Synthesis of Isoindole Derivatives by Palladium-Catalyzed Domino Reaction of (2-Alkynyl)phenylketone *O*-Pentafluorobenzoyloximes

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Abstract: Isoindole derivatives were synthesized by the palladium-catalyzed cyclization of (2-alkynyl)phenylketone *O*-pentafluorobenzoyloximes in the presence of organometallic compounds such as sodium formate and aryl boronic acid.

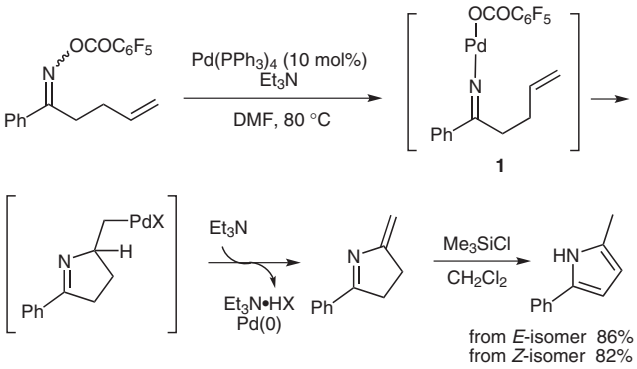
Key words: domino reaction, isoindoles, Mizoroki–Heck reaction, oximes, palladium

The palladium-catalyzed coupling reaction of aryl and vinyl halides or triflates with alkenes is known as the Mizoroki–Heck reaction[1] which is one of the most efficient carbon–carbon bond-formation reactions, given the advantages of its wide functional-group tolerance and its use of easily accessible alkenes.[2] Various carbocycles and heterocycles have been synthesized via the intramolecular Mizoroki–Heck reaction.[3]

Previously, we reported the oxidative addition of oxime derivatives to palladium(0) complexes to generate alkylideneaminopalladium(II) species.[4–6] This process was applied to the transformation of olefinic ketone *O*-pentafluorobenzoyloximes to various azaheterocycles via the intramolecular Mizoroki–Heck-type reaction (amino–Heck reaction).[4,5,7] This amino-Heck reaction is not affected by the geometry of oximes probably due to the linear-like structures of the alkylideneaminometal species such as **1**.[6,8] Both *E*- and *Z*-γ,δ-unsaturated ketoximes cyclize to give pyrroles in good yields (Scheme 1).[5a,b] The trial run of the Pd-catalyzed cyclization of the alkynyl ketone oxime and the successive capture by carbon monoxide has been examined while the yield of the cyclized product obtained was low.[9]

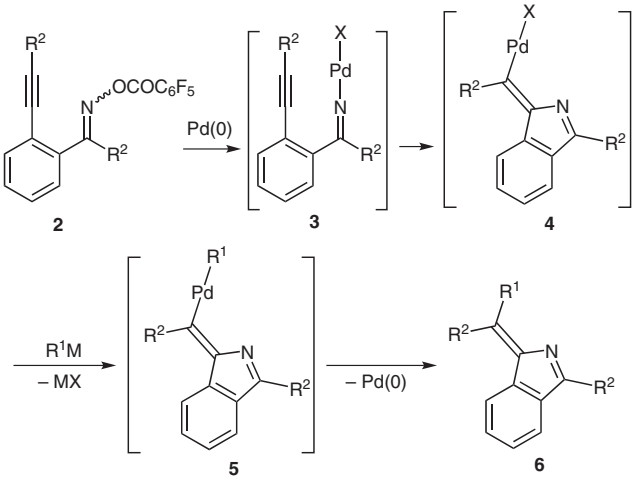
Isoindole derivatives have potential as functional materials such as organic light-emitting devices (OLED), solar cells,[10] and photodynamic therapy (PDT).[11] Therefore, the development of an efficient synthetic method to synthesize isoindole derivatives has recently drawn much attention.[12]

We envisaged that the amino-Heck-type cyclization of (2-alkynyl)phenylketone oximes could be applied to the synthesis of isoindole derivatives and thus examined. In this letter, we describe the outcome of this investigation.



Scheme 1 Amino-Heck reaction

In Scheme 2, the outline of our strategy towards isoindole derivatives based on the palladium(0)-catalyzed domino amino-Heck-type reaction is depicted, which is carried out using (2-alkynylphenyl)ketone *O*-pentafluorobenzoyloximes **2** in the presence of an organometallic compound (RM). The oxidative addition of *O*-pentafluorobenzoyloximes **2** to a Pd(0) complex would generate the alkylideneaminopalladium(II) species **3**, which cyclize smoothly to alkenyl palladium intermediate **4**, because phenylene tether in **3** hold on the reaction points, the alkylideneaminopalladium species, and the alkynyl group at nearby sites. Subsequently, transmetalation between **4** and RM and the successive reductive elimination would give isoindole derivatives **6**.



Scheme 2 Synthetic plan of isoindole derivatives via a domino amino-Heck type reaction

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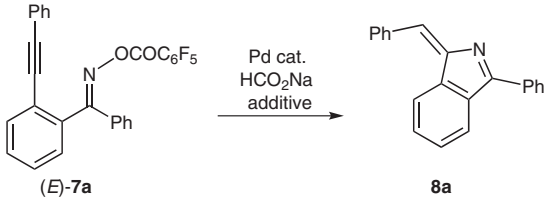
First we examined the reaction of 2-alkynylketone *O*-pentafluorobenzoyloxime (*E*)-**7a**[13] under various reaction conditions in the presence of sodium formate (Table 1). When the reaction was carried out by the treatment of 10 mol% $Pd(PPh_3)_4$ in acetonitrile at 70 °C, the oxime **7a** was consumed after three hours to give isoindole **8a** in 59% yield (entry 1). Addition of Et_3N or *N*,*N*-diisopropylethylamine increased the yield of the cyclization product **8a** to 66% and 71%, respectively (entries 2 and 3). In the presence of tetrabutylammonium bromide, the reaction became slower and the yield of **8a** decreased (entry 4). In the previous report on amino-Heck reaction, DMF was the best solvent in general[4,5] but was found to be unsuitable in this reaction (entry 5). Although we examined several combinations of $Pd(OAc)_2$ and phosphine ligands, the yield of isoindole **8a** did not increase (entries 6–8).

Table 1 Cyclization of 2-Alkynyl Ketone Oxime under Various Reaction Conditions[a]

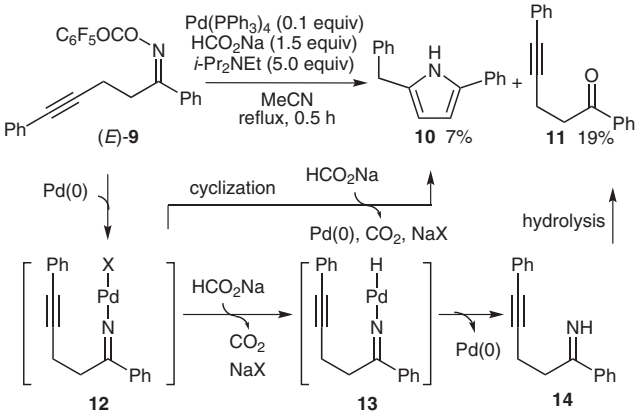


Entry	Pd cat (mol%)	Additive	Solvent	Conditions	Yield (%)[b]
1	$Pd(PPh_3)_4$ (10)	–	MeCN	70 °C 3.0 h	59
2	$Pd(PPh_3)_4$ (10)	Et_3N	MeCN	70 °C 3.0 h	66
3	$Pd(PPh_3)_4$ (10)	*i*-Pr_2NEt	MeCN	60 °C 1.5 h	71
4	$Pd(PPh_3)_4$ (10)	TBAB	MeCN	reflux 19 h	29
5	$Pd(PPh_3)_4$ (10)	Et_3N	DMF	60 °C 2.5 h	34
6	$Pd(OAc)_2$ (13) PPh_3 (72)	Et_3N	MeCN	60 °C 3.5 h	47
7	$Pd(OAc)_2$ (13) P(*o*-tol)$_3$ (53)	*i*-Pr_2NEt	MeCN	70 °C 8.5 h	40
8	$Pd(OAc)_2$ (16) DPPF (28)	*i*-Pr_2NEt	MeCN	70 °C 3.5 h	37

[a] Molar ratio: **7a**/HCO_2Na/additive = 1.0:1.5:5.0.
[b] Isolated yield.

o-Phenylene tether is important for the Pd(0)-catalyzed cyclization of β-alkynyl ketone oxime. When we treated ethylene-tethered alkynyl ketone oxime (*E*)-**9** with 10 mol% $Pd(PPh_3)_4$, 5 equivalents of *N*,*N*-diisopropylethylamine, and 1.5 equivalents of sodium formate in acetonitrile, the reaction was slow and the desired pyrrole **10** was obtained in 7% yield after stirring for 30 minutes at the reflux temperature (Scheme 3). In this reaction, ketone **11** was formed as a byproduct, which is supposed to be formed by the hydrolysis of the ketimine **14** formed by the transmetalation between alkylideneaminopalladium species **12** and sodium formate.

Then, to explore the scope of the domino cyclization of *O*-pentafluorobenzoyloximes of the (2-alkynyl)phenylcarbonyl compound, we subjected various oximes **7** to the optimized reaction conditions [10 mol% $Pd(PPh_3)_4$, *N*,*N*-diisopropylethylamine, sodium formate in MeCN], and Table 2 lists the results. Entries 1–7 show the results of the reaction of the oximes with the phenyl group R^2. In the reaction of **7b** (R^1 = 2-naphthyl) at 60 °C, it took 4.0 hours to consume the starting material **7b**, and the desired isoindole derivative **8b** was obtained in 84% yield (entry 1).



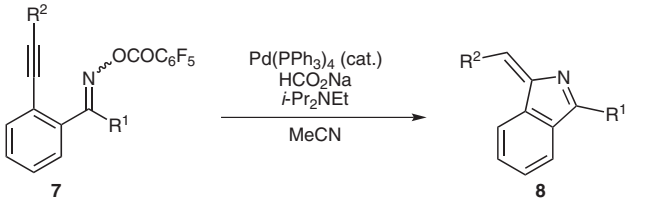
Scheme 3 Reaction of ethylene-tethered alkynyl ketone oxime **9**

The *trans*-styryl ketone oxime **7c** gave cyclized product in 53% yield (entry 2). The oximes (R^1 = Me and Bn) were also transformed to the corresponding isoindoles in good yields, which were unstable on silica gel relative to the isoindoles (R^1 = Ar or alkenyl; entries 3 and 4). In contrast, the isoindole derivative **8f** (R^1 = *t*-Bu) was stable and isolated in good yield (entry 5). As shown in entry 6, the α-keto ester oxime was not suitable for this cyclization. In the amino-Heck reaction, aldoxime could not be used generally because nitrile was formed under the cyclization conditions probably via the Beckmann fragmentation-type reaction.[5f]

In the cyclization reaction, aldoxime **7h** did not cyclize but gave nitrile **15** in 65% yield (entry 7; Figure 1). Next, we examined the effects of the substituent R^2 (entries 8–12). When R^2 was a *n*-alkyl group, the corresponding cyclized product **8i** was obtained in 21% yield (entry 8). The oximes with R^2 = *t*-Bu or TMS gave isoindole derivatives while the products **8j** and **8k** were unstable and low yields were obtained (entries 9 and 10). Reaction of the terminal alkynyloxime **7l** gave no cyclized product (entry 11). In the reaction of the terminal alkynyloxime **7l**, we did not obtain any cyclized product (entry 11).

Table 3 shows the results of the Pd(0)-catalyzed cyclization of (*E*)-**7a** in the presence of organoboronic acid. When phenylboronic acid was used, the reaction proceeded as expected to afford the isoindole derivative **16a** with

Table 2 Cyclization of Various (2-Alkynylphenyl)ketone *O*-Pentafluorobenzoyloximes **7**[a]



7 **8**

Entry	R^1	R^2	**7**	Conditions	**8**	Yield (%)[b]
1	2-naphthyl	Ph	**7b**[c]	60 °C, 4.0 h	**8b**	84
2	*trans*-styryl	Ph	**7c**[d]	reflux, 3.0 h	**8c**	53
3	Me	Ph	**7d**[c]	60 °C, 1.5 h	**8d**	77[e]
4	Bn	Ph	**7e**[f]	60 °C, 1.5 h	**8e**	60[e]
5	*t*-Bu	Ph	**7f**[c]	80 °C, 8.0 h	**8f**	57
6	CO_2Et	Ph	**7g**[c]	80 °C, 2.5 h	**8g**	c.m.[g]
7	H	Ph	**7h**[c]	60 °C, 1.0 h	**8h**	0[h]
8	Ph	pentyl	**7i**[c]	75 °C, 9.0 h	**8i**	21
9	Ph	*t*-Bu	**7j**[f]	80 °C, 5.0 h	**8j**	4
10	Ph	TMS	**7k**[d]	70 °C, 4.0 h	**8k**	8
11	Ph	H	**7l**[c]	60 °C, 8.0 h	**8l**	0

[a] Molar ratio: **7**/$Pd(PPh_3)_4$/HCO_2Na/*i*-Pr_2NEt = 1.0:0.1:1.5.5.0.
[b] Isolated yield.
[c] *E*-isomer.
[d] *E*/*Z* = 1:1
[e] ^1H NMR yield (1,1,2,2,-tetrachloroetane was used as an internal standard.).
[f] *E*/*Z* = ca. 2:1.
[g] Complex mixture.
[h] Nitrile **15** (Figure 1) was obtained in 65% yield.

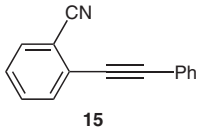


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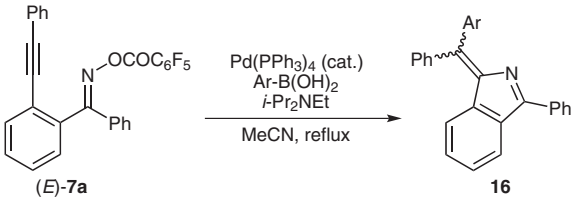
Figure 1

a diphenylmethylene group in 60% yield (entry 1). The reaction with *p*-tolyl boronic acid gave the isoindole derivative **16b** in 42% yield, which was a mixture of *E*- and *Z*-isomers (entry 2). When *p*-methoxyphenylboronic was used, isoindole derivative **16c** was obtained in high yield (entry 3). However, the use of electron-deficient-group-substituted boronic acid caused a decrease of the yield of the desired cyclized product (entry 4). By using *o*-tolyl boronic acid, isoindole derivative **16e** was formed in 18% (entry 5).

Similar isoindole derivative was synthesized by the amino-Heck reaction of *O*-pentafluorobenzoyloxime of (2-alkenyl)phenyl ketone **17** (Scheme 4). By treating $Pd(PPh_3)_4$ and *i*-Pr_2NEt in MeCN at 60 °C, the cyclization

Table 3 Pd-Catalyzed Cyclization of Oximes **7** in the Presence of Boronic Acids[a]

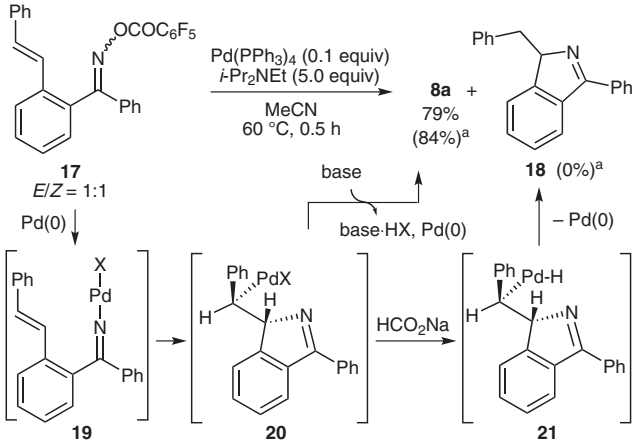


(*E*)-**7a** **16**

Entry	Ar	Time (h)	**16**	Yield (%)[b]
1	Ph	7.5	**16a**	60
2	4-Tol	8.5	**16b**[c]	42
3	4-$MeOC_6H_4$	6.0	**16c**[d]	78
4	4-$F_3CC_6H_4$	6.0	**16d**	33
5	2-Tol	7.0	**16e**[d]	18

[a] Molar ratio: **7a**/$Pd(PPh_3)_4$/Ar-$B(OH)_2$/*i*-Pr_2NEt = 1.0:0.1:1.5:5.0.
[b] Isolated yield.
[c] *E*/*Z* = 1:1
[d] *E*/*Z* mixture (3:2). Stereochemistry is undetermined.

proceeded rapidly to give the isoindole derivative **8a** in 79% yield. Although we expected to obtain isoindole **18** in the reaction with HCO_2Na, isoindole **8a** was obtained in 84% as the sole product under these reaction conditions.



Scheme 4 Amino-Heck reaction of (2-alkenylphenyl) ketone oxime **17**. [a] HCO_2Na (1.5 equiv) was added in the reaction.

In summary, we developed Pd-catalyzed synthesis of isoindole derivatives from (2-alkynyl)phenylketone *O*-pentafluorobenzoyl oximes in the presence of organometallic compounds In this reaction, *o*-phenylene tether in oxime is important for the efficient cyclization.

Typical Procedure for the Synthesis of Isoindole Derivatives 8 by Pd-Catalyzed Cyclization of (2-Alkynyl)phenylketone *O*-Pentafluorobenzoyloximes 7 (Table 2, Entry 1)

To a mixture of *O*-pentafluorobenzoyl oxime **7b** (183 mg, 0.338 mmol), *N*,*N*-diisopropylethylamine (0.30 mL, 1.8 mmol), and sodi-

um formate (38.3 mg, 0.56 mmol) in dry MeCN (6.7 mL), $Pd(PPh_3)_4$ (41.5 mg, 0.036 mmol) was added under an argon atmosphere at r.t. This mixture was stirred at 60 °C for 4 h. The mixture was diluted with EtOAc, and filtered through a Celite pad. The filtrate was evaporated under vacuum. The residue was purified by column chromatography (SiO_2, hexane–EtOAc = 9:1) to afford **8b** (94.7 mg, 84%) as a yellow solid.

Spectral Data for Isoindole Derivative 8b

IR (KBr): 2723, 2667, 2360, 2325, 1639, 1197, 1143, 1066, 917, 757, 740, 725, 713, 680, 493, 466 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (1 H, s), 7.38 (1 H, t, *J* = 7.3 Hz), 7.46–7.52 (4 H, m), 7.55–7.59 (2 H, m), 7.93 (2 H, t, *J* = 6.4 Hz), 8.02 (2 H, d, *J* = 8.8 Hz), 8.07 (1 H, d, *J* = 6.8 Hz), 8.38 (1 H, dd, *J* = 8.6, 1.5 Hz), 8.44 (2 H, d, *J* = 7.6 Hz), 8.69 (1 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.0, 122.5, 126.1, 126.4, 126.5, 127.3, 127.6, 127.9, 128.3, 128.5, 128.7, 129.0, 129.4, 132.4, 132.5, 133.2, 134.5, 135.9, 136.4, 143.4, 149.7, 169.3. Anal. Calcd (%) for $C_{25}H_{17}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.72; H, 5.33; N, 4.25.

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References and Notes

(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(2) For reviews, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, **1985**. (c) Heck, R. F. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M.; Flemming, I., Eds.; Pergamon: New York, **1991**, Chap. 4.3. (d) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley: Chichester, **1995**. (e) Bräse, S.; de Meijere, A. In *Metal Catalyzed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, **1998**, Chap. 3. (f) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (g) Casey, M.; Lawless, J.; Shirran, C. *Polyhedron* **2000**, *19*, 517. (h) Beletskaya, I. P.; Cheprakov, A. *Chem. Rev.* **2000**, *100*, 3009. (i) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (j) *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, **2009**.

(3) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, 2nd ed., Vol. 26; Li, J. J.; Gribble, G. W., Eds.; Elsevier: Amsterdam, **2006**.

(4) For reviews, see: (a) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. (b) Kitamura, M.; Narasaka, K. *Chem. Rec.* **2002**, *2*, 268.

(5) For the synthesis of pyrroles, see: (a) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45. (b) Tsutsui, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451. For the synthesis of pyridines, see: (c) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **2001**, 526. (d) Kitamura, M.; Kudo, D.; Narasaka, K. *ARKIVOC* **2006**, *(iii)*, 148. For the synthesis of spiro imines, see: (e) Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, 974. (f) Zaman, S.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055. For the synthesis of aza-azulenes, see: (g) Kitamura, M.; Chiba, S.; Saku, O.; Narasaka, K. *Chem. Lett.* **2002**, 606. (h) Chiba, S.; Kitamura, M.; Saku, O.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785. For the synthesis of imidazoles, see: (i) Zaman, S.; Kitamura, M.; Abell, A. D. *Org. Lett.* **2005**, *7*, 609.

(6) Reports on the oxidative addition of metal complex to oxime by other groups, see: (a) Ferreira, C. M. P.; Guedes da Silva, M. F. C.; Kukushkin, V. Y.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *J. Chem. Soc., Dalton Trans.* **1998**, 325. (b) Tillack, A.; Arndt, P.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Z. Anorg. Allg. Chem.* **1998**, *624*, 737.

(7) Similar cyclization of oximes, see: (a) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 2777. (b) Fürstner, A.; Radkowski, K.; Peters, H.; Seidel, G.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chem. Eur. J.* **2007**, *13*, 1929. (c) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(8) (a) Erker, G.; Frömberg, W.; Krüger, C.; Raabe, E. *J. Am. Chem. Soc.* **1988**, *110*, 2400. (b) Huang, J.-S.; Leung, S. K.-Y.; Cheung, K.-K.; Che, C.-M. *Chem. Eur. J.* **2000**, *6*, 2971.

(9) Zaman, S.; Kitamura, M.; Abell, A. D. *Aust. J. Chem.* **2007**, *60*, 624.

(10) (a) Varotto, A.; Nam, C.-Y.; Radivojevic, I.; Tome, J. P. C.; Cavaleiro, J. A. S.; Black, C. T.; Drain, C. M. *J. Am. Chem. Soc.* **2010**, *132*, 2552. (b) Mori, S.; Nagata, M.; Nakahata, Y.; Yasuta, K.; Goto, R.; Kimura, M.; Taya, M. *J. Am. Chem. Soc.* **2010**, *132*, 4054.

(11) Jiang, X.-J.; Lo, P.-C.; Tsang, Y.-M.; Yeung, S.-L.; Fong, W.-P.; Ng, D. K. P. *Chem. Eur. J.* **2010**, *16*, 4777.

(12) (a) Emmett, J. C.; Veber, D. F.; Lwowski, W. *Chem. Commun.* **1965**, 272. (b) Fryer, R. I.; Earley, J. V.; Sternbach, L. H. *J. Am. Chem. Soc.* **1966**, *88*, 3173. (c) Stobaugh, J. F.; Repta, A. J.; Sternson, L. A. *J. Org. Chem.* **1984**, *49*, 4306. (d) Ito, S.; Murashima, T.; Uno, H.; Ono, N. *Chem. Commun.* **1998**, 1661. (e) Ding, Y.; Hay, A. S. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 3293. (f) Chen, Z.; Muller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273. (g) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. (h) Hou, D.-R.; Wang, M.-S.; Chung, M.-W.; Hsieh, Y.-D.; Tsai, H.-H. G. *J. Org. Chem.* **2007**, *72*, 9231. (i) Dieltiens, N.; Stevens, C. V. *Org. Lett.* **2007**, *9*, 465. (j) Grise, C.; Murry, J. A.; Reamer, R. A.; Hughes, D. L.; Savarin, C. G. *Org. Lett.* **2007**, *9*, 981. (k) Hui, B. W.-Q.; Chiba, S. *Org. Lett.* **2009**, *11*, 729. (l) Heugebaert, T. S. A.; Stevens, C. V. *Org. Lett.* **2009**, *11*, 5018. (m) Serrano, O.; Sole, D. *J. Org. Chem.* **2010**, *75*, 6267. (n) Tomimori, Y.; Nakamura, J.; Yamada, H.; Uno, H.; Ono, N.; Okujima, T. *Tetrahedron* **2010**, *66*, 6895.

(13) Oxime **7a** was synthesized from 2-hydroxybenzophenone in 4 steps: i) $(CF_3SO_2)_2O$, *N*,*N*-dimethyl-4-aminopyridine (cat.), pyridine, CH_2Cl_2, –78 °C to 0 °C, 1.5 h (99% yield); ii) PhC≡CH, $Pd(PPh_3)_4$ (cat.), CuI (cat.), Et_3N, *n*-Bu_4NBr, DMF, 70 °C, 2.5 h (97% yield);[14] iii) NH_2OH·HCl, pyridine, 100 °C, 2.5 h (86% yield); iv) C_6F_5COCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h (92% yield). Other (2-alkynyl)phenylketone *O*-pentafluorobenzoyloximes were synthesized in a similar way of the synthesis of **7a**.

(14) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.