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Tandem Functionalization of Nonactivated Alkenes and Alkynes in Intramolecular *N*-Acyloxyiminium Ion Carbocyclization. Synthesis of 6-Substituted Hydroindole 2-Carboxylic Acids

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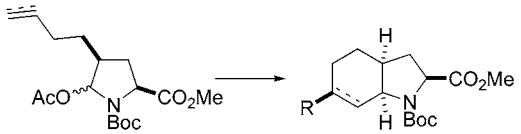
ABSTRACT



R= Halides, aryls

Five-membered *N*-Boc acyliminium ions derived from L-pyroglutamic acid harboring 4-butenyl and 4-butynyl tethers undergo Lewis acid-mediated halo and tandem Friedel–Crafts carbocyclization within minutes at −78 °C to give stereodefined 6-substituted octahydroindole and hexahydroindole 2-carboxylic acid methyl esters, respectively. The cyclic vinyl bromides are excellent substrates for Pd-catalyzed Suzuki–Miyaura, Heck, and Stille couplings. The method also provides access to enantiopure sp^2- and sp^3-arylated azabicyclics that are novel and versatile scaffolds for chemical diversification.

The octahydrohydroindole ring and related heterocycles are important components of many natural products and medicinally relevant compounds. For example, (6*R*,2*R*)-6-hydroxy-2-carboxy-octahydroindole and its (5*R*,6*R*)-dihydroxy variant are the core subunits of marine metabolites such as aeruginosin 298A[1] and dysinosin A,[2] respectively. The octahydroindole motif is also embedded in the structures of several polycylic alkaloids and the clinically relevant angiotensin converting enzyme (ACE) inhibitor perindoprilat.[3]

The occurrence of this bicyclic heterocycle in the aeruginosin family of cyanobacterial metabolites[4] has stimulated interest in its synthesis by enantioselective methods.[5−10] We recently reported a novel azonia-Prins-type (the prefix azonia rather than aza is in accord with the IUPAC rules on nomenclature; Heterocyclic Systems; rule B-6. Cationic heteroatoms) halocarbocyclization of readily available *C*-branched

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(1) (a) Rios Steiner, J. L.; Murakami, M.; Tulinsky, A. *J. Am. Chem. Soc.* **1998**, *120*, 597. (b) Matsuda, H.; Okino, T.; Murakami, M.; Yamaguchi, K. *Tetrahedron* **1996**, *52*, 14501. (c) Murakami, M.; Ishida, K.; Okino, T.; Okita, Y.; Matsuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 2785. (d) Murakami, M.; Okita, Y.; Matsuda, H.; Okino, H.; Yamaguchi, K.; *Tetrahedron Lett.* **1994**, *35*, 3129.

(2) Carroll, A. R.; Pierens, G.; Fechner, G.; de Almeidaleona, P.; Ngo, A.; Simpson, M.; Hooper, J. N. A.; Böstrom, S. L.; Musil, D.; Quinn, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 13340.

(3) (a) Vincent, M.; Marchand, B.; Remond, G.; Jaguelin-Guinamant, S.; Damien, G.; Portevin, B.; Baumal, J. Y.; Volland, J. P. *Drug Design and Discovery* **1992**, *9*, 11. For related structures (ramipril), see: (b) Warner, G. T.; Perry, C. M. *Drugs* **2002**, *62*, 1381.

(4) For recent reviews, see: (a) Leusch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 179. (b) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J.-G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347. (c) Shiori, T.; Hamada, Y. *Synlett* **2001**, 184. (d) Lewis, J. R. *Nat. Prod. Rep.* **1998**, 417. (e) Namikoshi, M.; Rinehart, K. L. *J. Indust. Microbiol.* **1996**, *17*, 373. (f) Rinehart, K. L.; Namikoshi, M.; Choi, B. W. *J. Appl. Phycol.* **1994**, *6*, 159.

(5) (a) Wipf, P.; Methot, J.-L. *Org. Lett.* **2000**, *2*, 4213. (b) Wipf, P.; Maresko, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723. (c) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576. (d) Wipf, P.; Kim, Y.; Goustein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 1106.

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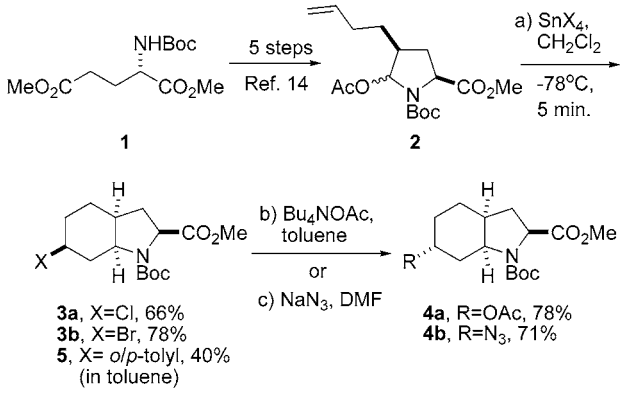
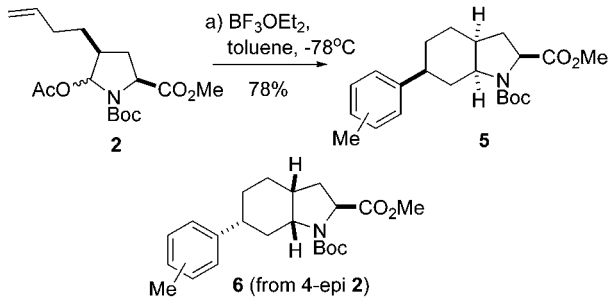
Scheme 1 *N*-Acyloxyiminium Ion Azonia-Prins Cyclizations



Scheme 2. Tandem Azonia-Prins/Friedel−Crafts Reactions

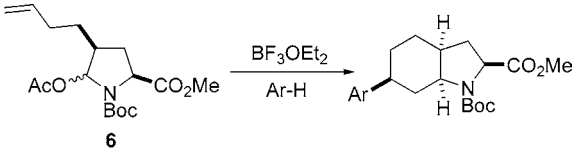


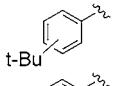
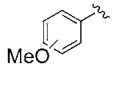
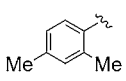
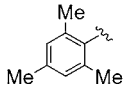
ω-alkenyl *N*-acyloxyiminium ion intermediates such as **2** in connection with the total synthesis and structural confirmation of oscillarin,[11] a new member of the aeruginosin family (Scheme 1). In the presence of $SnCl_4$ or $SnBr_4$ in CH_2Cl_2, cyclization occurred within a few minutes at −78 °C to afford the corresponding (2*S*,6*S*)-6-halo-octahydroindole 2-carboxylic acid methyl esters **3a** and **3b** (Scheme 1). Nucleophilic displacement with Bu_4NOAc and NaN_3 gave the (6*R*)-acetate and (6*R*)-azido analogues **4a** and **4b**, respectively.

When the reaction was run in toluene as a solvent, a facile Friedel−Crafts-type tandem carbocyclization took place resulting in the formation of **3a**, and an *o*/*p*-mixture of (6*R*)-tolyl-octahydroindole 2-carboxylic acid methyl ester as a byproduct (Scheme 1). Using BF_3OEt_2 instead of $SnCl_4$ and using toluene as a solvent gave the Friedel−Crafts product **5** in 78% yield (Scheme 2). The stereochemistry at C-6 was determined by NOESY experiments and by comparison with an X-ray structure (see below). Other mono- and disubstituted benzenes of similar nucleophilicity[12] (*o*-xylene, methylenedioxy benzene, isopropylbenzene, anisole, etc.) gave analogous results (Table 1, entries 1−6). Mesitylene and *m*-xylene gave single positional isomers as major products (Table 1, entries 7 and 8). Moderately nucleophilic halobenzenes gave modest yields of the corresponding *o*/*p*-substituted (6*S*)-halophenyl adducts, accompanied by 20−30% yield of the 5,6-elimination product and the ene-carbamate arising from **2**. Electron-rich aromatics such as 2,4-dimethoxybenzene and furan added to the iminium ion directly, even in the presence of excess anisole.[13] The formation of **5** and related adducts (Table 1) took place within a few minutes at temperatures between −15 and −78 °C depending on the freezing temperature of the solvent. Decreasing the amount of the arene by mixing with increasing volumes of CH_2Cl_2 progressively diminished the yield, but the main adducts were the same as when the arene was used as a solvent. The reaction was also done with the C-4-epimeric analogue of **2** to afford **6** in 74% yield (Scheme 2).

A plausible mechanism takes into account an antiperiplanar alignment[11−14] of the π-nucleophilic extremity with the *endo*-*N*-acyloxyiminium ion[15] in a chairlike conformation[16] as

Table 1. Tandem Azonia-Prins/Friedel−Crafts Reaction of **6** with a Variety of Arenes as a Solvent



Entry	Ar	Temperature	Yield[a]
1		-20°C	67%
2		-15°C	58%
3		-78°C	70%
4		-78°C	50%
5		-35°C	69%
6		-25°C	50%
7		-45°C	64%
8		-40°C	78%

[a] Isolated as *o*/*p*-mixtures, except for entries **7** and **8**, which were single adducts.

(6) (a) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. Eur. J.* **2001**, *7*, 3446. (b) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248. (c) Bonjoch, J.; Catena, J.; Isabal, E.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1996**, *7*, 1899. (d) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106.

(7) Ohshima, T.; Gnanadesikan, V.; Shibughushi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206.

(8) Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342.

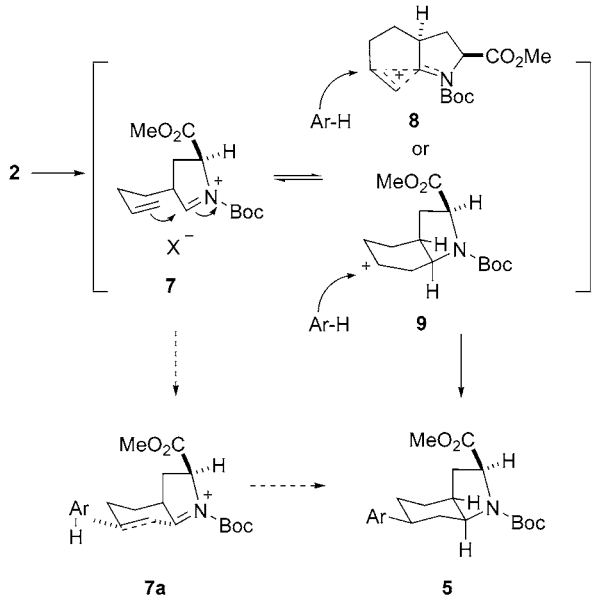
(9) Belvisi, L.; Colombo, L.; DiGiacomo, M.; Manzoni, L.; Vodopivec, B.; Scolastico, C. *Tetrahedron* **2001**, *57*, 6463.

(10) Toyooka, N.; Okumura, M.; Himiyama, T.; Nakazawa, A.; Nemoto, H. *Synlett* **2003**, 55.

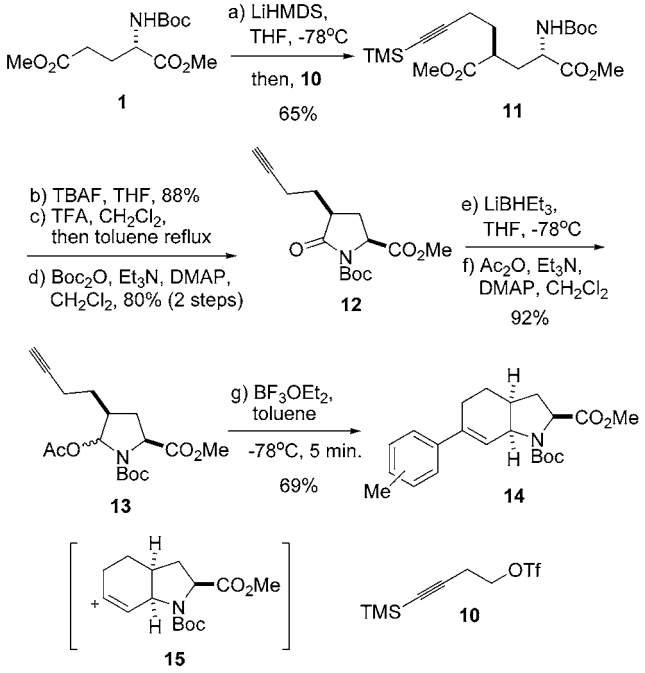
(11) Hanessian, S.; Tremblay, M.; Petersen, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064.

(12) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

Scheme 3. Proposed Reactive Intermediates in the Tandem Azonia-Prins/Friedel−Crafts Cyclizations



Scheme 4. Terminal Yne Tandem Azonia-Prins/Friedel−Crafts Cyclization



shown in **7** (Scheme 3). A putative π-cationic specie **8**,[17,18] or the cyclic carbenium ion **9**, is attacked by the solvent in an equatorial trajectory to afford the observed stereochemistry. Vicinal H-abstraction from **9** can lead to the 5,6-unsaturated analogue (in addition to the ene-carbamate of **2**), especially in the case of less reactive arenes. A synchronous formation of a C−C and C−O bonds was originally suggested[16a] in the formic acid-mediated intramolecular carbocyclization of an iminium ion lactam. Although a similar pathway as depicted in **7a** cannot be excluded, it is more likely that the carbocyclization of **2** proceeds in an asynchronous manner especially when weak carbon nucleophiles are involved.

We then extended the halocarbocyclization reaction to *N*-acyloxyiminium ions bearing a *C*-tethered terminal alkyne[19] (Scheme 4). Formation of the Li dianion from *N*-Boc dimethyl L-glutamate **1**, followed by alkylation with 4-trimethylsilanyl-but-3-yn-1-ol triflate **10** capitalizing on internal 1,3-induction,[20] gave **11** as a single isomer. Removal of the TMS, followed by a two-step lactamization gave **12**, which was converted to the 5-acetoxy intermediate **13** as previously reported.[11,20] Treatment of **13** with BF_3OEt_2 in toluene gave the vinylic 6-tolyl adduct **14**, as an *o*/*p*-mixture in 69% yield. An intermediate cyclic vinyl cation,[21] **15** (or a π-complex),[18,22] can be invoked as in the case of the alkene tether (Scheme 3).[23]

(13) For selected examples of intermolecular Friedel−Crafts-type C-arylation of *N*-acyloxyiminium ions, see: (a) Manfré, F.; Pulicani, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 235. (b) Matsumura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, *49*, 8503. (c) Malmberg, M.; Nyberg, K. *Acta Chem. Scand.* **1981**, *B35*, 411. See also ref 18.

(14) For examples, see: (a) Ent, H.; de Koning, H.; Speckamp, W. N. *J. Org. Chem.* **1986**, *51*, 1687. (b) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515. (c) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *103*, 1255. For Prins cyclization, see: (d) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4079. For related examples of stereoelectronic effects in the intermolecular addition of nucleophiles to iminium ions, see: (e) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054. (f) Demailly, G.; Solladié, G. *J. Org. Chem.* **1981**, *46*, 3102. (g) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 6, 2833. (h) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (i) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. (j) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (k) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (l) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon: New York, 1983; Chapter 6.

(15) For authoritative reviews, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Royer, J.; Bonin, M.; Micouin, J. *Chem. Rev.* **2004**, *104*, 2311. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (d) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: New York, 1991, *2*, 1047. (e) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (f) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345.

(16) Analogy with Stork−Eschenmoser proposals for polyene cyclizations has been made; see: (a) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

(17) For an early example, see: Dijkink, J.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 4043.

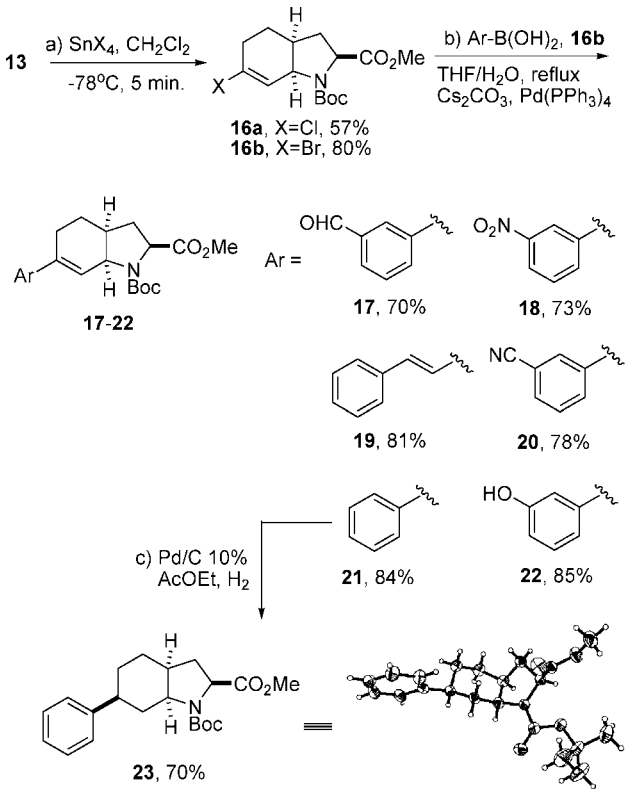
(18) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.

(19) For a recent example, see: Beyersbergen van Henegouwen, W. G.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862 and references therein.

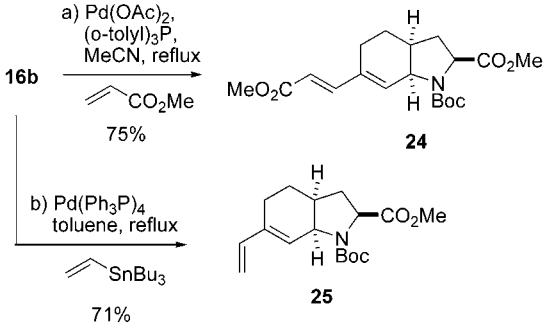
(20) Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887.

(21) For examples of cyclic vinyl cations, see: (a) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1. (b) Balog, A.; Curran D. P. *J. Org. Chem.* **1995**, *60*, 337. (c) Johnson, W. S.; Yarnell, T. M.; Myers, R. F.; Morton, D. R. *Tetrahedron Lett.* **1978**, 2549. (d) Kozar, L. G.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1977**, *42*, 1386. (e) Schleyer, P. V. R.; Pfeifer, W. D.; Bahn, C. A.; Bocher, S.; Harding, C. E.; Hummel, K.; Hanack, M.; Stang, P. J. *J. Am. Chem. Soc.* **1971**, *93*, 1513. (f) Peterson, P. E.; Kamat R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521. For reviews on vinyl cations, see: (g) Nefedov, V. D.; Sinotova, E. N.; Lebedev, V. P. *Russ. Chem. Rev.* **1992**, *61*, 283. (h) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. B. *Vinyl Cations*; Academic Press: New York, 1979. (i) Stang, P, J. *Acc. Chem. Res.* **1978**, *11*, 107. (j) Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 333. (k) Rappoport, Z. *Acc. Chem. Res.* **1976**, *9*, 265.

Scheme 5. Terminal Yne Azonia-Prins Cyclizations and Suzuki Cross-Coupling with **2b**



Scheme 6. Heck and Stille Cross-Coupling reactions with **22b**



In the presence of $SnCl_4$ or $SnBr_4$ in CH_2Cl_2, **13** was rapidly transformed into the versatile vinylic 6-halo hexahydroindoles **16a** and **16b** in 57 and 80% yields, respectively (Scheme 5). We were then in a position to apply well-known Pd-catalyzed substitution reactions of vinylic bromides in an effort to introduce further functional diversification. Thus, treatment of **16b** with a variety of commercially available substituted arylboronic acids in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in aqueous THF at reflux temperature gave excellent yields of the corresponding 6-aryl adducts **17**−**22**. This is a useful and practical alternative to the tandem Friedel−Crafts azonia-Prins-type carbocyclization described above (Scheme 4),[24] since the latter is limited by the freezing temperature of the solvent and can give *o*/*p*-mixtures. Catalytic hydrogenation of **21** gave the corresponding (6*S*)-phenyl analogue **23**, whose absolute stereochemistry was determined by X-ray crystallography.

The Suzuki−Miyaura[25] products **17**−**22** are versatile 6-aryl-functionalized appendages on the original hexahydroindole 2-carboxylic acid core motif. Further exploitation of the vinylic bromide functionality involved Heck[26] and Stille[27] coupling reactions (Scheme 6). Thus, treatment of **16b** with methyl acrylate in the presence of $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$ in refluxing toluene gave the extended diene ester **24**. Reaction in the presence of vinyltributylstannane and $Pd(PPh_3)_4$ in refluxing toluene gave the exocyclic diene **31** in 71% yield.

We have described novel and practical methods for the synthesis of enantiopure 6-halo, 6-azido, and 6-*C*-substituted hydroindole 2-carboxylic acid methyl esters from readily available 4-ω-butenyl and butynyl *N*-Boc L-pyroglutamic acid esters in the presence of Lewis acids. The terminal alkene and alkyne tethers act as latent π-nucleophiles, which also undergo concomitant attack by an external nucleophile such as a halide or an aromatic hydrocarbon, most likely via cationic intermediates. In the case of an alkene, an intramolecular tandem Friedel−Crafts-type carbocyclization takes place with the creation of a new sp^3 stereogenic carbon bearing an equatorially disposed aryl substituent. Alkynes lead to vinylic halides or vinylic aryls within the newly formed 6-substituted hexahydroindole motif. Chemical manipulation of the vinylic halides and capitalizing on the orthogonal functionality in the hexahydroindole 2-carboxylic acids expands their utility as versatile scaffolds toward the synthesis of pharmaceutically relevant entities and as intermediates in natural product synthesis.

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Supporting Information Available: Typical experimental procedures of key reactions and NMR, X-ray, and other data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744.

(23) For examples of vinyl cation arylations, see: (a) Stang, P. J.; Anderson, A. G. *J. Am. Chem. Soc.* **1978**, *100*, 1520. (b) Roberts, R. M.; Abdel-Baset, M. B. *J. Org. Chem.* **1976**, *41*, 1698.

(24) For recent examples of intramolecular Friedel−Crafts arylation of *N*-acyliminium ions, see: (a) Hanessian, S.; Papeo, G.; Angiolini, M.; Fettis, K.; Beretta, M.; Munro, A. *J. Org. Chem.* **2003**, *68*, 7204. (b) Luker, J.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220. (c) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905. (d) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149. (e) Marson, C. M.; Pink, J. H.; Smith, C. *Tetrahedron Lett.* **1995**, *36*, 8107. (f) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348. (g) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 7115. (h) Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969. (i) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1985**, *23*, 365. (j) Maryanoff, B. E.; Molinari, A. J.; McComsey, D. F.; Maryanoff, C. A.; Wooden, G. P.; Olofson, R. A. *J. Org. Chem.* **1983**, *48*, 5074. See also ref 18a.

(25) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(26) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

(27) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.