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REGIOSELECTIVITY OF THE INTRAMOLECULAR BIARYL COUPLING REACTION OF 3-SUBSTITUTED PHENYL 2-IODOBENZOATE USING A PALLADIUM REAGENT

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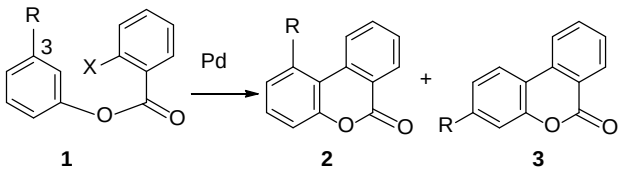
Abstract – This study investigated the regioselectivity of the intramolecular coupling reaction of the phenyl benzoate derivative which possesses a methyl or methoxy group at the *meta*-position of the phenoxy moiety. The type of base and the presence/absence of the phosphine ligand influenced the product ratio. A transition state model and the regioselectivity of the reaction are discussed.

The 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton is an important heterocyclic system because many natural products and biologically active compounds involve this ring system.[1] Among the various preparations for this ring system,[2] the palladium-mediated aryl-aryl coupling reaction is one of the most convenient techniques for the carbon-carbon bond formation between two aromatic rings.[3] We recently reported that the intramolecular aryl-aryl coupling reaction of phenyl benzoate derivatives using the palladium reagent is widely useful for the syntheses of several biaryl-type natural products.[4] In some cases, the regioselectivity has been a significant issue for the natural product synthesis, however, there are a few examples of the systematic study of the regioselectivity of the intramolecular aryl-aryl coupling reaction.[5] As shown in Scheme 1, when the substrate possesses a substituent at the *m*-position as **1**, there are two reactive positions on the phenoxy part to generate two regioisomers **2** and **3**.

In this report, we investigated in detail the reactivity and regioselectivity of the palladium-mediated

coupling reaction of *m*-substituted phenyl benzoate derivatives.



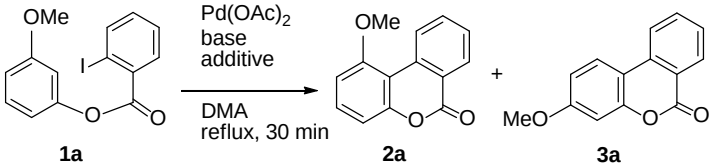
Scheme 1. Pd-mediated intramolecular coupling reaction of 3-substituted phenyl benzoate

We first examined the substrate **1a** which possesses a methoxy group at the *m*-position in the phenoxy part. The results are summarized in Table 1. In each case, all the reactions were completed in 30 min using $Pd(OAc)_2$ (10 mol %), base (100 mol %), ligand (20 mol %), and DMA (*N*,*N*-dimethylacetamide) as the solvent. We employed several bases for the reaction in the presence/absence of $^{n}Bu_3P$ as the ligand. When using K_2CO_3 as the base without the phosphine ligand, the reaction proceeded with a slight regioselectivity (**2a**:**3a** = 1:2.0) (entry 1). Employing $^{n}Bu_3P$ under the same reaction conditions, the regioselectivity changed to 1:1.4 (entry 2), which was almost the same ratio compared to the result for entry 1. A similar outcome was also observed for entries 3-6, namely, the regioselectivity was in the range of 1:1.2 to 2.0 for each case whether the phosphine ligand was present or absent. When DABCO (diazabicyclo[2.2.2]octane) was used as the base, the chemical yield decreased to around 40% with the ratios of 1:3.5 and 1:2.0 (entries 7 and 8).

In entries 9 and 10, we evaluated Ag_2CO_3 as the base to investigate the effect of a metal ion. The major product was compound **3a** with the regioselectivity of 1:4.5 when using no phosphine ligand (entry 9). In sharp contrast to this result, employing $^{n}Bu_3P$ lead to a dramatic change in the regioselectivity (**2a**:**3a** = 1:0.5) (entry 10). The same tendency was found for entries 11-14, when using Ag_2O or AgOAc as the base. CuOAc was also examined as the base to investigate the difference in the type of the metal. Entries 15 and 16 showed results similar to that of silver.

Next, in order to investigate the coordination effect of the methoxy group, we employed a methyl-substituted compound **1b**. In Table 2, very different results from the methoxy derivative **1a** were observed, that is, the coupling reaction proceeded with a poor regioselectivity. It was also found that using the phosphine ligand did not affect the product ratio (entries 1 and 2). In spite of changing the base from K_2CO_3 to Ag_2CO_3, a low regioselectivity was observed (entries 3 and 4). These results indicated that the methoxy group in **1a** has a significant effect on the regioselectivity.

Table 1. Reaction of 3-methoxyphenyl 2-iodobenzoate (**1a**)

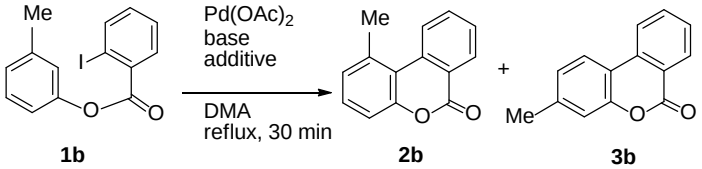


1a **2a** **3a**

run	base	additive	yield (%)	ratio[a] **2a** : **3a**	run	base	additive	yield (%)	ratio[a] **2a** : **3a**
1	K_2CO_3	-	93	1 : 2.0	9	Ag_2CO_3	-	92	1 : 4.5
2	K_2CO_3	$^nBu_3P$	73	1 : 1.4	10	Ag_2CO_3	$^nBu_3P$	81	1 : 0.5
3	Na_2CO_3	-	92	1 : 2.0	11	Ag_2O	-	70	1 : 4.5
4	Na_2CO_3	$^nBu_3P$	76	1 : 1.2	12	Ag_2O	$^nBu_3P$	94	1 : 0.5
5	KOAc	-	74	1 : 1.8	13	AgOAc	-	61	1 : 4.3
6	KOAc	$^nBu_3P$	72	1 : 1.5	14	AgOAc	$^nBu_3P$	63	1 : 0.6
7	DABCO	-	46	1 : 3.5	15	CuOAc	-	53	1 : 4.5
8	DABCO	$^nBu_3P$	36	1 : 2.0	16	CuOAc	$^nBu_3P$	60	1 : 0.6

a) Determined by ^{1}H-NMR analysis

Table 2. Reaction of 3-methylphenyl 2-iodobenzoate (**1b**)



1b **2b** **3b**

run	base	additive	yield (%)	ratio[a] **2b** : **3b**
1	K_2CO_3	-	93	1 : 0.9
2	K_2CO_3	$^nBu_3P$	68	1 : 0.9
3	Ag_2CO_3	-	86	1 : 1.4
4	Ag_2CO_3	$^nBu_3P$	94	1 : 1.0

a) Determined by ^{1}H-NMR analysis

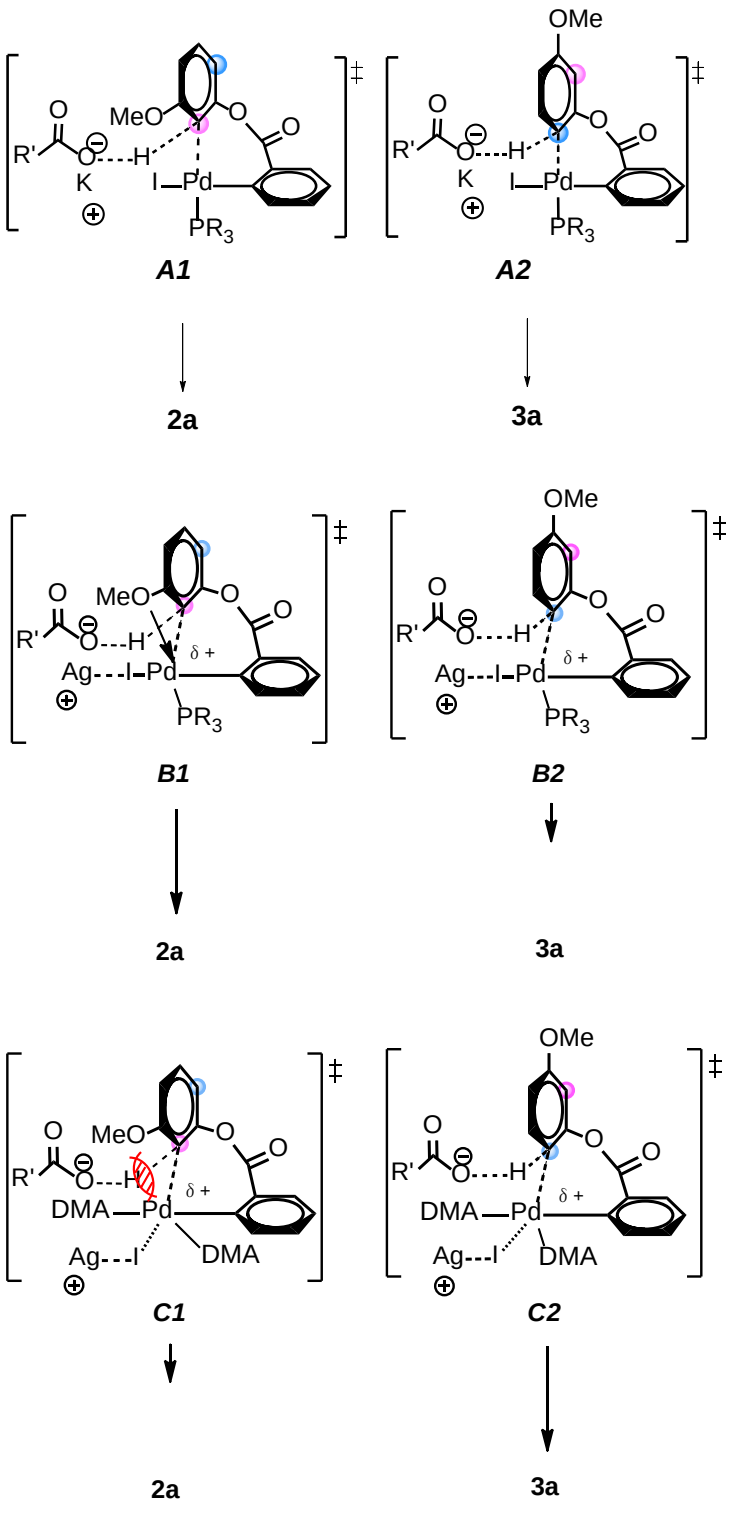
Based on the above results, we would be able to provide a reasonable explanation for the regioselectivity of the intramolecular coupling reaction by considering transition state models. In 2007, Echavarren *et al.* proposed the intermolecular-assisted mechanism for the Pd-mediated aryl-aryl coupling reaction.[6] Based on their model, we illustrate the transition stage in our substrates (Fig.1). Model *A* describes the reaction under the condition of using K_2CO_3, Na_2CO_3, or AcOK as the base. In this case, there is no predominant difference between *A1* and *A2* to control the reaction path, leading to an almost equal ratio of products **2** and **3**. On the other hand, when using the silver salt, the soft character of the metal would be crucial by

contributing an attractive interaction with the iodine atom. This strong attractive property between iodine and silver causes a partially positive charge on the palladium atom, which makes coordination of the methoxy group easier. Thus, the *B1* transition state, which exhibits a tight interaction of O-Pd, must be more preferable than *B2*. This coordination effect is also supported by the result of entry 4 in Table 2, where the product ratio of **2b** and **3b** is 1:1.

Contrary to the above model, it is necessary to consider a different transition state when using no phosphine ligand. As depicted in *C1* and *C2*, DMA molecules, which are employed as the solvent, would possibly coordinate around the palladium atom. Since the DMA molecules would be much bulkier than the phosphine ligand, the coordination between the methoxy group and the palladium atom cannot be developed. Besides, a severe electrostatic repulsion of the methoxy group and the Pd-solvent complex leads to produce compound **3a** as the major isomer.

In summary, we systematically investigated the regioselectivity of the intramolecular coupling reaction of 3-substituted phenyl 2-iodobenzoates using a Pd catalyst. Based on the product ratio, plausible transition state models were proposed. Further application of this work is now ongoing in our laboratory.

Figure 1. Transition state illustration



EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro-melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The NMR spectra were obtained using a Varian MERCURY-300

instrument with the chemical shifts being reported as δ ppm and the couplings expressed in Hertz. The elemental analysis was performed using a Yanaco MT-5 analyzer. Silica gel column chromatography was carried out using Daisogel 1002W or Merck 9385 Kieselgel 60. All reactions were carried out under an argon atmosphere.

3-Methoxy-6*H*-dibenzo[*b,d*]pyran-6-one (**3a**),[7] **1-methyl-6*H*-dibenzo[*b,d*]pyran-6-one** (**2b**),[8] and **3-methyl-6*H*-dibenzo[*b,d*]pyran-6-one** (**3b**)[9] are known compounds.

3-Methoxyphenyl 2-iodobenzoate (**1a**)

A mixture of $SOCl_2$ (8 mL), 2-iodobenzoic acid (4.96 g, 20.0 mmol), and 2 drops of DMF was heated under reflux. After 1 h, the excess $SOCl_2$ was removed under reduced pressure to give a brown residue which was diluted with CH_2Cl_2. To the solution of the obtained acid chloride, a mixture of 3-methoxyphenol (2.48 g, 2.16 mL, 20 mmol), Et_3N (3.34 mL, 24.0 mmol), and CH_2Cl_2 (10 mL) was added, and then the mixture was stirred for 3 h at rt. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was subjected to silica gel column chromatography using AcOEt : hexane = 1:6. Colorless **1a** (6.32 g, 89%) was obtained in a pure form.

Colorless needles, mp 54.1−55.0 °C (Et_2O-hexane). IR (KBr) cm^{-1} : 1750, 1240. ^{1}H-NMR（300 MHz, $CDCl_3$) δ: 3.83 (s, 3H, OCH3), 6.81−6.89 (m, 3H), 7.23 (m, 1H), 7.34 (ddd, 1H, J_1=7.8 Hz, J_2=7.8 Hz, J_3=0.9 Hz), 7.48 (ddd, 1H, J_1=7.8 Hz, J_2=7.8 Hz, J_3=1.6 Hz), 8.04 (dd, 1H, J_1=7.8 Hz, J_2=1.2 Hz), 8.07 (dd, 1H, J_1= 7.8 Hz, J_2=0.9 Hz). ^{13}C-NMR（75 MHz, $CDCl_3$）δ: 55.7, 94.8, 107.8, 112.2, 114.0, 128.3, 130.1, 131.7, 133.4, 134.3, 141.8, 151.8, 160.7, 165.0. *Anal.* Calcd for $C_{14}H_{11}IO_3$,C, 47.48; H, 3.13; Found: C, 47.67; H, 3.02.

3-Methylphenyl 2-iodobenzoate (**1b**)

A mixture of $SOCl_2$ (4 mL), 2-iodobenzoic acid (2.48 g, 10.0 mmol), and 2 drops of DMF was heated under reflux. After 1 h, the excess $SOCl_2$ was removed under reduced pressure to give a brown residue which was diluted with CH_2Cl_2. To the solution of the obtained acid chloride, a mixture of 3-methylphenol (1.08 g, 1.05 mL, 10 mmol), Et_3N (1.66 mL, 12.0 mmol), and CH_2Cl_2 (5 mL) was added, and then the mixture was stirred for 3 h at rt. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was subjected to silica gel column chromatography using AcOEt : hexane = 1:6. Colorless **1b** (2.77 g, 82%) was obtained in a pure form.

Colorless needles, mp 41.4–42.6 °C (Et_2O-hexane). IR (KBr) cm^{-1} : 1740, 1230. ^{1}H-NMR（300 MHz,

$CDCl_3$) δ: 2.40 (s, 3H), 7.05–7.11 (m, 3H), 7.20–7.35 (m, 2H), 7.48 (ddd, 1H, J_1=7.5 Hz, J_2=7.5 Hz, J_3=1.2 Hz), 8.03 (dd, 1H, J_1=7.8 Hz, J_2=1.8 Hz), 8.07 (dd, 1H, J_1=8.1 Hz, J_2=1.2 Hz). ^{13}C-NMR（75 MHz, $CDCl_3$）δ: 21.5, 94.8, 118.7, 122.3, 127.1, 128.2, 129.4, 131.7, 133.3, 134.4, 139.9, 141.8, 150.79, 165.2. MS (FAB, positive ion mode) : 339 ($M+1^+$). *Anal.* Calcd for $C_{14}H_{11}IO_2$, C, 49.73; H, 3.28; Found: C, 49.76; H, 3.10.

General Procedure of Coupling Reaction of 1a

To a solution of **1a** (88.5 mg, 0.25 mmol) in DMA (3 mL), $Pd(OAc)_2$, base, and additive were successively added. The mixture was heated for 30 min under reflux, and then diluted with ethyl acetate. After filtration, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue which was subjected to silica gel column chromatography using AcOEt : hexane = 1:4 and CH_2Cl_2 : hexane = 1:1 as the eluent. Colorless crystals of **2a** and **3a** were separately obtained in a pure form.

1-Methoxy-6*H*-dibenzo[*b,d*]pyran-6-one (**2a**)

Colorless needles, mp 164.2–166.1 ℃ (AcOEt-hexane). IR (KBr) cm^{-1}: 1740, 1260. ^{1}H-NMR（300 MHz, $CDCl_3$) δ: 4.00 (s, 3H), 6.80 (m, 1H), 6.95 (m, 1H), 7.33 (m, 1H), 7.49 (m, 1H), 7.73 (m, 1H), 8.37 (m, 1H), 8.91 (m, 1H). ^{13}C-NMR（75 MHz, $CDCl_3$) δ: 56.0, 106.9, 108.2, 110.4, 120.9, 127.6, 128.03, 129.9, 130.1, 134.6, 134.7, 152.6, 158.4, 161.5. *Anal.* Calcd for $C_{14}H_{10}O_3$, C, 74.33; H, 4.46; Found: C, 74.18; H, 4.42.

General Procedure of Coupling Reaction of 1b

To a solution of **1b** (84.5 mg, 0.25 mmol) in DMA (3 mL), $Pd(OAc)_2$, base, and additive were successively added. The mixture was heated for 30 min under reflux, and then diluted with ethyl acetate. After filtration, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue which was subjected to silica gel column chromatography using AcOEt : hexane = 1:4 as the eluent. Inseparable mixture of **2b** and **3b** was obtained. All efforts to separate these compounds were unsuccessful. The product ratio was determined by ^{1}H-NMR analysis based on the integration of 1-methyl and 3-methyl groups of **2b** and **3b**, respectively. **2b**: δ 2.89 (s, 3H). **3b**: δ 2.50 (s, 3H). These chemical shifts were referred to the already reported compounds.[2d, 2e, 4b, 4d]

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REFERENCES AND NOTES

1. (a) H.-W. Zhang, W.-Y. Huang, Y.-C. Song, J.-R. Chen, and R.-X. Tan, *Helv. Chim. Acta*, 2005, **88**, 2861; (b) T. Tanahashi, M. Kuroishi, A. Kuwahara, N. Nagakura, and N. Hamada, *Chem. Pharm. Bull.*, 1997, **45**, 1183; (c) N. Hamada, T. Tanahashi, S. Goldsmith, and T. H. Nash III, *Symbiosis*, 1997, **23**, 219; (d) T. Tanahashi, Y. Takenaka, N. Nagakura, and N. Hamada, *Phytochemistry*, 2003, **62**, 71; (e) E. Hormazabal, G. Schmeda-Hirschmann, L. Astudillo, J. Rodriguez, and C. Theoduloz, *Z. Naturforsch*, 2005, **60c**, 11; (f) Y.-C. Song, W.-Y. Huang, C. Sun, F.-W. Wang, and R.-X. Tan, *Biol. Pharm. Bull.*, 2005, **28**, 506; (g) T. Matsumoto, T. Hosoya, and H. Shigemori, *Heterocycles*, 2010, **81**, 1231.
2. (a) For a pioneering work on the synthesis of 6*H*-dibenzo[*b,d*]pyran-6-one, see: B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, and P. D. Josephy, *J. Org. Chem.*, 1991, **56**, 3763; (b) R. Singha, S. Roy, S. Nandi, P. Ray, and J. K. Ray, *Tetrahedron Lett.*, 2013, **54**, 657; (c) C.-L. Sun, J. Liu, Y. Wang, X. Zhou, B.-J. Li, and Z.-J. Shi, *Synlett*, 2011, 883; (d) J. Cudaj and J. Podlech, *Tetrahedron Lett.*, 2010, **51**, 3092; (e) M. Altemöller, T. Gehring, J. Cudaj, J. Podlech, H. Goesmann, C. Feldmann, and A. Rothenberger, *Eur. J. Org. Chem.* 2009, 2130; (f) C. A. James and V. Snieckus, *Tetrahedron Lett.*, 1997, **38**, 8149; (g) J. Luo, Y. Lu, S. Liu, J. Liu, and G.-J. Deng, *Adv. Synth. Catal.*, 2011, **353**, 2604; (h) I. R. Pottie, P. R. Nandaluru, W. L. Benoit, D. O. Miller, L. N. Dawe, and G. J. Bodwell, *J. Org. Chem.*, 2011, **76**, 9015; (i) K. Koch, J. Podlech, E. Pfeiffer, and M. Metzler, *J. Org. Chem.*, 2005, **70**, 3275; (j) G. A. Molander, K. M. George, and L. G. Monovich, *J. Org. Chem.*, 2003, **68**, 9533.
3. For reviews, see, (a) J. Yamaguchi, A. D. Yamaguchi, and K. Itami, *Angew. Chem. Int. Ed.*, 2012, **51**, 8960; (b) D. Alberico, M. E. Scott, and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (d) G. Bringmann, T. Gulder, T. A. M. Gulder, and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (e) G. Bringmann, M. Breuning, and S. Tasler, *Synthesis*, 1999, 525; (f) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, and M. Breuning, *Angew. Chem. Int. Ed.*, 2005, **44**, 5384; (g) H. Abe and T. Harayama, *Heterocycles*, 2008, **75**, 1305.
4. (a) H. Abe, T. Kawai, Y. Komatsu, M. Kamimura, Y. Takeuchi, and Y. Horino, *Heterocycles*, 2012, **86**, 785; (b) H. Abe, T. Fukumoto, Y. Horino, T. Harayama, and Y. Takeuchi, *Heterocycles*, 2010, **82**, 851; (c) H. Abe, N. Kobayashi, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2010, **80**, 873; (d) H. Abe, T. Fukumoto, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2007, **74**, 265; (e) H. Abe, T. Fukumoto, K. Nishioka, M. Arai, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2006, **69**, 217; (f) H.

Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2005, **46**, 3197; (g) S. Takeda, H. Abe, Y. Takeuchi, and T. Harayama, *Tetrahedron*, 2007, **63**, 396; (h) H. Abe, S. Takeda, T. Fujita, K. Nishioka, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2004, **45**, 2327.

5. (a) R. Bernini, S. Cacchi, G. Fabrizi, and A. Sferrazza, *Synthesis*, 2008, 729; (b) T. Harayama, Y. Kawata, C. Nagura, T. Sato, T. Miyagoe, H. Abe, and Y. Takeuchi, *Tetrahedron Lett.*, 2005, **46**, 6091; (c) T. Harayama, C. Nagura, T. Miyagoe, Y. Kawata, H. Abe, and Y. Takeuchi, *Heterocycles*, 2010, **81**, 2609; (d) H. Nishioka, C. Nagura, H. Abe, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2006, **70**, 549; (e) T. Harayama, M. Asai, T. Miyagoe, H. Abe, Y. Takeuchi, A. Yamaguchi, and S. Fujii, *Heterocycles*, 2010, **81**, 1881.
6. (a) D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880; (b) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras, and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; see also, (c) M. Lafrance, D. Lapointe, and K. Fagnou, *Tetrahedron*, 2008, **64**, 6015; (d) L.-C. Campeau, M. Parisien, M. Leblanc, and K. Fagnou, *J. Am. Chem. Soc.*, 2004, **126**, 9186; (e) S. I. Gorelsky, *Coord. Chem. Rev.*, 2013, **257**, 153; (f) S. Pascual, P. deMendoza, A. A. C. Braga, F. Maseras, and A. M. Echavarren, *Tetrahedron*, 2008, **64**, 6021.
7. D. J. Hart, A. Kim, R. Krishnamurthy, G. H. Merriman, and A.-M. Waltos, *Tetrahedron*, 1992, **48**, 8179.
8. C. Grundmann and E. Litten, *Chem. Ber.*, 1952, **85**, 261.
9. U. Kraatz and F. Korte, *Chem. Ber.*, 1973, **106**, 62.