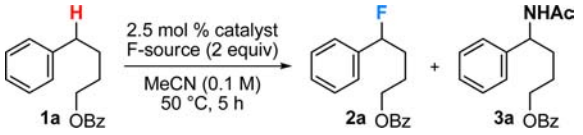
Figure 1. Biologically active compounds incorporating C(sp^3)–F bonds.

Scheme 1. C(sp^3)–H Fluorination Using *N*,*N*-Dihydroxypyromellitimide (NDHPI) and Selectfluor



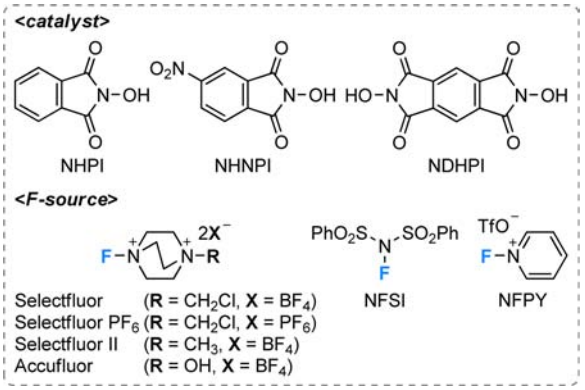
Previously, we developed methodologies for the high-yield transformations of benzylic C(sp^3)–H bonds to C(sp^3)–O and C(sp^3)–N bonds, using NHPI as the precursor of the hydrogen-abstracting *N*-oxyl radical.[13] In the present study, the benzylic compound **1a** and a number of NHPI derivatives were employed in combination with various fluorinating reagents to realize the C(sp^3)–H fluorination (Table 1).[14] Treatment of **1a** with 2.5 mol % of NHPI and 2 equiv of Selectfluor at 50 °C for 5 h in MeCN[15] chemoselectively provided the desired benzylfluoride **2a** in low yield along with a significant quantity of unreacted **1a** (entry 1). As shown in entries 2 and 3, we subsequently applied two NHPI analogues[16] in an attempt to enhance the catalytic activity. Although the use of *N*-hydroxy-4-nitrophthalimide (NHNPI) decreased the yield of **2a** (entry 2), *N*,*N*-dihydroxypyromellitimide (NDHPI),[17] which has an additional imide-*N*-hydroxy group, was found to significantly increase the yield (entry 3). A longer reaction time (entry 4) resulted in lower yield of **2a** and the formation of acetamide **3a** through nucleophilic attack by MeCN,[13a] suggesting the activated nature of the resulting benzylic C(sp^3)–F bond. The lack of any products in the

Table 1. Screening of Reaction Conditions for the Direct Fluorination of Benzylic C(sp^3)–H Bonds[a]



			yield[b] (%)		
entry	catalyst	F-source	**2a**	**3a**	**1a** (recovery)
1	NHPI	Selectfluor	21	0	73
2	NHNPI	Selectfluor	10	0	90
3	**NDHPI**	**Selectfluor**	**72**[c]	**0**	**21**
4[d]	NDHPI	Selectfluor	42	21	13
5		Selectfluor	0	0	100
6	NDHPI	Selectfluor PF_6	55	15	16
7	NDHPI	Selectfluor II	51	13	21
8	NDHPI	Accufluor	17	25	39
9	NDHPI	NFSI	0	0	88
10	NDHPI	NFPY	0	0	98

[a] Conditions: aromatic compound **1a**, catalyst (2.5 mol %), F-source (2 equiv), MeCN (0.1 M), at 50 °C for 5 h under an Ar atmosphere. [b] Yield was determined by NMR analysis of the crude mixture. [c] Isolated yield. [d] The reaction time was 8 h.



(11) For reviews on NHPI-catalyzed reactions, see: (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393. (b) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800. (c) Coseri, S. *Catal. Rev.* **2009**, *51*, 218.

(12) For reviews on Selectfluor, see: (a) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Stavber, S. *Molecules* **2011**, *16*, 6432.

(13) (a) Kamijo, S.; Amaoka, Y.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 4654. (b) Amaoka, Y.; Kamijo, S.; Hoshikawa, T.; Inoue, M. *J. Org. Chem.* **2012**, *77*, 9959.

(14) Fluorination of carbon radicals has been demonstrated; see: (a) Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026. (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401. (c) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588.

(15) The choice of MeCN as a solvent was critical to obtain **2a**. No reaction occurred in any other solvent.

(16) Sun, Y.; Zhang, W.; Hu, X.; Li, H. *J. Phys. Chem. B* **2010**, *114*, 4862.

(17) Shibamoto, A.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 8859.

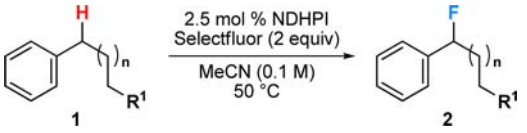
absence of NDHPI confirmed its importance as the *N*-oxyl radical precursor (entry 5).[18,19] Three structural variants of Selectfluor[20] (entries 6−8) were shown to be less effective fluorinating reagents than Selectfluor itself, while the application of *N*-fluorobenzenesulfonimide (NFSI, entry 9) and *N*-fluoropyridinium triflate (NFPY, entry 10) did not give any fluorinated products. The results in entries 6−10 clarified the superiority of Selectfluor for metal-free C(sp^3)−H fluorination.[21]

To examine the functional group compatibility, various benzene derivatives having different functionalities on their side chains were submitted to the optimized conditions determined previously (Table 2). The reactions of benzoates **1a**−**c** all took place, producing benzylfluorides **2a**−**c** (entries 1−3). The lower yield of **2c** (55%, entry 3) in comparison to those of **2a** (72%, entry 2) and **2b** (72%, entry 1) reflects the general preference of electrophilic *N*-oxyl radical for electron-rich C−H bonds.[13,22] Specifically, the lower reactivity of **1c** results from the electron-deficient nature of the benzylic C−H bond, due to the shorter tether length between the benzyl methylene and the electron-withdrawing benzoyloxy group.

As long as alcohol and amine functionalities on the substrate were properly protected, our reagent system allowed formation of the expected benzylfluorides in high yields. Namely, methanesulfonyl (Ms) ester **2d** (entry 4) and phthaloyl (Phth) imide **2e** (entry 5) were obtained in good yields. In addition, the reaction occurred without affecting electrophilic methyl ester (**1f**, entry 6) and cyanide (**1g**, entry 7) moieties to provide **2f** and **2g**, respectively. Importantly, the C−H fluorination proceeded even in the presence of a free carboxyl group (**1h**, entry 8) and a free tertiary hydroxyl group (**1i**, entry 9), resulting in formation of **2h** and **2i**, respectively. Despite the radical mechanism of the reaction (vide infra), the C(sp^3)−Br bond of **1j** remained intact, and **2j** was isolated in good yield (entry 10).

The subsequent synthesis of a wide variety of benzyl fluorides **2k**−**u** from the corresponding aromatic compounds **1k**−**u** demonstrated the versatility of the present methodology (Scheme 2). Electron-rich phenol (**2k**) and aniline derivatives (**2l**) could be synthesized using reduced reaction times, whereas longer time spans were necessary when the reaction involved substrates with

Table 2. Direct C(sp^3)−H Fluorination of Aromatic Compounds Having a Functional Group on the Side Chain[a]



	substrate **1**				
entry	R^1	*n*	time (h)	product **2**	yield (%)
1	OBz	3 (**1b**)	5	**2b**	72
2	OBz	2 (**1a**)	5	**2a**	72
3	OBz	1 (**1c**)	7	**2c**	55
4	OMs	2 (**1d**)	6	**2d**	70
5	NPhth	2 (**1e**)	5	**2e**	74
6	CO_2Me	2 (**1f**)	6	**2f**	70
7	CN	2 (**1g**)	5	**2g**	64
8	CO_2H	2 (**1h**)	5	**2h**	51
9	$C(Me)_2OH$	1 (**1i**)	3	**2i**	72
10	Br	2 (**1j**)	6	**2j**	51

[a] Conditions: aromatic compound **1**, NDHPI (2.5 mol %), Selectfluor (2 equiv), MeCN (0.1 M), at 50 °C for the indicated time under an Ar atmosphere.

electron-withdrawing methoxycarbonyl (**2m**) and acetyl (**2n**) functionalities. No significant differences in reactivity were observed between *p*-benzoyloxy-substituted **1k**, *meta*-substituted **1o**, and *ortho*-substituted **1p** when generating **2k**, **2o**, and **2p**. The tertiary C−H bonds of **1q** and **1r** were also fluorinated to introduce the tetrasubstituted carbon centers of **2q** and **2r**, respectively. The reaction of 1,3-diphenylpropane **1s** gave the monofluorinated compound **2s** as the major product. Moreover, the C−H fluorinations of homophenylalanine derivative **1t** and ibuprofen derivative **1u** exhibited high chemoselectivity for the benzylic positions despite their structural complexity, delivering monofluorides **2t** and **2u**, respectively.

Finally, this synthetic protocol was successfully applied to the direct fluorination of the C−H bonds of alkanes (**1v**−**z**), which are known to be less reactive than benzylic C−H bonds (Scheme 2). The secondary aliphatic C−H bonds of cyclododecane **1v** underwent the functionalization, providing the expected monofluoride **2v**. The reaction of adamantane derivatives **1w**−**y** proceeded chemoselectively at the tertiary C−H bonds, in the presence of several secondary C−H bonds, to give the corresponding fluorides **2w**−**y** as the sole products. Furthermore, the fluorination of 2-oxaadamantan-1-ol **1z** proceeded chemoselectively at the nonoxygen substituted position to provide **2z**.

A proposed reaction mechanism for the NDHPI/Selectfluor-promoted fluorination of C(sp^3)−H bonds is presented in Scheme 3. In the first step, NDHPI is oxidized by Selectfluor in situ to generate the electrophilic *N*-oxyl radical, which is the key reactive species.[11,13] Then, chemoselective abstraction from the electron-rich C(sp^3)-H bond takes place to form carbon radical **A** and NDHPI. The subsequent trapping of the carbon radical **A** by Selectfluor in turn provides the corresponding fluoride **2**

(18) While compound **2a** was recovered in 90% yield upon submission of **2a** to the reaction conditions of entry 3, treatment of HBF_4 (1 equiv) in MeCN efficiently converted **2a** into **3a** in 87% yield. These separate experiments suggested that the C(sp^3)−F bond was activated by HBF_4 that was generated during the course of the reaction.

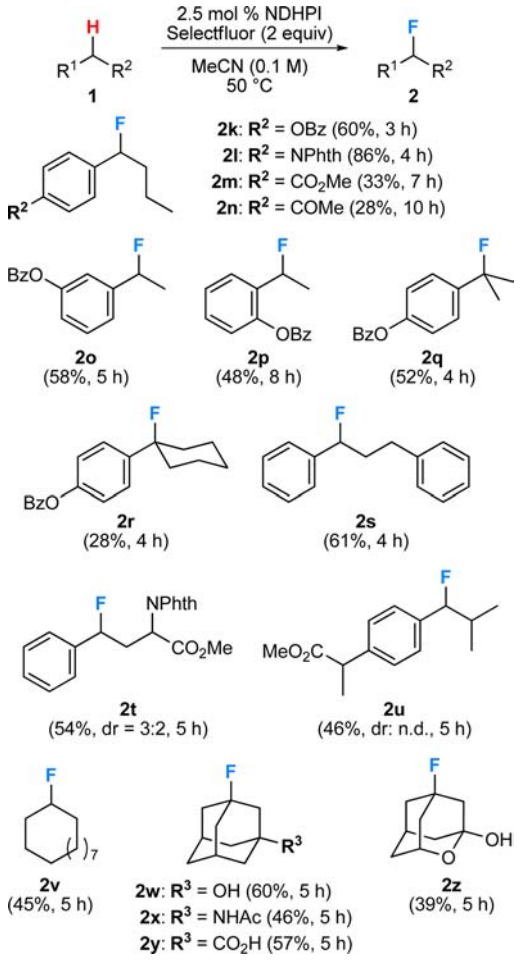
(19) Addition of stoichiometric 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) completely inhibited the formation of **2a**, whereas addition of catalytic TEMPO (0.1 equiv) partially suppressed the formation of **2a** (25% yield). These results indicate continuous generation of *N*-oxyl radical from NDHPI. Therefore, not only **B** but also Selectfluor would participate in oxidation of NDHPI (see Scheme 3).

(20) Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069.

(21) High electrophilicity of Selectfluor appears to be important for generation of *N*-oxyl radical. Gilicinski, A. G.; Pez, G. P.; Syvret, R. G.; Lal, G. S. *J. Fluorine Chem.* **1992**, *59*, 157.

(22) (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042. (c) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (d) White, M. C. *Science* **2012**, *335*, 807.

Scheme 2. Direct C(sp^3)–H Fluorination of Various Substrates[a]

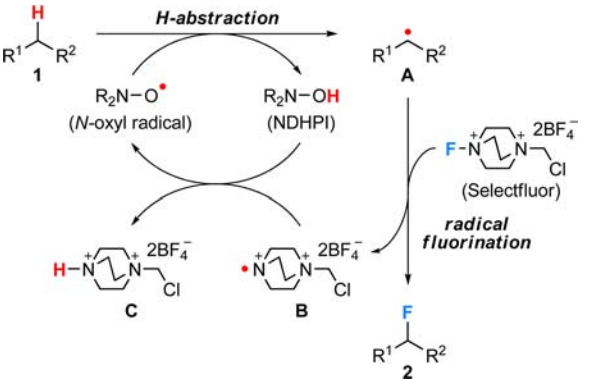


[a] Conditions: starting material **1**, NDHPI (2.5 mol %), Selectfluor (2 equiv), MeCN (0.1 M), at 50 °C for the indicated time under an Ar atmosphere.

and the amino radical cation **B**. When **B** abstracts a hydrogen from NDHPI, it regenerates the *N*-oxyl radical species and forms protonated amine **C**, thus closing the catalytic cycle.

In conclusion, this paper describes the metal-free fluorination of C(sp^3)–H bonds under mild conditions, employing a simple reagent system composed of NDHPI and Selectfluor. This radical-based reaction is initiated by hydrogen abstraction at the electron-rich position, and the carbon radical is intermolecularly trapped by Selectfluor, resulting in installation of a fluorine atom. The most important features of this synthetic procedure are: (1) predictable chemoselectivity toward the benzylic C(sp^3)–H bonds of aromatic compounds and the tertiary C(sp^3)–H bonds of aliphatic compounds and (2) high compatibility with various functionalities, including benzoyl- and methanesulfonyl-protected alcohols and phthaloyl-protected amines, as well as carboxylic acids, tertiary alcohols, cyanides, and bromides. As the result of these advantages, the present one-step methodology should serve as a unique tool for the efficient synthesis of various fluorinated compounds with pharmaceutical and agrochemical applications.

Scheme 3. Proposed Mechanism for Transformation of C(sp^3)–H Bonds to C(sp^3)–F Bonds



Acknowledgment. This research was financially supported by the Funding Program for Next Generation World-Leading Researchers (JSPS) to M.I. A fellowship from JSPS to Y.A. is gratefully acknowledged.

Supporting Information Available. Experimental procedures and spectroscopic and analytical data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.