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Orthogonal Synthesis of Isoindole and Isoquinoline Derivatives from Organic Azides

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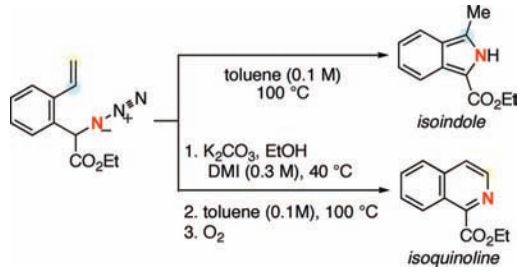
ABSTRACT



α-Azido carbonyl compounds bearing a 2-alkenylaryl moiety at the α-position are found to be promising precursors for synthesis of isoindole and isoquinoline derivatives via 1,3-dipolar cycloaddition of azides onto alkenes and 6π-electrocyclization of *N*-H imine intermediates, respectively.

Among numerous diverse approaches toward the synthesis of azaheterocycles, both 1,3-dipolar cycloaddition of azides onto alkenes[1] and 6π-electrocyclization of azatrienes[2,3] have proven to be versatile methods for providing ready access to azaheterocycles. Herein, we report an orthogonal methodology for the synthesis of isoindole and isoquinoline derivatives from α-azido carbonyl compounds possessing a 2-alkenylaryl moiety at the α-position, in which either azide−alkene cycloaddition for isoindoles or 6π-electrocyclization for isoquinolines can be induced selectively by slight modification of the reaction conditions.

Isoindoles and their derivatives are attractive candidates for organic light-emitting devices (OLEDs) due to their high fluorescent and electroluminescent properties,[4] and they are regarded as highly reactive substrates in [4+2]-cycloadditions with various dienophiles for preparation of oligoacenes.[5] We envisaged that the intramolecular azide−alkene cycloaddition reaction of **1** and subsequent elimination of dinitrogen from

(1) (a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (b) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed; Wiley-Interscience: New York, 1984; Vol. 2, p 316. (c) Feldman, K. S.; Iyer, M. R.; López, C. S.; Faza, O. N. *J. Org. Chem.* **2008**, *73*, 5090. (d) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777. (e) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886. (f) Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534. (g) Feldman, K. S.; Iyer, M. R.; Hester, D. K., II. *Org. Lett.* **2006**, *8*, 3116. (h) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 4590. (i) Hassner, A.; Amarasekara, A. S.; Andisik, D. *J. Org. Chem.* **1988**, *53*, 27. (j) Liu, J.-M.; Young, J.-J.; Li, Y.-J.; Sha, C.-K. *J. Org. Chem.* **1986**, *51*, 1120. (k) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725. (l) Smith, P. A. S.; Chou, S. P. *J. Org. Chem.* **1981**, *46*, 3970, and references therein.

(2) For reviews of 6π-electrocyclization, see: (a) Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, p 699. (b) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

(3) For recent examples of 6π-electrocyclization of azatriene, see: (a) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (b) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (d) Meketa, M. L.; Weinreb, S. M.; Nakao, Y.; Fusetani, N. *J. Org. Chem.* **2007**, *72*, 4892. (e) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099, and references therein.

(4) (a) Mi, B.-X.; Wang, P.-F.; Liu, M.-W.; Kwong, H.-L.; Wong, N.-B.; Lee, C.-S.; Lee, S.-T. *Chem. Mater.* **2003**, *15*, 3148. (b) Ding, Y.; Hay, A. S. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 3293. (c) Gauvin, S.; Santerre, F.; Dodelet, J. P.; Ding, Y.; Hlil, A. R.; Hay, A. S.; Anderson, J.; Armstrong, N. R.; Gorjanc, T. C.; D'Iorio, M. *Thin Sold Films* **1999**, *353*, 218. (d) Matuszewski, B. K.; Givens, R. S.; Srinivasachar, K.; Carlson, R. G.; Higuchi, T. *Anal. Chem.* **1987**, *59*, 1102. (e) Zweig, A.; Metzler, G.; Maurer, A.; Roberts, B. G. *J. Am. Chem. Soc.* **1967**, *89*, 4091.

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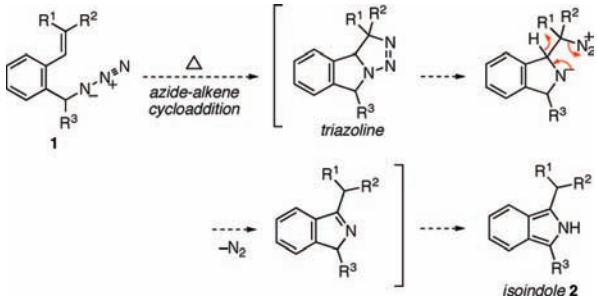
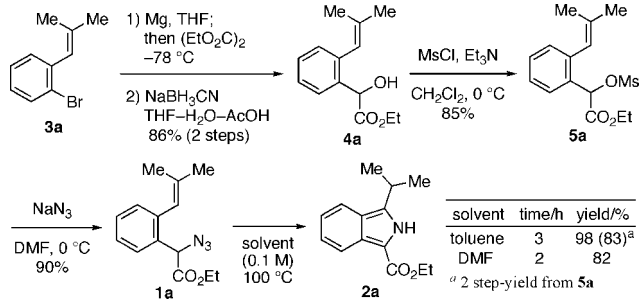
the resulting triazolines[6,7] would produce isoindoles as shown in Scheme 1.[8,9]

Scheme 1. Synthetic Plan of Isoindoles



First, azide **1a** was prepared from aryl bromide **3a** as shown in Scheme 2. Treatment of Grignard reagent prepared from **3a** with diethyl oxalate followed by reduction of the resulting α-keto ester with $NaBH_3CN$ afforded α-hydroxy ester **4a**. Mesylation of **4a** gave **5a**, which was treated with NaN_3 in DMF at 0 °C to lead to azide **1a**. Next, isoindole formation via the intramolecular azide−alkene cycloaddition was investigated. As expected, the reaction proceeded smoothly by heating of azides **1a** in toluene or DMF (0.1 M concentration) at 100 °C to give isoindole **2a**[10] in good yield (Scheme 2).[11]

Scheme 2. Synthesis of Isoindole **1a**



A variety of substituted isoindoles **2** were synthesized as shown in Table 1.[12] At the C3-position of isoindoles were installed methyl and benzyl groups as well as some cycloalkyl moieties (entries 1−6). The reaction of azide **1h** having a 4-methylbenzoyl group instead of ethoxycarbonyl also proceeded smoothly to afford isoindole **2h** in 85% yield (entry 7). A fluorine or a bromine atom also could be introduced at the C5- or C4-position on an isoindole ring, respectively (entries 8 and 9). It is noteworthy that a heterocyclic framework such as 6*H*-pyrrolo[3,4-*b*]pyridine could be readily accessible using this method (entry 10).

Table 1. Synthesis of Isoindole Derivatives[a]

entry	azide **1**	isoindole **2**	yield/%[b]
1	**1b** (R^1, R^2 = H)	**2b**	94 (75)
2	**1c** (R^1 = C_6H_5, R^2 = H)[c]	**2c**	(99)
3	**1d** (R^1 = 4-MeO-C_6H_4, R^2 = H)	**2d**	(87)
4	**1e** (n = 4)	**2e**	(87)
5	**1f** (n = 2)	**2f**	(70)
6	**1g** (n = 1)	**2g**	(54)
7	**1h**	**2h**	85
8	**1i**	**2i**	(82)
9	**1j**	**2j**	(57)
10	**1k**	**2k**	(61)

[a] Reaction conditions: treatment of azide **1** in toluene (0.1 M) at 100 °C for 3 h. [b] The two-step-yield from mesylate **5** is in parentheses. Reaction conditions: treatment of mesylate **5** with NaN_3 (1.2 equiv) in DMF (0.3 M) at 0 °C; then after work up, exposure of resulting crude azide in toluene (0.1 M) at 100 °C for 3−5 h. [c] *Z*:*E* = 5.4:1.

(5) (a) Duan, S.; Sinha-Mahapatra, D. K.; Herndon, J. W. *Org. Lett.* **2008**, *10*, 1541. (b) Chen, Y.-L.; Lee, M.-H.; Wong, W.-Y.; Lee, A. W. M. *Synlett* **2006**, 2510. (c) Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273. (d) LeHoullier, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2364.

(6) For reports on the mechanism of the elimination of dinitrogen from triazoline intermediates with heterolytic cleavage of the N−N bond, see: (a) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 4864. (b) Wladkowski, B. D.; Smith, R. H., Jr.; Michejda, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7893, and references therein.

(7) A radical pathway via homolytic cleavage of the N−N bond of triazoline intermediates is also proposed, for examples, see references1c,g,h and: Broeckx, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'abbé, G. *Tetrahedron* **1971**, *27*, 3527.

(8) One of the most common synthetic methods of isoindoles are the reactions of phthalaldehyde and amine in the presence of reductants or nucleophiles. For examples, see: (a) Watanabe, Y.; Shim, S. C.; Uchida, H.; Mitsudo, T.; Takegami, Y. *Tetrahedron* **1979**, *35*, 1433. (b) Simons, S. S., Jr.; Johnson, D. F. *J. Chem. Soc., Chem. Commun.* **1977**, 374. (c) Bonnett, R.; Brown, R. F. C. *J. Chem. Soc., Chem. Commun.* **1972**, 393.

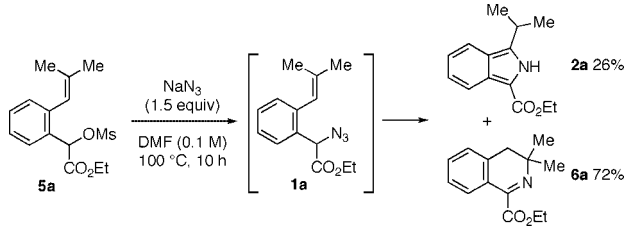
(9) For recent reports on isoindole formation by the other methods, see: (a) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (b) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. (c) Murashima, T.; Tamai, R.; Nishi, K.; Nomura, K.; Fujita, K.; Uno, H.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 995. (d) Dialer, H.; Polborn, K.; Beck, W. *J. Organomet. Chem.* **1999**, *589*, 21.

(10) The structure of **2a** was secured by X-ray crystallographic analysis (see Supporting Information). CCDC-710407 contains the supplementary crystallographic data for compound **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/conts/retrieving.html.

(11) The introduction of a carbonyl moiety at the C1-position on isoindoles is indispensable for this isoindole formation. For an example, the reaction of 2′-vinylbenzyl azide under same reaction conditions gave a complex mixture without desired isoindoles.

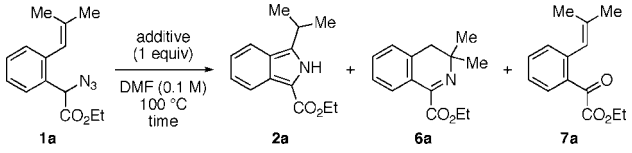
Upon this discovery of the formation of isoindoles **2**, we next attempted a direct transformation of mesylate **5a** to isoindole **2a** by treatment of **5a** with 1.5 equiv of NaN_3 in DMF at 100 °C (Scheme 3). However, in this case, the major product was not isoindole **2a** (26% yield) but dihydroisoquinoline **6a** (72% yield). In this reaction, the formation of azide **1a** as an intermediate was confirmed by monitoring the reaction with TLC. This unprecedented isoquinoline formation prompted us to investigate the reaction course and optimize the reaction conditions.[13]

Scheme 3. Competitive Formation of Dihydroisoquinoline



The reactions of azide **1a** with some additives were examined as shown in Table 2. Treatment of **1a** with 1 equiv of NaN_3 gave isoindole **2a** and dihydroisoquinoline **6a** in 9% and 87% yield, respectively (entry 1). Addition of 1 equiv of NaOAc[14] also gave almost the same results as that of NaN_3 (entry 2). When the reaction of **1a** with NaOAc was quenched by addition of 1 M aq. HCl within 1 h, α-keto ester **7a** was isolated in 70% yield (entry 3).

Table 2. Investigation of Additives[a]

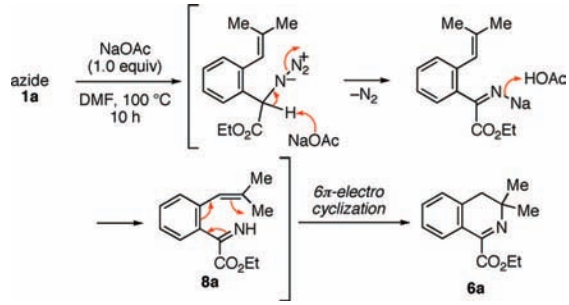


entry	additive	time/h	**2a** (%)[a]	**6a** (%)[a]	**7a** (%)[a]
1	NaN_3	10	9	87	0
2	NaOAc	10	6	85	0
3	NaOAc	1[b]	5	13	70

[a] Isolated yield. [b] The reaction was quenched with 1 M aq. HCl and stirred for 1 h.

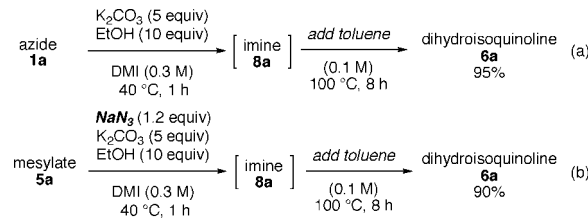
From this experimental evidence, it was concluded that NaN_3 or NaOAc induces elimination of dinitrogen from azide **1a** by deprotonation and subsequent protonation to afford *N*-H imine **8a**,[15] which then undergoes an intramolecular 6π-electrocyclization to afford dihydroisoquinoline **6a** (Scheme 4).[16,17]

Scheme 4. Proposed Reaction Mechanisms



Thus, for selective synthesis of dihydroisoquinoline **6a**, the formation of *N*-H imine **8a** should be achieved at relatively low temperature to prevent the intramolecular 1,3-dipolar cycloaddition. It was realized that treatment of azide **1a** with K_2CO_3 (5 equiv as a base) and EtOH (10 equiv as a proton source)[18] in 1,3-dimethyl-2-imidazolidinone (DMI) (0.3 M concentration) can provide *N*-H imine **8a** at 40 °C. Subsequent 6π-electrocyclization was found to be promoted by dilution of the concentration with toluene (0.1 M) and heating at 100 °C (Scheme 5a). On the basis of the above findings, a direct transformation of mesylates **5a** to dihydroisoquinoline **6a** was finally achieved in 90% yield by treatment of **5a** with NaN_3 (1.2 equiv), K_2CO_3 (5 equiv), and EtOH (10 equiv) in DMI at 40 °C followed by cyclization of the resulting imine **8a** in toluene−DMI at 100 °C (Scheme 5b).

Scheme 5. Optimized Reaction Conditions



We have found the scope of this method to be quite broad and have synthesized a range of structurally diverse iso-

(12) The starting materials were prepared by almost the same procedures as Scheme 2; see Supporting Information.

(13) For recent reviews on isoqunoline derivatives, see: (a) Keller, P. A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon: Oxford, 2008; Vol. 7, p 217. (b) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 167. (c) Blently, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (d) Kartsev, V. G. *Med. Chem. Res.* **2004**, *13*, 325. (e) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(14) The pK_a value of the conjugate acid of NaN_3 (HN_3) is almost same as that of NaOAc (HOAc).

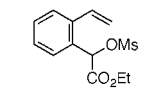
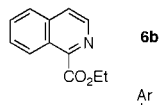
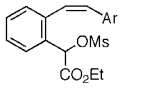
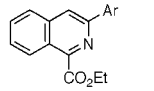
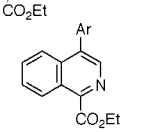
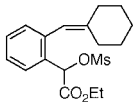
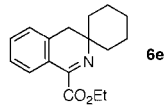
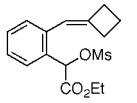
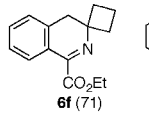
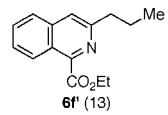
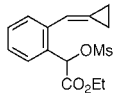
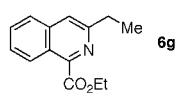
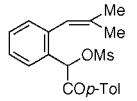
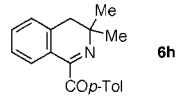
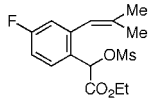
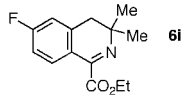
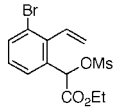
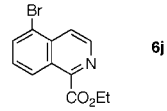
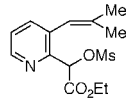
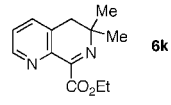
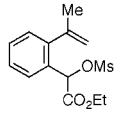
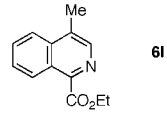
(15) For generation of imine from α-azido ketones and esters under the strong basic conditions, see: (a) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952. (b) Edwards, O. E.; Purushothaman, K. K. *Can. J. Chem.* **1964**, *42*, 712.

(16) For preparation of isoquinoline by 6π-electrocyclization of oxime derivatives, see: Kumemura, T.; Chosi, T.; Yukawa, J.; Hirose, A.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2005**, *66*, 87.

(17) 6π-Electrocyclization of 1-azatriene possessing *N*-H imine moiety is quite rare. For an example, see: Jutz, C.; Löbering, H.-G.; Trinkl, K.-H. *Synthesis* **1977**, 326.

(18) H_2O (10 equiv) can be used as a proton source, giving dihydroisoquinoline **6a** in 88% yield from azide **1a**.

Table 3. Synthesis of Isoquinoline and Dihydroisoquinoline Derivatives[a]

entry	mesylate **5**	isoquinoline **6** (yield / %)
1[b]	 **5b**	 **6b** (82)
2[b]	 **5c** (Ar = C_6H_5)[c]	 **6c** (52)  **6c'** (16)
3[b]	**5d** (Ar = 4-MeO-C_6H_4)	**6d** (50) **6d'** (14)
4	 **5e**	 **6e** (96)
5	 **5f**	 **6f** (71)  **6f'** (13)
6	 **5g**	 **6g** (88)
7	 **5h**	 **6h** (78)
8	 **5i**	 **6i** (89)
9[b]	 **5j**	 **6j** (79)
10	 **5k**	 **6k** (77)
11[b]	 **5l**	 **6l** (65)

[a] Reaction conditions unless otherwise noted: treatment of mesylate **5** with NaN_3 (1.2 equiv), K_2CO_3 (5 equiv), and EtOH (10 equiv) in DMF (0.3 M) at 40 °C for 1−3 h; then addition of toluene (0.1 M) and heat at 100 °C for 8 h. [b] After consumption of imine **8**, purge of O_2 and heat at 100 °C. [c] *Z*:*E* = 5.4:1.

quinoline and dihydroisoquinoline derivatives from the corresponding mesylates **5** (Table 3). From the mesylate **5b** having a vinyl group, the 6π-cyclization followed by oxidation of the resulting dihydroisoquinoline under an oxygen atmosphere gave ethyl isoquinoline-1-carboxylate (**6b**) in 82% yield (entry 1). The reaction of **5c** possessing a styryl moiety afforded 3-phenylisoquinoline **6c** in 52% yield along with 4-phenylisoquinoline **6c′** (16% yield), which may be formed via rearrangement of the phenyl group during oxidation of the resulting dihydroisoquinoline (entry 2). Mesylate **5d** bearing a 4-methoxyphenyl group, which has higher migratory aptitude than a phenyl group,[19] however, gave nearly identical distribution of products (entry 3). Dihydroisoquinoline **6e** having a spiro-cyclohexyl moiety was successfully prepared in excellent yield from mesylate **5e** (entry 4). Mesylate **5f** having a cyclobutylidenemethyl moiety gave spiro-dihydroisoquinoline **6f**[20] in 71% yield along with 13% yield of 3-propylisoquinoline **6f′** via ring opening of a cyclobutyl moiety/aromitization (entry 5). The reaction of mesylate **5g** with a cyclopropylidenemethyl group resulted in only 3-ethylisoquinoline **6g** in 88% yield (entry 6).[21] Replacement of the ethoxycarbonyl with a 4-methylbenzoyl group and introduction of halogen atoms on the aryl ring did not affect this transformation, giving the desired isoquinoline derivatives in good yield (entries 7−9). 1,6-Naphthyridine derivative **6k** could be synthesized in good yield from mesylate **5k** (entry 10). Finally, the reaction of mesylate **5l** having an α-methylvinyl group was examined, and the corresponding 4-methylisoquinoline **6l** was obtained in 65% yield (entry 11).

In summary, an orthogonal method has been developed for the synthesis of isoindole and isoquinoline derivatives using α-azido carbonyl compounds bearing a 2-alkenylaryl moiety. Further studies on the scope and synthetic applications of these reactions are currently in progress.

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Supporting Information Available: Experimental procedures, characterization of new compounds, and CIF files giving crystallographic data for compounds **2a** and **6f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Curtin, D. Y.; Crew, M. C. *J. Am. Chem. Soc.* **1955**, *77*, 354.

(20) The structure of **6f** was secured by X-ray crystallographic analysis (see Supporting Information). CCDC-710406 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/conts/retrieving.html.

(21) The ring-opening reactions to lead isoquinolines **6f′** and **6g** seem to occur just after 6π-electrocyclization, not from the corresponding dihydroisoquinolines like **6f**. The detailed investigation is discussed in Supporting Information.