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Synthesis of [60]Fullerene-Fused Tetrahydroazepinones and Azepinonimines via $Cu(OAc)_2$-Promoted *N*-Heteroannulation Reaction

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S *Supporting Information*

ABSTRACT: A convenient and efficient $Cu(OAc)_2$-mediated *N*-heteroannulation reaction of [60]fullerene with *N*-sulfonylated *o*-amino-aromatic methyl ketones or *O*-alkyl oximes has been reported for the synthesis of novel and scarce [60]fullerene-fused tetrahydroazepinones and -azepinonimines in a highly selective manner. Moreover, a possible mechanism involving two pathways is proposed on the basis of the experimental observations.

Chemical functionalization of fullerenes is an important subject in fullerene chemistry for the creation of novel diversified fullerene-based materials with potential applications in nanoscience, electronic devices, and biomedicine.[1] During the past two decades, a large number of chemical reactions of fullerenes have been developed, and a great diversity of fullerene derivatives with different functional and structural units have been prepared.[2] Among these reactions, free radical reactions have been proven to be an efficient and important tool for the synthesis of various fullerene derivatives.[3] Especially in recent years, increasing attention has been focused on the transition-metal-catalyzed/mediated radical reactions for their excellent ability to create novel functional fullerenes and remarkable advantages over the traditional peroxide- or light-initiated processes, such as high selectivity and efficiency, mild reaction conditions, and high compatibility with a wide range of functional groups.[2i,3b,4]

To the best of our knowledge, among numerous [60]-fullerene derivatives with various fused rings, there are only a few reports on the construction of more challenging seven-membered ring systems up to now. These examples include the photochemical cycloaddition of C_{60} with dienyl cyclopropanes,[5] $Pd(OAc)_2$-catalyzed annulation of C_{60} with *N*-sulfonyl-2-aminobiaryls *via* directed C(sp^2)−H bond activation,[6] and Co-catalyzed radical cycloaddition of C_{60} with 1,8-bis(bromomethyl)naphthalene.[7] Despite these advances, the development of new approaches to construct diversified seven-membered [60]fullerene adducts in an efficient way with a broad substrate scope still remains largely unrealized. Herein, we present a flexible and efficient synthetic method for the highly selective preparation of novel [60]fullerene-fused tetrahydroazepinones and -azepinonimines from C_{60} with *N*-sulfonylated *o*-amino-aromatic methyl ketones or *O*-alkyl oximes through a $Cu(OAc)_2$-promoted C−C/C−N bond forming annulation reaction under aerobic conditions.

Our investigations began by choosing the $Cu(OAc)_2$-mediated reaction of C_{60} with *N*-tosyl-*o*-aminoacetophenone **1a** as the model reaction for the optimization of the reaction conditions. The effect of the different bases, including organic and inorganic bases, was first examined (Table 1, entries 1−6). To our delight, when organic base DMAP was employed, the reaction selectively afforded the desired seven-membered ring C_{60}-fused tetrahydroazepinone **2a** in 8% yield at 80 °C after 2 h (Table 1, entry 1), instead of corresponding methanofullerene derivative, C_{60}-fused dihydrofuran adduct, or their mixtures generated from C_{60} with aromatic methyl ketone **1a** under similar conditions.[8] With this preliminary and intriguing result in hand, we turned to extensively screen various bases, such as organic base DABCO (1,4-diazabicyclo[2.2.2]octane) and inorganic bases Na_2CO_3, K_2CO_3, K_3PO_4, and Cs_2CO_3, to improve the product yield (Table 1, entries 1−6). Compared to the other bases, it was found that Cs_2CO_3 showed the highest reactivity, with the formation of **2a** in 40% yield (69% based on consumed C_{60}). Further conditions screening revealed that lowering the reaction temperature or shortening the reaction time gave inferior yields (Table 1, entries 7 and 9). By contrast, raising the reaction temperature or prolonging the reaction time also proved to be nonbeneficial to achieve a higher yield, and it led to more byproducts and a significant consumption of C_{60} (Table 1, entries 8 and 10). When decreasing the amount of $Cu(OAc)_2$ from 2 to 1 equiv, an obvious decrease in the yield of **2a** was observed (40% to 29%, Table 1, entry 11 vs 6).

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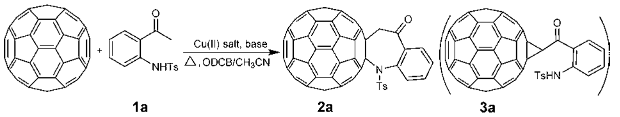
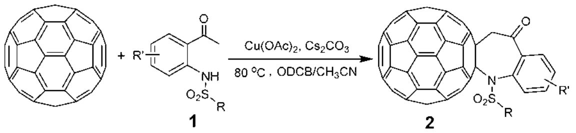
Table 1. Optimization of the Reaction Conditions[a]

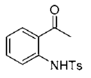
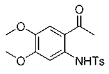
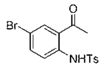
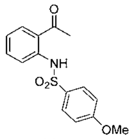
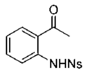
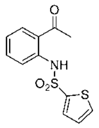
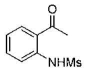


entry	Cu(II)	base	molar ratio[b]	time (h)	yield (%)[c]
1	Cu(OAc)$_2$	DMAP	1:4:2:1	2	8 (80)
2	Cu(OAc)$_2$	DABCO	1:4:2:1	2	trace
3	Cu(OAc)$_2$	Na$_2$CO$_3$	1:4:2:1	2	trace
4	Cu(OAc)$_2$	K$_2$CO$_3$	1:4:2:1	2	trace
5	Cu(OAc)$_2$	K$_3$PO$_4$	1:4:2:1	2	trace
6	**Cu(OAc)$_2$**	**Cs$_2$CO$_3$**	**1:4:2:1**	**2**	**40 (69)**
7[d]	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:2:1	2	32 (74)
8[e]	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:2:1	2	36 (50)
9	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:2:1	1	34 (68)
10	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:2:1	3	35 (56)
11	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:1:1	2	29 (60)
12	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:3:1	2	37 (71)
13	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:4:2:2	2	32 (51)
14	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:3:2:1	2	34 (70)
15	Cu(OAc)$_2$	Cs$_2$CO$_3$	1:5:2:1	2	40 (73)
16	Cu(OTf)$_2$	Cs$_2$CO$_3$	1:4:2:1	2	trace
17	Cu(NO$_3$)$_2$	Cs$_2$CO$_3$	1:4:2:1	2	trace
18	CuCl$_2$	Cs$_2$CO$_3$	1:4:2:1	2	trace
19[f]	CuSO$_4$	Cs$_2$CO$_3$	1:4:2:1	2	trace

[a] All reactions were carried out with C$_{60}$/**1a**/Cu(II)/base in a designated molar ratio in cosolvent of anhydrous ODCB (7 mL) and CH$_3$CN (1 mL) at 80 °C under air unless specified otherwise. [b] Molar ratio refers to C$_{60}$/**1a**/Cu(II)/base. [c] Isolated yield; that in parentheses was based on consumed C$_{60}$. [d] Reaction at 70 °C. [e] Reaction at 90 °C. [f] Methanofullerene derivative **3a** was obtained in 16% yield.

Table 2. Cu(OAc)$_2$-Mediated Synthesis of [60]Fullerene-Fused Tetrahydroazepinones[a]



entry	substrare **1**	product **2**	time (h)	yield (%)[b]
1	 NHTs **1a**	**2a**	2	40 (69)
2	 NHTs **1b**	**2b**	2	39 (78)
3	 Br NHTs **1c**	**2c**	2	38 (67)
4	 NH O$_2$S OMe **1d**	**2d**	2	33 (61)
5	 NHNs **1e**	**2e**	1	34 (69)
6	 NH O$_2$S S **1f**	**2f**	3	44 (81)
7[c]	 NHMs **1g**	**2g**	2	28 (88)

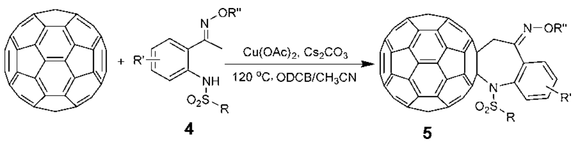
[a] All reactions were performed with a molar ratio of C$_{60}$/**1**/Cu(OAc)$_2$/Cs$_2$CO$_3$ = 1:4:2:1 in a solvent mixture of anhydrous ODCB (7 mL) and CH$_3$CN (1 mL) at 80 °C. [b] Isolated yield; that in parentheses was based on consumed C$_{60}$. [c] Reaction at 90 °C. Ns = 4-nitrobenzenesulfonyl, Ms = methanesulfonyl.

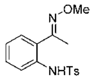
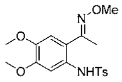
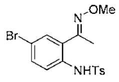
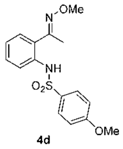
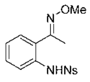
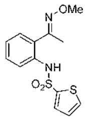
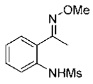
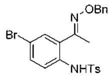
If the loading of Cu(OAc)$_2$ was increased to 3 equiv, the reaction only gave a comparable yield (Table 1, entry 12). An attempt in increasing the quantity of Cs$_2$CO$_3$ to 2 equiv led to an obvious decrease in the yield of **2a** (40% to 32%), as well as the formation of a small amount of byproduct methanofullerene derivative **3a** (Table 1, entry 13). Achieving a higher yield by changing the ratio of C$_{60}$/**1a** was unsuccessful (Table 1, entries 14 and 15). In addition, other copper salts such as Cu(OTf)$_2$, Cu(NO$_3$)$_2$, and CuCl$_2$ were ineffective in providing expected product **2a** (Table 1, entries 16–18). Intriguingly, when the reaction was carried out in the presence of CuSO$_4$, methanofullerene derivative **3a** was selectively obtained in 16% isolated yield instead of **2a** (Table 1, entry 19).

With the optimized reaction conditions in hand, the substrate scope of the annulation was investigated for the synthesis of [60]fullerene-fused tetrahydroazepinones, and the results are shown in Table 2. Notably, a wide variety of *N*-sulfonyl-*o*-aminoacetophenones **1** could effectively react with C$_{60}$ to selectively afford the corresponding products **2a–g**. Aryl-substituted substrates **1b–e** bearing electron-donating and -withdrawing groups on the aromatic ring all underwent reaction smoothly under the optimized conditions to give the expected products **2b–e** in good yields (33–39%), indicating that the electronic effect of the substituent group on the aromatic ring has no significant influence on the reaction (Table 2, entries 2–5). In addition, *N*-heteroaryl sulfonylated 2-aminoacetophenone **1f** was also a suitable substrate for this reaction and gave a slightly higher yield (Table 2, entry 6). When the *N*-protecting group of the substrates was changed to alkylsulfonyl from arylsulfonyl as in the case of *N*-mesyl-*o*-aminoacetophenone **1g**, the cyclization reaction also performed well, providing the corresponding product **2g** in 28% yield, although a higher reaction temperature (90 °C) was required (Table 2, entry 7). To our disappointment, when other *N*-substituted substrates such as *N*-acetyl-*o*-aminoacetophenone and ethyl (2-acetylphenyl)carbamate were employed under the same reaction conditions, no or trace expected products were detected.

Next, we further explored the possibility of extending the substrates from *N*-sulfonyl-*o*-aminoacetophenones to *N*-sulfonyl-*o*-aminoacetophenone *O*-alkyl oximes for the synthesis of another novel type of fullerenyl cycloaddition products, namely, [60]fullerene-fused tetrahydroazepinonimines. It was pleasing to find that a range of *N*-sulfonyl-*o*-aminoacetophenone *O*-alkyl oximes **4** containing different substitution patterns could also successfully react with C$_{60}$ under similar conditions to afford the expected derivatives in 15–33% yields, as illustrated in Table 3. Compared with *N*-sulfonyl-*o*-aminoacetophenones **1**,

Table 3. Cu(OAc)$_2$-Mediated Synthesis of [60]Fullerene-Fused Tetrahydroazepinonimines[a]



entry	substrare **4**	product **5**	time (h)	yield (%)[b]
1	 **4a**	**5a**	3	22 (76)
2	 **4b**	**5b**	2	18 (78)
3	 **4c**	**5c**	2	33 (68)
4	 **4d**	**5d**	4	15 (65)
5	 **4e**	**5e**	3	32 (68)
6	 **4f**	**5f**	3	32 (82)
7[c]	 **4g**	**5g**	2	27 (56)
8	 **4h**	**5h**	2	18 (55)

[a] All reactions were performed with a molar ratio of C_{60}/**4**/Cu(OAc)$_2$/Cs_2CO_3 = 1:4:2:2 in a solvent mixture of anhydrous ODCB (7 mL) and CH_3CN (1 mL) at 120 °C. [b] Isolated yield; that in parentheses was based on consumed C_{60}. [c] Reaction at 130 °C. Ns = 4-nitrobenzenesulfonyl, Ms = methanesulfonyl.

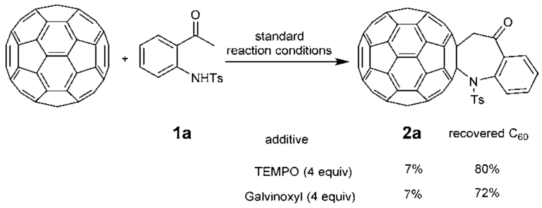
N-sulfonyl-*o*-aminoacetophenone *O*-alkyl oximes **4** were less reactive substrates for the present oxidative annulation, requiring a higher reaction temperature (120 or 130 °C) (Table 3, entries 1−8), which may be attributed to the lower acidity of CH_3 adjacent to C═NOR than C═O. It was noteworthy that the electronic nature of the substituents on the phenyl ring played an important role in the reaction, which was not in agreement with the observations in the reaction of C_{60} with *N*-sulfonyl-*o*-aminoacetophenones. For example, by employing the aryl-substituted substrates with electron-withdrawing groups on both phenyl rings, the reactions afforded the corresponding [60]fullerene-fused tetrahydroazepinonimines in good yields (33% and 32%), while the aryl-substituted substrates possessing electron-donating groups on both phenyl rings just led to the desired products in lower yields (18% and 15%) (Table 3, entries 2 and 4 vs entries 3 and 5). *N*-(2-Thenoyl)-*o*-aminoacetophenone *O*-methyl oxime **4f** exhibited a similar reactivity to the aryl-substituted substrates featuring electron-withdrawing groups on both phenyl rings and gave the target product **5f** in 32% yield (Table 3, entry 6). To our satisfaction, *N*-methyl sulfonylated substrate **4g** was also compatible, furnishing the desired adduct efficiently (Table 3, entry 7). In addition, upon changing the substrate from *O*-methyl oxime **4c** to *O*-benzyl oxime **4h**, C_{60}-tetrahydroazepinonimine derivative **5h** was also obtained, albeit in relatively low yield, possibly due to the steric hindrance of the benzyl group (Table 3, entry 8).

C_{60}-fused tetrahydroazepinonimines **5** were also obtained through the condensation of C_{60}-fused tetrahydroazepinones **2** with methoxyamine hydrochloride in the presence of a base. However, compared with the above synthesis of derivatives **5**, this indirect transformation was not a practical synthetic route. For example, when **2a** was treated with excess methoxyamine hydrochloride and NaOAc, the reaction only afforded **5a** in 27% isolated yield (11% overall yield in two steps; see Supporting Information (SI)).

The identification of novel C_{60}-fused tetrahydroazepinones **2a−g** and C_{60}-fused tetrahydroazepinonimines **5a−h** were unambiguously confirmed by their HRMS, ^{1}H NMR, ^{13}C NMR, FT-IR, and UV−vis spectroscopy, except for the ^{13}C NMR data of **5e** and **5g** due to their poor solubility (see SI).

To obtain further insights into the mechanism, the reaction of C_{60} with **1a** in the presence of radical inhibitors was conducted, as illustrated in Scheme 1. Adding TEMPO (2,2,6,6-tetramethylpiperidine-1-oxy) or Galvinoxyl (2,6-di-*tert*-butyl-*α*-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene-1-ylidene)-*p*-tolyloxy) severely retarded the heteroannulation reaction, thus strongly suggesting that this transformation may involve a free radical process.

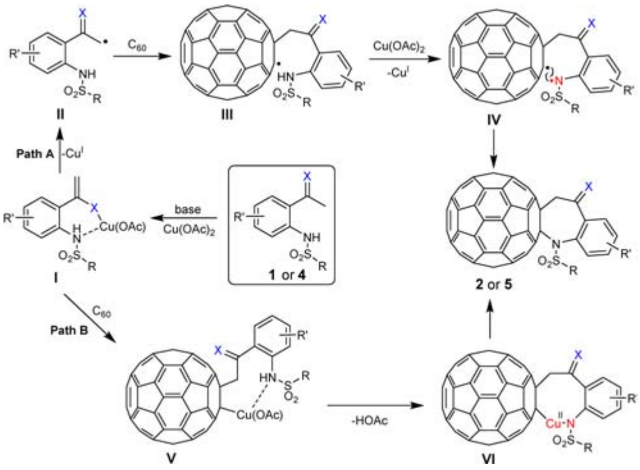
Scheme 1. Evidence in Support of a Radical Pathway



additive	**2a**	recovered C_{60}
TEMPO (4 equiv)	7%	80%
Galvinoxyl (4 equiv)	7%	72%

Based on the above control experiments and literature survey, a possible mechanism involving two pathways for the oxidative formation of C_{60}-fused tetrahydroazepinones **2** and azepinonimines **5** is depicted in Scheme 2. Under the basic conditions, the formed enolate or enamine of the substrate **1** or **4** could coordinate to Cu(OAc)$_2$ to generate Cu(II) complex **I**.[8,9] Next, the radical species **II** was generated from complex **I** via one-electron oxidation by Cu(II) in the radical pathway (Path A), which could be captured by C_{60} to produce the fullerenyl radical **III**, after which the active species **III** was further oxidized by another molecule of Cu(OAc)$_2$ to provide uncommon nitrogen radicals,[10] leading to a C- and N-centered biradical intermediate **IV**.[7,11] Subsequently, intramolecular cyclization occurred to selectively afford seven-membered annulated azepinones **2** and azepinonimines **5** *via* the biradical C−N coupling, instead of methanofullerene or C_{60}-fused dihydrofuran derivative. We thought species **IV** was a key intermediate, which made the reaction switch the pathway and

Scheme 2. Proposed Mechanism of Copper-Mediated Oxidative Cascade Formation of C_{60}-Fused Tetrahydroazepinones 2 and Azepinonimines 5



thus favor the formation of these intriguing seven-membered ring systems. An alternative pathway involving N−Cu(II) bond formation might coexist with the above radical process in the cyclization. In Path B, the C_{60}−Cu(II) complex **V** might be generated by the nucleophilic addition of carbanion **I** to C_{60}[12] and then underwent ligand exchange to give the C_{60}−Cu(II) complex **VI** accomplished by the loss of one molecule of HOAc,[10a,13] which further converted into the final product through reductive elimination. The exact reason for the formation of methanofullerene **3a** is not clear at the present stage in the presence of $CuSO_4$.

In summary, we have developed a new and efficient synthetic method for the highly selective construction of the scarce C_{60}-fused tetrahydroazepinones and -azepinonimines through the $Cu(OAc)_2$-mediated [5 + 2] oxidative cycloaddition of C_{60} with *N*-sulfonylated *o*-aminoaromatic methyl ketones or *O*-alkyl oximes. This methodology features a broad substrate scope, high chemoselectivity, readily available starting materials, and simple operation of the process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectral data, and NMR spectra of products **2a−g**, **3a** and **5a−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Nakamura, E.; Isobe, H. *Acc. Chem. Res.* **2003**, *36*, 807. (b) Hirsch, A.; Brettreich, M. *Fullerenes: Chemistry and Reactions*; Wliey-VCH: Weinheim, Germany, 2005. (c) *Fullerenes: Principles and Applications*; Langa, F., Nierengarten, J.-F., Eds.; RSC: Cambridge, 2007. (d) Guldi, D. M.; Illescas, B. M.; Atienza, C. M.; Wielopolski, M.; Martín, N. *Chem. Soc. Rev.* **2009**, *38*, 1587. (e) Giacalone, F.; Martín, N. *Adv. Mater.* **2010**, *22*, 4220. (f) Li, C.-Z.; Yip, H.-L.; Jen, A. K.-Y. *J. Mater. Chem.* **2012**, *22*, 4161.

(2) For selected reviews, see: (a) Hirsch, A. *Synthesis* **1995**, 895. (b) Thilgen, C.; Diederich, F. *Chem. Rev.* **2006**, *106*, 5049. (c) Matsuo, Y.; Nakamura, E. *Chem. Rev.* **2008**, *108*, 3016. (d) Murata, M.; Murata, Y.; Komatsu, K. *Chem. Commun.* **2008**, 6083. (e) Vougioukalakis, G. C.; Roubelakis, M. M.; Orfanopoulos, M. *Chem. Soc. Rev.* **2010**, *39*, 817. For recent representative examples: (f) Filippone, S.; Maroto, E. E.; Martín-Domenech, Á.; Suarez, M.; Martín, N. *Nat. Chem.* **2009**, *1*, 578. (g) Nambo, M.; Wakamiya, A.; Yamaguchi, S.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 15112. (h) Tzirakis, M. D.; Orfanopoulos, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5891. (i) Xiao, Z.; Matsuo, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 12234. (j) Zhang, G.; Liu, Y.; Liang, D.; Gan, L.; Li, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 5293. (k) Kurotobi, K.; Murata, Y. *Science* **2011**, *333*, 613. (l) Xin, N.; Huang, H.; Zhang, J.; Dai, Z.; Gan, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 6163. (m) Chang, W.-W.; Li, Z.-J.; Gao, X. *Org. Lett.* **2013**, *15*, 1642.

(3) For reviews, see: (a) Morton, J. R.; Negri, F.; Preston, K. F. *Acc. Chem. Res.* **1998**, *31*, 63. (b) Tzirakis, M. D.; Orfanopoulos, M. *Chem. Rev.* **2013**, *113*, 5262.

(4) For reviews, see: (a) Wang, G.-W.; Li, F.-B. *Curr. Org. Chem.* **2012**, *16*, 1109. (b) Li, F.-B.; Wang, G.-W. *Chin. Sci. Bull.* **2012**, *55*, 2009. For recent representative examples: (c) Lu, S.; Jin, T.; Bao, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2011**, *133*, 12842. (d) Lu, S.; Jin, T.; Kwon, E.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 802.

(5) Hatzimarinaki, M.; Orfanopoulos, M. *Org. Lett.* **2006**, *8*, 1775.

(6) Rajeshkumar, V.; Chan, F.-W.; Chuang, S.-C. *Adv. Synth. Catal.* **2012**, *354*, 2473.

(7) Lu, S.; Si, W.; Bao, M.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2013**, *15*, 4030.

(8) Wang, G.-W.; Li, F.-B. *Org. Biomol. Chem.* **2005**, *3*, 794.

(9) (a) Sun, Y.; Fan, R. *Chem. Commun.* **2010**, *46*, 6834. (b) Ilangovan, A.; Satish, G. *Org. Lett.* **2013**, *15*, 5726.

(10) (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (b) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679. (c) Wang, Y.-F.; Chen, H.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 11980. (d) Tang, D.; Wu, P.; Liu, X.; Chen, Y.-X.; Guo, S.-B.; Chen, W.-L.; Li, J.-G.; Chen, B.-H. *J. Org. Chem.* **2013**, *78*, 2746. (e) He, C.-L.; Liu, R.; Li, D.-D.; Zhu, S.-E.; Wang, G.-W. *Org. Lett.* **2013**, *15*, 1532. (f) Yang, H.-T.; Liang, X.-C.; Wang, Y.-H.; Yang, Y.; Sun, X.-Q.; Miao, C.-B. *Org. Lett.* **2013**, *15*, 4650. (g) Si, W.; Lu, S.; Bao, M.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**, *16*, 620. (h) Yang, H.-T.; Liang, X.-C.; Wang, Y.-H.; Yang, Y.; Sun, X.-Q.; Miao, C.-B. *J. Org. Chem.* **2013**, *78*, 11992.

(11) Hatzimarinaki, M.; Roubelakis, M. M.; Orfanopoulos, M. *J. Am. Chem. Soc.* **2005**, *127*, 14182.

(12) Zhang, T.-H.; Wang, G.-W.; Lu, P.; Li, Y.-J.; Peng, R.-F.; Liu, Y.-C.; Murata, Y.; Komatsu, K. *Org. Biomol. Chem.* **2004**, *2*, 1698.

(13) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802.