Addition of Transiently-Generated Methyl *o*-Lithiobenzoate to Imines. An Isoindolone Annulation

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Addition of phenyllithium to a mixture of an imine, methyl *o*-iodobenzoate, and BF_3·etherate at −105 °C gives good to excellent yields of isoindolones. The transient formation of methyl *o*-lithiobenzoate is proposed, which is formed by a rapid lithium/iodide exchange reaction of the phenyllithium with methyl *o*-iodobenzoate in the presence of the imine. The transiently generated anions can then be captured by the BF_3-activated imines to form the isoindolones in good to high yield. The reactions conditions are sufficiently mild, and selective, to permit functional groups such carbmethoxy and aryl bromide, which could otherwise react with the added PhLi, to be tolerated.

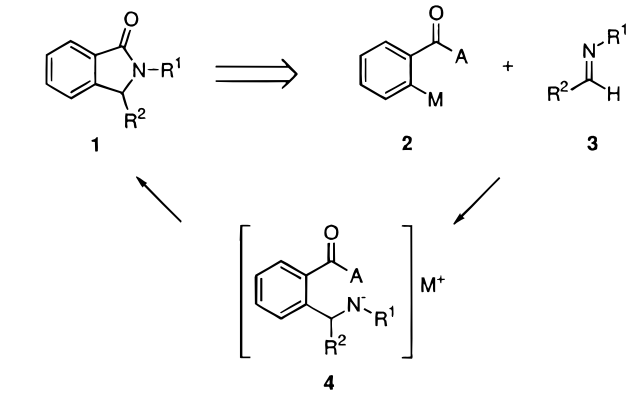
Introduction

Recently, we required a practical synthesis of isoindolones of generic structure **1**. Direct annulative approaches were appealing due to synthetic convergency and the capacity to more widely vary substituents on the targeted isoindolone ring. In particular cases, such as in isoindolone **15**, the presence of the two stereogenic centers necessitated strict synthetic control of both relative and absolute stereochemistry. Finally, since we required multigram quantities of the isoindolones, a synthesis would have to be sufficiently robust for scale-up.

We considered the addition of an appropriately functionalized *ortho*-substituted aryl organometallic derivative to an imine as a synthetic approach to generation of the isoindolone ring system (Scheme 1).[1] We envisioned that the aryl organometallic derivative **(2)**, an *ortho*-metalated benzamide, for example, would add to an imine **(3)** to form an intermediate nitrogen-based anion **4**. This intermediate could then directly cyclize onto the *ortho*-substituent of the aryl ring to form the isoindolone ring **1**. For the case of α-chiral imines as reaction partners, addition of an aryl organometallic would be predicted to proceed through a Felkin−Ahn transition state to afford the *syn*-diastereoisomer as the major product (Figure 1).[2] The use of an enantiomerically enriched imine should then produce diastereodefined and enantioenriched isoindolone, assuming no racemization occurred during the course of the reaction.

The addition of *ortho*-substituted aryllithium reagents to imines has been described by Bradsher and Hunt as a synthetic approach to isoindolones.[3] Their procedure required use of either the very unstable isopropyl *o*-lithiobenzoate anion[4] or, as an alternative, *o*-lithiobenzonitrile[5] as a more stable reaction partner. In general,

Scheme 1



however, the yields of the isoindolones were poor. Furthermore, their procedures could not accommodate imines with hydrogens α to the imine carbon, due to suspected competing proton transfer. A related synthetic strategy, based upon the addition of lithiated *N*,*N*-diethyl-*o*-toluamide to imines, was used to prepare a series of dihydroisoquinolones.[6] The yields of dihydroisoindolones were, however, modest to poor.

In this paper, we describe our investigations of the addition of *o*-lithiated benzoates, and the dianion derived from *N*-methylbenzamide, to imines. We have found that

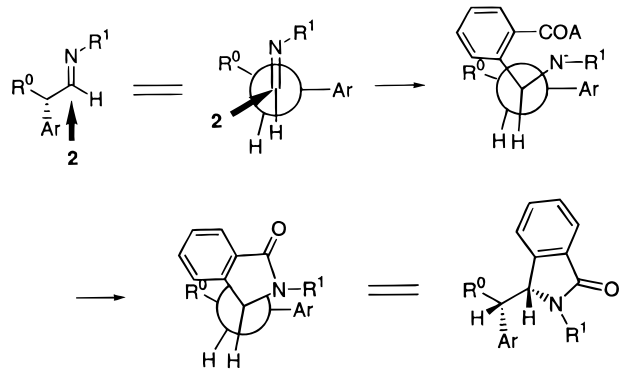


Figure 1.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

(1) For recent examples of addition of organometallics to imines see: (a) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1995**, *60*, 3405. (b) Higashiyama, K.; Fujikura, H.; Takahashi, H. *Chem. Pharm Bull Tokyo* **1995**, *43*, 722.

(2) (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031. (b) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079. (c) Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865.

(3) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 327.

(4) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2704.

(5) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.

(6) Clark, R. D.; Jahangir *J. Org. Chem.* **1987**, *52*, 5378.

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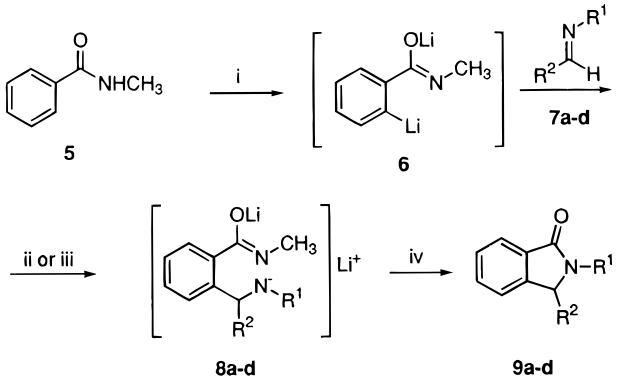
Scheme 2[a]



a: R^1 = Et, R^2 = Ph; **b**: R^1 = Pr, R^2 = Ph; **c**: R^1 = Ph, R^2 = Ph; **d**: R^1 = Bu, R^2 = Pr

[a] Key: (i) 2 BuLi, THF, −20 to 0 °C; (ii) 0 °C to rt; (iii) −78 °C, 1.1 mmol equiv of BF_3·OEt_2; (iv) 130 °C.

alkyl *o*-lithiobenzoates, generated in the presence of imines and boron trifluoride diethyl etherate (BF_3·OEt_2), undergo addition to imines to give isoindolones. Furthermore, the addition of alkyl *o*-lithiobenzoates, generated *in-situ*, to imines with α hydrogens proceeds in high yields without any apparent competing proton transfer. Imines with α-chiral centers react with methyl *o*-lithiobenzoate, generated *in-situ*, with high diastereoselective bias, which is consistent with Felkin−Ahn transition state models.

Results and Discussion

Reactions of Imines with the *N*-Methylbenzamide Dianion (6). To initiate our investigations, we first evaluated the addition of *o*-lithiobenzonitrile to a simple representative imine, benzylidenethylamine (**7a**). Our use of *o*-lithiobenzonitrile, while successfully exploited by Bradsher[4] and Parham,[5] failed to afford more than traces of the expected isoindolone. We next focused our attention on the use of the *N*-methylbenzamide dianion (**6**), which was prepared by the addition of 2 equiv of BuLi to *N*-methylbenzamide.[7] The *N*-methylbenzamide dianion **(6)** reacted effectively at 0 °C with **7a** to give a mixture of two products, the simple imine 1,2-addition product and the desired isoindolone **9** (Scheme 2). Heating the reaction mixture to 130 °C for 30 min completed cyclization of the initially formed addition product to afford the desired isoindolone (**9a**) in excellent yield. The reaction was shown to be general for producing isoindolones from several other simple benzylideneamines not containing acidic α hydrogens (Table 1, entries 1−3).

However, in a substrate in which acidic α-hydrogens were present, **6** was found to not add effectively (Table 1, entry 4). Imines are known to have an increased propensity to undergo organometallic addition reactions in the presence of strong Lewis acids.[8] We found that the addition of **6** to butylidenebutylamine (**7d**), in the presence of 1 equiv of BF_3·OEt_2, proceeded at −78 °C to give the imine adduct in 48% yield. The very rapid rate of addition of **6** to imines at −78 °C, in the presence of BF_3·OEt_2, should be noted in contrast to the same dianion requiring a temperature of 0 °C to add effectively to **7d** in the absence of BF_3.[9] Heating to 130 °C was required to cyclize the 1,2-addition product and to give the desired isoindolone **9d** in a 40% overall yield.

Table 1. Addition of the *N*-Methylbenzamide Dianion (6) to Imine 7[a]

entry	product	R_1	R_2	% yield[b]
1	**9a**	Et	Ph	79
2	**9b**	Pr	Ph	72
3	**9c**	Ph	Ph	47
4	**9d**	Bu	Pr	12
5	**9d**	Bu	Pr	40[c]

[a] Reactions conducted at 0 °C using 1.35 equiv of *N*-methylbenzamide and 2.7 equiv of nBuLi to generate the dianion. [b] Yields refer to isolated products. See Experimental Section. [c] Conducted at −78 °C in the presence of 1.1 equiv of BF_3·OEt_2.

Reaction of Imines with Alkyl *ortho*-Lithiobenzoates. During the course of our investigations, we became intrigued with the possibility of adding alkyl *o*-lithiobenzoates, prepared *in-situ*, to imines. We reasoned that alkyl *o*-lithiobenzoates would exhibit greater reactivity in the addition to imines relative to the more extensively, and intramolecularly complexed, dianion **6**. Also, the initially formed imine adduct, derived from a lithiated benzoate, would be more likely to cyclize onto the *o*-carbalkoxy group to afford the isoindolone ring system.

Isopropyl and *tert*-butyl *o*-lithiobenzoate have been reported to be modestly stable at −100 °C.[4] However, their synthetic utility has been limited. This is partially due to their relative instability toward self-condensation. Thus, warming solutions of these anions to −78 °C results in their decomposition and/or self-addition. Methyl *o*-lithiobenzoate, in particular, has been reported to be too reactive toward self-condensation, even at −100 °C, to be synthetically useful.[10] We proposed that BF_3-activated imines might be able to capture the *ortho*-lithiated carbalkoxybenzoates if these reactive anions could be stabilized or could be generated transiently.

We viewed lithium−halogen exchange using a suitable *o*-bromo or -iodobenzoate as an attractive approach for the transient generation of carbalkoxy-substituted aryllithium reagents. Adjusting the rate of addition of an "inducing" organolithium reagent to the alkyl *o*-halobenzoate would provide a means to control the formation of the alkyl *o*-lithiobenzoate, *in situ*. The rate of formation of the *o*-lithiated carbalkoxybenzoates, induced by lithium−halogen exchange, would have to be exceptionally fast to avoid unwanted side reactions. Potential competing processes would include addition of the "inducing" organolithium to the imine, deprotonation of imine α-or α′-hydrogens, and self-condensation, or decomposition, of the *o*-lithiobenzoate. However, we were encouraged by previous reports that described the preparation, and trapping, of organolithium reagents in the presence of nontethered reactive electrophiles.[9,11]

To test this synthetic approach to isoindolones, a solution of isopropyl *o*-bromobenzoate, **7d**, and BF_3·OEt_2

(7) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853.
(8) (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.12.

(9) BF_3·OEt_2 promotes the addition of perfluoroalkylcarbanions to imines with acidic α-hydrogens. See: Uno, H.; Shiraishi, Y.; Shimokawa, K.; Suzuki, H. *Chem. Lett.* **1988**, 729. For a discussion of the kinetic acidity of imine α-hydrogens see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166.
(10) Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2053.
(11) Perfluoroalkyl carbanions: Reference 8. (a) Johncock, P. *J. Organomet. Chem.* **1969**, *19*, 257. (b) Gassman, P. G.; O'Reilly, N. J. *Tetrahedron Lett.* **1985**, *26*, 5243. Allyllithiums: (c) Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326. Alkenyllithiums: (c) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. Lee, S. W.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 5209.

in THF was cooled to −78 °C. Phenyllithium (1 equiv) was added dropwise to induce metal−halogen exchange. After the mixture was stirred at −78 °C for 1 h and for an additional interval at ambient temperature, the reaction was quenched with water. Isoindolone **9d** was isolated in a 27% yield. Use of isopropyl *o*-iodobenzoate as a reaction partner, under otherwise identical reaction conditions, afforded a 48% yield of isoindolone **9d**. We suspect the faster rate of lithium−iodide exchange, compared to lithium−bromide exchange, might be enhancing the desired course of reaction, therein obviating some of the competing side processes.[12,13]

We also examined the suitability of other alkyl *o*-iodobenzoates to function as reaction partners.[14] We were pleased to find that the use of methyl *o*-iodobenzoate, and lowering the reaction temperature to between −105 and −110 °C, provided a further improvement in the yield of isoindolone. In light of the reported instability of methyl *o*-lithiobenzoate, this was an unexpected discovery.[10] Thus, conducting the reaction of **7d**, BF_3·OEt_2, methyl *o*-iodobenzoate, and phenyllithium at −110 °C, according to the above-described procedure, afforded the isoindolone **9d** in 65% yield.

Finally, the influence of phenyllithium stoichiometry on the reaction was briefly evaluated. We found that increasing the amount of phenyllithium to between 1.3 and 1.4 equiv raised the yield of **9d** to 89%.[15] The only byproducts that were identified were iodobenzene, methyl benzoate, and methyl *o*-iodobenzoate. Only traces of the self-condensation products derived from methyl benzoate and methyl *o*-iodobenzoate could be detected. No products derived from addition of phenyllithium to the methyl benzoates were found.

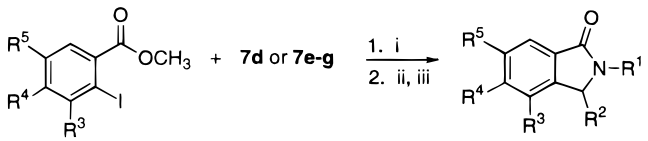
The isoindolone annulation proved to be quite general using methyl *o*-iodobenzoate as a reaction partner. Thus, the reaction of methyl *o*-iodobenzoate, and several substituted analogs, with a variety of imines provided good to excellent yields of the corresponding isoindolones (see Schemes 2 and 3 and Table 2).

Isoindolones were obtained in good to excellent yields, even when substituted with reactive functional groups. Thus, a pendant 4-carbmethoxy group on the methyl *o*-iodobenzoate afforded the corresponding isoindolone **11c** in a 64% yield (Table 2, entry 11). However, in this case, only 1.1 equiv of phenyllithium was used to promote the reaction. As expected, the use of greater amounts of phenyllithium gave an increase in the formation of byproducts, especially benzophenones derived from addition of phenyllithium to the pendent carbmethoxy group. The excellent yield of isoindolone that was obtained in the presence of an aryl bromide (Table 2, entry 13) is exemplary of the remarkable selectivity that may be achieved in the lithium−iodide exchange-induced annulation reaction.

The isoindolone annulation reaction does appear to be subject to certain steric constraints. For example, the steric demands of the isopropyl group (Table 2, entry 8) may be preventing adequate coordination of BF_3 with the imine nitrogen. This would prevent activation of the imine, which may then seriously impede the desired addition reaction. The poor result obtained with benzylideneaniline as the imine was surprising (Table 2, entry 5). We can only speculate that the extended π system of the benzylideneaniline may be too good of an electron acceptor, thereby allowing competing reaction pathways, e.g., reductive dimerization,[16] to supersede the desired course of addition. In general, however, the reaction procedure appears to accommodate a variety of substrates and provides access to a number of substituted isoindolones.

Application of the Isoindolone Annulation Reaction to the Synthesis of 15. We next applied our

Scheme 3[a]



10a-f **9 or 11a-f**

a: R^3 = Me, R^4 = R^5 = H; **b**: R^3 = R^5 = H, R^4 = Cl;
c: R^3 = R^5 = H, R^4 = CO_2Me; **d**: R^3 = R^4 = H, R^5 = Me;
e: R^3 = R^4 = H, R^5 = Br; R^3 = H, R^4 = R^5 = OMe

Reaction of **10** (R^3 = R^4 = R^5 = H) with **7e**: R^1 = Bn, R^2 = c-hexyl; **7f**: R^1 = Pr, R^2 = 2-furyl; **7g**: R^1 = iPr, R^2 = Ph gives isoindolones **9e-g**

[a] Key: (i) BF_3·OEt_2, −78 °C; (ii) PhLi, −78 or −105 °C; (iii) H_2O, warm to 50 °C overnight.

Table 2. Synthesis of Isoindolones 9 and 11[a] using Methyl *O*-Lithiobenzoates

entry	product	R_1	R_2	R_3	R_4	R_5	% yield
1	**9d**	Bu	Pr	H	H	H	89
2	**9d**	Bu	Pr	H	H	H	89[b]
3	**9d**	Bu	Pr	H	H	H	65[c]
4	**9b**	Pr	Ph	H	H	H	57[d]
5	**9c**	Ph	Ph	H	H	H	<5
6	**9e**	Bn	c-hexyl	H	H	H	72
7	**9f**	Pr	2-furyl	H	H	H	71
8	**9g**	iPr	Ph	H	H	H	0
9	**11a**	Bu	Pr	Me	H	H	46
10	**11b**	Bu	Pr	H	Cl	H	76
11	**11c**	Bu	Pr	H	CO_2Me	H	64[c]
12	**11d**	Bu	Pr	H	H	Me	89
13	**11e**	Bu	Pr	H	H	Br	84[c]
14	**11f**	Bu	Pr	H	OMe	OMe	72

[a] Unless otherwise specified reactions were conducted at −105 °C (±3 °C) using 1.35 equiv of PhLi and 1.1 equiv each of the methyl *o*-iodobenzoates and BF_3·OEt_2. Yields are for isolated chromatographed or recrystallized products. [b] 1.45 equiv of PhLi used. [c] 1.1 equiv of PhLi used. [d] Reaction conducted at −78 °C.

(12) (a) Rogers, H. R.; Houk, J. *J. Am. Chem. Soc.* **1982**, *104*, 522. (b) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101. (c) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (d) Beak, p.; Musick, T. J.; Liu, C.; Cooper, T.; Gallagher, D. J. *J. Org. Chem.* **1993**, *58*, 7330.

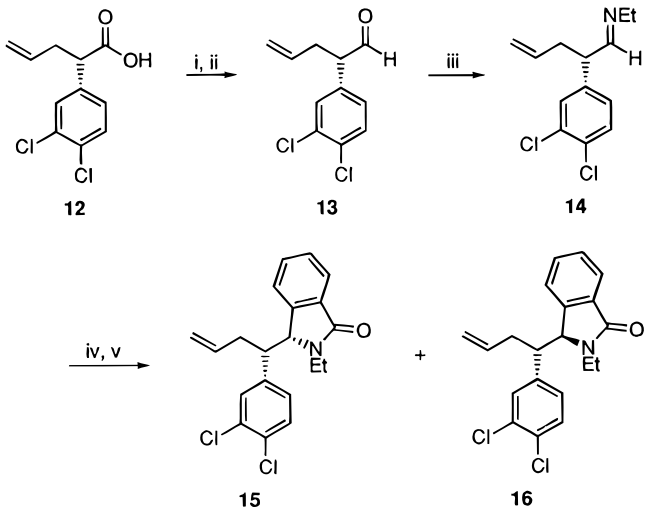
(13) The annulation was tried using isopropyl *o*-(trimethylstannyl)-benzoate as an alternative precursor to the organolithium reagent. Thus, reaction of the stannane with **7d**, in the presence of BF_3·OEt_2, gave only ca. 20% of isoindolone **9d**. Previous attempts to prepare organolithium reagents from stannanes in the presence of esters failed unless additional stabilizing groups were present. See: (a) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438. (b) Imanieh, H.; MacLeod, D.; Quayle, P.; Zhao, Y.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 405. (c) Booth, C.; Imanieh, H.; Quayle, P.; Shui-Yu, L. *Tetrahedron Lett.* **1992**, *33*, 413.

(14) We also tried to exploit the dianion derived from *o*-bromobenzoic acid, especially given the reported stability of the dianion at −78 °C. Isoindolones could be prepared in 35−45% yield. However, the poor solubility of the dianion tended to give variable results. See: Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2051.

(15) Several other organolithium reagents were evaluated in the isoindolone annulation process. Both MeLi·LiBr and *tert*-butyllithium proved to be inferior to phenyllithium. nBuLi, when used in a strict stoichiometry of 1.30 equiv relative to the imine, gave good yields of isoindolone. However, small variations in the amount of nBuLi, e.g., 1.2 equiv, gave significantly lower yields.

(16) Thies, H.; Schönenberger, H. *Chem. Ber.* **1956**, *89*, 1918.

Scheme 4[a]



[a] Key: (i) $(COCl)_2$, cat. DMF, CH_2Cl_2; (ii) Li(*t*-BuO)$_3$AlH, diglyme, −78 °C; (iii) $EtNH_2$, cat. Bu_2SnCl_2, Na_2SO_4; (iv) methyl *o*-iodobenzoate, $BF_3{\cdot}OEt_2$, −78 °C; (v) PhLi, −105 °C.

isoindolone synthesis process to the assembly of isoindolone **15**, which was of especial interest to us. Previous work described the preparation of (*S*)-(−)-2-(3,4-dichlorophenyl)-4-pentenoic acid (**12**) of 96−97% ee.[17] The acid was easily converted to the sensitive aldehyde **13** as shown in Scheme 4. The chiral purity of **13** was determined indirectly. Thus, treatment of **13** with $NaBH_4$ in ethanol gave the corresponding alcohol. HPLC analysis of the alcohol, using a chiral stationary phase, indicated a chiral purity of 92−94% ee. Thus, a slight erosion in the chiral purity was indicated from the starting acid **12**. Formation of imine **14** required the use of dibutyltin dichloride as a catalyst to accelerate the reaction and minimize epimerization of the chiral center.[18] Significant epimerization of the α-chiral center is observed when the reaction is conducted in the absence of the tin catalyst. The very sensitive imine **14** was then used immediately for the isoindolone annulation.

Our initial attempts to prepare isoindolone **15** from imine **14** using the dianion derived from *N*-methylbenzamide, in the presence of $BF_3{\cdot}OEt_2$, gave only small quantities of the desired product, which was accompanied by numerous byproducts. However, application of the procedure using methyl *o*-iodobenzoate and phenyllithium at −105 °C, with imine **14**, afforded a mixture of the isoindolone diastereomers **15** and **16** in a combined yield of 69%. We were gratified to find that the diastereomeric ratio was 18:1, favoring formation of the desired *syn* isomer **15**. Thus, the addition of the lithiated benzoate to imine **14** was consistent with that predicted by the Felkin−Ahn transition state model (Figure 1). Also, examination of the major diastereomer **15** by HPLC, using a chiral support phase, indicated a chiral purity of 92−94% ee. Thus, there was no loss of the chiral integrity from the starting aldehyde (and imine) during the isoindolone annulation step. Isoindolone **15** was found to be highly crystalline, so enantiomeric enrichment could be achieved by simple recrystallization to give purified product of >99.3% ee. Single-crystal X-ray analysis established the relative and absolute stereochemistry of **15** to be as predicted (see the supporting information). Furthermore, despite the very low temperatures employed for the synthesis of isoindolone **15**, we were able to routinely conduct reactions using 50−60 g of imine **14** as a starting material. The chemical yields, distereomeric ratios, and enantiomeric purity of **15** all remained consistent with the aforementioned results.

Conclusions

We have described a novel, direct annulation approach for the synthesis of isoindolones based upon the addition of methyl *o*-lithiobenzoate, and the dianion derived from *N*-methylbenzamide, to imines activated with BF_3. Acidic imine α-hydrogens are tolerated by the reaction conditions, as is the presence of relatively reactive functional groups, such as an ester and an aryl bromide. More importantly, we have demonstrated that the unstable methyl *o*-lithiobenzoate[19] can be prepared by lithium−iodide exchange in the presence of reactive acceptor electrophiles such as the BF_3-activated imines. The transient generation of methyl *o*-lithiobenzoate, and related functionalized aryllithium derivatives, in the presence of imines, and perhaps a range of other electrophiles, should extend the scope of functionally substituted organometallic reagents.[20]

Experimental Section

General Information. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Methyl *o*-iodobenzoate (Lancaster Synthesis) was redistilled under argon, wrapped with aluminum foil to protect from the light, and stored refrigerated. Imines were prepared using standard literature procedures using commercially available amines and aldehydes.[21] Volatile aldehydes were purified by distillation prior to imine formation. In most cases the imines were distilled and stored refrigerated. Boron trifluoride diethyl etherate was distilled from CaH_2 and stored refrigerated in an ampule fitted with a Teflon stopcock. Phenyllithium was purchased from Alfa and transferred under argon to a storage ampule surmounted with a Teflon stopcock. The phenyllithium was titrated periodically using diphenylacetic acid as the titrant and the acid dianion color as the endpoint.[22] Ambiguous titers were obtained using the procedure of Watson and Eastham[23] and related procedures using different indicators.[24] THF was distilled from sodium benzophenone ketyl immediately prior to use. HPLC analyses were performed using a Chiracel OD column (4.6 × 250 mm) with 10% 2-propanol/hexanes as the mobile phase. TLC analyses were performed on silica gel GHLF. All reactions were performed under a nitrogen or argon atmosphere using standard techniques for manipulation of air- and moisture-sensitive reagents.[25] Internal reaction temperatures

(17) Hale, J. J.; Finke, P. E.; MacCoss, M. *Biorg.Med. Chem. Lett.* **1993**, *3*, 319.

(18) Stetin, C.; de Jeso, B.; Pommier, J. C. *Synth. Commun.* **1982**, *12*, 495.

(19) We have chosen to formally designate the reactive species generated by the PhLi-induced lithium−iodide exchange on methyl *o*-iodobenzoate as the *o*-lithiated benzoate derivative. However, we have no structural evidence that confirms the lithio-derivative as the reactive intermediate. An alternative reactive intermediate might be a hypervalent "ate" complex. See: Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444.

(20) We have also added phenyllithium to a mixture of isopropyl *o*-iodobenzoate and trimethylsilyl chloride, at −78 °C, to produce isopropyl *o*-(trimethylsilyl)benzoate in a 72% yield.

(21) (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic Press: New York, 1972; Vol. II, Chapter 12. (b) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241.

(22) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(23) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(24) Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219.

(25) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. In *Organic Synthesis via Boranes*; John Wiley & Sons, Inc.: New York, 1975; Chapter 9.

were monitored using a Fluke 52K/J thermocouple, with digital readout. The thermocouple probe was inserted into a glass well containing ethanol, which was immersed into the reaction solution. Ambient temperature refers to 23 °C (±3 °C). Melting points were taken on a capillary apparatus. ^{1}H NMR spectra were obtained at 300 or 400 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Mass spectra were recorded on an atmospheric pressure chemical ionization platform. Elemental analyses were performed by the departmental analytical laboratory at Zeneca Pharmaceuticals, Inc.

General Procedure for the Addition of the *N*-Methylbenzamide Dianion 6 to Imines. The procedure for the preparation of 2-ethyl-3-phenyl-2,3-isoindol-1-one **(9a)** is representative. A solution of *N*-methylbenzamide (0.184 g, 1.36 mmol) in THF was cooled to −20 °C. BuLi (1.19 mL, 2.40 M in hexanes, 2.73 mmol) was then added dropwise. The resulting yellow-orange solution was stirred for a few minutes at −20 °C followed by placing in an ice bath and stirring for 1 h. Imine **7a** (0.143 mL, 0.133 g, 1.0 mmol) in THF (1 mL) was then added dropwise. The resulting red solution was stirred for 30 min in the ice bath. After removal of the ice bath, the solution was warmed to ambient temperature and stirred for an additional 30 min. Water was added and the mixture extracted several times with ethyl acetate. The combined extracts were washed once with brine and then dried (Na_2SO_4) and concentrated to leave an oil. TLC analysis revealed the presence of *N*-methylbenzamide and two new additional components. Mass spectral analysis suggested the identity of the three major components as follows: *N*-methylbenzamide (m/z = 136, [M + H]), the imine adduct (m/z = 269, [M + H]), and **9a** (m/z = 238, [M + H]). The mixture containing the crude reaction products was then heated in an oil bath at 130 °C for 1 h. TLC analysis revealed *N*-methylbenzamide and one other component. Purification of the crude product by flash chromatography using ethyl acetate:hexanes (3:7) as the eluent afforded 0.187 g (0.79 mmol, 79%) of the product as a white solid: mp 97−98 °C; ^{1}H NMR ($CDCl_3$) 1.14 (t, 3H, J = 7.3 Hz), 2.98 (dq, 1H, J = 7.2 ,14.1 Hz), 3.99 (dq, 1H, J = 7.3, 14.1 Hz), 5.47 (s, 1H) 7.16 (m, 4H), 7.33 (m, 2H), 7.45 (m, 2H), 7.89 (m, 1H); ^{13}C ($CDCl_3$)13.49, 34.95, 63.96, 122.99, 123.42, 127.53, 128.24, 128.60, 129.06, 131.59, 131.77; MS (m/z) = 238 [M + H]. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.78; H, 6.46; N, 5.93.

2-Propyl-3-phenyl-2,3-dihydroisoindol-1-one (9b): mp 92−93 °C; ^{1}H NMR ($CDCl_3$) 0.88 (t, 3H, J = 7.4 Hz), 1.58 (m, 2H), 2.84 (m, 1H), 3.88 (dt, 1H, J = 7.4, 13.7 Hz), 5.45 (s, 1H), 7.14 (m, 3H), 7.34 (m, 3H), 7.45 (m, 2H), 7.89 (m, 1H); ^{13}C NMR ($CDCl_3$) 11.34, 21.52, 41.79, 64.36, 122.99, 123.50, 127.52, 128.24, 128.59, 129.06, 131.58, 131.72, 137.17, 146.22, 168.59; MS (m/z) = 252 [M + H]. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57. Found: C, 80.87; H, 6.85; N, 5.68.

2,3-Diphenyl-2,3-dihydroisoindol-1-one (9c): mp 190−192 °C; ^{1}H NMR ($CDCl_3$) 6.10 (s, 1H), 7.10 (m, 1H), 7.20 (m, 4H), 7.50 (m, 2H), 7.61 (m, 2H), 7.98 (m, 1H); ^{13}C NMR ($CDCl_3$) 65.60, 122.48, 122.96, 124.09, 124.92, 126.87, 128.32, 128.54, 128.83, 129.07, 131.08, 132.44, 137.57, 145.62, 167.50; MS (m/z) = 286 [M + H]. Anal. Calcd for $C_{20}H_{15}NO{\cdot}2H_2O$: C, 83.13; H, 5.37; N, 4.87. Found: C, 83.00; H, 5.33; N, 5.27.

2-Butyl-3-propyl-2,3-dihydroisoindol-1-one (9d): ^{1}H NMR ($CDCl_3$) 0.82 (m, 4H), 0.95 (t, 3H, J = 7.3 Hz), 1.08 (m, 1H), 1.37 (m, 2H), 1.60 (m, 2H), 1.93 (m, 2H), 3.08 (m, 1H), 4.02 (dt, 1H, J = 8.0, 13.9 Hz), 4.59 (t, 1H, J = 3.8 Hz), 7.46 (m, 3H), 7.83 (d, 1H, J = 7.4); ^{13}C NMR ($CDCl_3$) 13.72, 13.96, 15.67, 20.09, 30.38, 32.60, 39.36, 58.87, 121.90, 123.41, 127.85, 131.03, 132.76, 145.16, 168.36; MS (m/z) = 232 [M + H]. Anal. Calcd for $C_{15}H_{21}NO{\cdot}0.25H_2O$: C, 76.39; H, 9.19; N, 5.93. Found: C, 76.20; H, 8.82; N, 55.95.

Addition of the *N*-Methylbenzamide Dianion 6 to Imine 7d in the Presence of $BF_3{\cdot}OEt_2$. A solution of **6** was prepared as described above using *N*-methylbenzamide (0.36 g, 2.6 mmol) and BuLi (2.26 mL of a 2.40 M solution in hexanes, 5.46 mmol) in THF (8 mL). The solution was cooled to −78 °C. In a separate flask, **7d** (0.34 mL, 2.0 mmol) was dissolved in THF (1 mL) and cooled to −25 °C. $BF_3{\cdot}OEt_2$ (0.24 mL, 2.0 mmol) was then added dropwise to the solution of **7d**. After being stirred for 5 min, the solution containing **7d** and $BF_3{\cdot}OEt_2$ was added, by cannula, to the −78 °C solution of **6**. The reaction mixture was stirred at −78 °C for 1 h and then was allowed to warm slowly to ambient temperature. After the mixture was stirred for 1 h at ambient temperature, water was added. The mixture was extracted three times with diethyl ether. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The resulting gum was heated in an oil bath at 150 °C for 1 h. After being cooled to ambient temperature, the crude product was purified by flash chromatography using ethyl acetate:hexanes (1:3) to afford **9d** as an oil, 0.183 g (0.79 mmol, 40%).

General Procedure for Imine Isoindolone Annulation Using Methyl *o*- Iodobenzoate, $BF_3{\cdot}OEt_2$, and Phenyllithium. To a −78 °C solution of the imine (1 mmol equiv) and methyl *o*-iodobenzoate (1.1 mmol equiv) in THF (3.5 mL/mmol of imine) was added dropwise $BF_3{\cdot}OEt_2$ (1.1 mmol equiv). The internal temperature was maintained below −73 °C during the addition of the $BF_3{\cdot}OEt_2$. Following the addition, the reaction was then cooled to −105 °C ± 3 °C using a methanol:ethanol (1:1) bath with liquid nitrogen as the coolant. A solution of phenyllithium (1.3 mmol equiv, typically 1.8−1.9 M in diethyl ether/cyclohexane) was diluted in THF (25% of the volume of phenyllithium used). This solution was then added dropwise to the reaction mixture while the temperature was maintained at −105 °C. (Note: The dilution of the phenyllithium with THF is necessary to prevent precipitation of the phenyllithium during the addition) Following the addition of the phenyllithium, the reaction was cooled to −110 ± 3 °C and stirred for 1 h. The cooling bath was removed, and the reaction was placed in a dryice/acetone bath (ca. −78 °C). After being stirred at −78 °C for 1 h, the cooling bath was removed and the reaction again allowed to warm. Upon reaching −25 to −30 °C, internal temperature, water was added. The reaction mixture was allowed to warm to ambient temperature, after which it was placed in a heating bath. The reaction mixture was heated overnight (15−18 h) at 45−50 °C. After the mixture was cooled to ambient temperature, the pH was adjusted to 2−3, if necessary. The mixture was extracted several times with diethyl ether or ethyl acetate. The combined extracts were dried (Na_2SO_4 and then $MgSO_4$), filtered, and concentrated. Products were typically purified by flash chromatography or recrystallization. Physical and spectroscopic data for the additional isoindolones listed in Table 2 are given below.

2-Benzyl-3-cyclohexyl-2,3-dihydroisoindol-1-one (9e): mp 163−164.5 °C; ^{1}H NMR ($CDCl_3$) 0.42 (m, 1H), 1.06 (m, 2H), 1.26 (m, 2H), 1.43 (m, 2H), 1.68 (m, 2H), 2.03 (m, 1H), 4.20 (d, 1H, J = 15.2 Hz), 4.26 (d, 1H, J = 3.1 Hz), 5.40 (d, 1H, J = 15.2 Hz), 7.35 (m, 5H), 7.45 (m, 3H), 7.90 (d, 1H, J = 6.45 Hz); ^{13}C NMR ($CDCl_3$) 25.76, 25.95, 26.35, 26.90, 29.69, 39.38, 43.98, 63.57, 123.27, 123.77, 127.46, 127.93, 128.06, 128.66, 128.90, 130.92, 132.82, 137.17, 144.09, 168.68; MS (m/z) = 306 [M + H]. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.85. Found: C, 82.11; H, 7.53; N, 5.14.

2-Propyl-3-(2-furyl)-2,3-dihydroisoindol-1-one (9f): mp 101−102 °C; ^{1}H NMR ($CDCl_3$) 0.90 (t, 3H, J = 7.40 Hz), 1.57 (m, 2H), 3.08 (m, 1H), 3.8 (dt, 1H, J = 7.4, 12.2 Hz), 5.60 (s, 1H), 6.31 (d, 1H, J = 3.2 Hz), 6.37 (dd, 1H, J = 3.2, 1.6 Hz), 7.35 (m, 1H), 7.47 (d, 1H, J = 1.6 Hz), 7.50 (m, 2H), 7.88 (m, 1H); ^{13}C NMR ($CDCl_3$) 11.29, 21.47, 42.27, 57.80, 109.33, 110.50, 122.84, 123.62, 128.67, 131.51, 132.28, 142.85, 143.33; MS (m/z) = 242 [M + H]. Anal. Calcd for $C_{15}H_{15}NO_2{\cdot}H_2O$: C, 74.39; H, 6.28; N, 5.78. Found: C, 74.33; H, 6.28; N, 5.72.

2-Butyl-3-propyl-4-methyl-2,3-dihydroisoindol-1-one (11a): ^{1}H NMR ($CDCl_3$) 0.60 (m, 1H), 0.77 (t, 3H, J = 7.0 Hz), 0.87 (m, 1H), 0.95 (t, 3H, J = 7.4 Hz), 1.37 (m, 2H), 1.62 (m, 2H), 2.04 (m, 2H), 2.41 (s, 3H), 3.05 (m, 1H), 4.05 (dt, 1H, J = 8.2, 13.9 Hz), 4.66 (t, 1H, J = 3.5 Hz), 7.26−7.37 (m, 2H), 7.67 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) 13.84, 13.97, 14.94, 18.46, 20.21, 30.17, 30.39, 39.14, 58.69, 121.11, 128.11, 132.13, 132.71, 133.19, 143.00, 168.66; MS (m/z) = 246 [M + H]. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.94; H, 9.29; N, 5.84.

2-Butyl-3-propyl-5-chloro-2,3-dihydroisoindol-1-one (11b): ^{1}H NMR ($CDCl_3$) 0.85 (m, 4H), 0.95 (t, 3H, J = 7.4 Hz), 1.09 (m, 1H), 1.36 (m, 2H), 1.60 (m, 2H), 1.93 (m, 2H), 3.08

(m, 1H), 4.0 (dt, 1H, J = 8.3, 14.2 Hz), 4.58 (t, 1H, J = 4.4 Hz), 7.40 (s, 1H), 7.42 (d, 2H, J = 7.7 Hz), 7.75 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) 13.71, 13.92, 15.71, 20.10, 30.32, 32.52, 39.51, 58.62, 122.41, 124.67, 128.50, 131.36, 137.42, 146.82, 167.30; MS (m/z) = 266 [M + H]. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.55; H, 7.48; N, 5.31.

2-Butyl-3-propyl-5-carbomethoxy-2,3-dihydroisoindol-1-one (11c): mp 62−64 °C; ^{1}H NMR ($CDCl_3$) 0.85 (m, 4H), 0.96 (t, 3H, J = 7.3 Hz), 1.08 (m, 1H), 1.38 (m, 2H), 1.62 (m, 2H), 1.98 (m, 1H), 3.11 (m, 1H), 3.96 (s, 3H), 4.03 (dt, 1H, J = 8.3, 14 Hz), 4.65 (t, 1H, J = 4.3 Hz), 7.88 (d, 1H, J = 7.8 Hz), 8.10 (s, 1H), 8.15 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) 13.72, 13.92, 15.70, 20.13, 30.32, 32.44, 39.64, 52.43, 59.00, 123.33, 123.45, 129.47, 132.60, 136.83, 145.11, 166.60, 167.30; MS (m/z) = 290 [M + H]. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.53; H, 8.01; N, 4.98.

2-Butyl-3-propyl-6-methyl-2,3-dihydroisoindol-1-one (11d): ^{1}H NMR ($CDCl_3$) 0.85 (m, 4H), 0.94 (t, 3H, J = 7.4 Hz), 1.08 (m, 1H), 1.36 (m, 2H), 1.60 (m, 2H), 1.90 (m, 2H), 2.43 (s, 3H), 3.07 (m, 1H), 4.01 (dt, 1H, J = 8.2, 13.9 Hz), 4.55 (t, 1H, J = 3.7 Hz), 7.27−7.34 (m, 2H), 7.63 (d, 1H); ^{13}C NMR ($CDCl_3$) 13.77, 14.01, 15.77, 20.15, 21.27, 30.44, 32.77, 39.39, 58.70, 121.69, 123.71, 132.01, 133.00, 137.87, 142.45, 168.48; MS (m/z) = 246 [M + H]. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.96; H, 9.48; N, 5.76.

2-Butyl-3-propyl-6-bromo-2,3-dihydroisoindol-1-one (11e): ^{1}H NMR ($CDCl_3$) 0.84 (m, 4H), 0.95 (t, 3H, J = 7.5 Hz), 1.08 (m, 1H), 1.36 (m, 2H), 1.61 (m, 2H), 1.92 (m, 2H), 3.08 (m, 1H), 4.00 (dt, 1H, J = 8.0, 13.9 Hz), 4.56 (t, 1H, J = 3.7 Hz), 7.29 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.76, 13.97, 15.70, 20.13, 30.35, 32.45, 39.57, 58.75, 122.00, 123.61, 126.69, 134.04, 134.91, 143.84, 166.90; MS (m/z) = 310, 312 [M + H]. Anal. Calcd for $C_{15}H_{20}NO$: C, 58.07; H, 6.50; N, 4.51. Found: C, 57.76; H, 6.47; N, 4.60.

2-Butyl-3-propyl-5,6-dimethoxy-2,3-dihydroisoindol-1-one (11f): ^{1}H NMR ($CDCl_3$) 0.85 (m, 4H), 0.95 (t, 3H, J = 7.3 Hz), 1.07 (m, 1H), 1.36 (m, 2H), 1.60 (m, 2H), 1.90 (m, 2H), 3.06 (m, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 3.99 (m, 1H), 4.52 (t, 1H, J = 4.2 Hz), 6.86 (s, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.72, 13.98, 15.53, 20.06, 30.15, 32.68, 39.41, 56.10, 56.16, 58.46, 104.16, 105.08, 125.12, 138.58, 149.43, 152.20, 168.55; MS (m/z) = 292 [M + H]. Anal. Calcd for $C_{17}H_{25}NO_3 \cdot 0.15H_2O$: C, 69.43; H, 8.67; N, 4.76. Found: C, 69.46; H, 8.64; N, 4.90.

(*S*)-(−)-2-(3,4-Dichlorophenyl)-4-pentenal (13). A magnetically stirred solution of (*S*)-(−)-2-(3,4-dichlorophenyl)-4-pentenoic acid (**12**) (30.4 g, 124 mmol)[17] in methylene chloride (375 mL) was cooled in an ice bath and treated with oxalyl chloride (13 mL, 149 mmol) in one portion, followed by the addition of DMF (1 mL), also in one portion. The mixture was stirred in the ice bath for an additional 10 min. The cooling bath was removed and the mixture allowed to stir at ambient temperature overnight. The solvent was then removed, without heating, on the rotary evaporator. The residue was dissolved in anhydrous diglyme (375 mL) and added to a round-bottom flask equipped with a mechanical stirrer and a 500 mL dropping funnel. The solution of the acid chloride was cooled to −78 °C. The dropping funnel was charged with lithium tri-*tert*-butoxyaluminohydride (262 mL, 0.49 M solution in diglyme, 0.128 mol). The hydride solution was added to the rapidly stirring acid chloride solution at such a rate that the temperature was kept mostly below −72 °C. The addition took 75 min. When the addition was complete the reaction mixture was stirred at −78 °C for an additional 45 min and then poured into a 4 L beaker containing a mechanically stirred mixture of ice (1200 g), hexane (1200 mL), and a solution of L-tartaric acid (39 g, 0.26 mol) in water (100 mL). This mixture was stirred for 10 min. The aqueous phase was separated and extracted with additional hexane. The combined hexane extracts were washed with ice−water (3 × 1 L) and saturated brine solution (200 mL) and dried (Na_2SO_4). After 10 min a portion of the mixture was filtered and the volatiles removed by rotary evaporation with no heat applied to the bath. The unfiltered portion of the hexane solution was cooled on ice to slow decomposition of the crude aldehyde until filtered. When all the hexane had been removed, the residual oil was set under high vacuum for 30 min. There was obtained 27.5 g (97%) of **13** as a pale yellow oil. Aldehyde **13** was stored under argon at −78 °C (on dry ice): ^{1}H NMR ($CDCl_3$) 2.47 (m, 1H), 2.83 (m, 1H), 3.60 (m, 1H), 5.02−5.09 (m, 2H), 5.68 (m, 1H), 7.04 (dd, 1H, J = 2.2, 8.2 Hz), 7.30 (d, 1H, J = 2.2 Hz), 7.45 (d, 1H, J = 8.2 Hz), 9.67 (d, 1H, J = 1.6); MS (m/z) = 229 (80/231 (53) [M + H].

[(*S*)-(−)-2-(3,4-Dichlorophenyl)-4-pentenyliden]ethylamine (14). To a solution of dibutyltin dichloride (1.94 g, 6.39 mmol) in methylene chloride (100 mL) was added Na_2SO_4 (55 g, anhydrous). The stirred mixture was cooled in an ice bath, and a solution containing freshly-prepared (*S*)-(−)-2-(3,4-dichlorophenyl)-4-pentenal (**13**) (28.39 g, 123.9 mmol) in dry methylene chloride (50 mL) was added. Additional methylene chloride (2 × 25 mL) was used to wash in residual aldehyde. The mixture was stirred for 5 min, and then a solution containing ethylamine (32.0 mL, 4.06 M in methylene chloride, 129.9 mmol) was slowly added. The slightly-yellowish mixture was stirred for 75 min and then cooled to −78 °C. After the mixture was stirred for 5 min at −78 °C, the mixture was filtered through an in-line glass frit to remove Na_2SO_4 while maintaining strictly anhydrous conditions. The solids were washed with additional dry methylene chloride (100 mL total, in portions). The combined filtrates and washings were concentrated without external heating. The remaining residue was placed under high vacuum (∼100 mTorr) until a stable pressure reading was obtained (5−10 min). The recovered viscous liquid residue weighed 33.1 g (or 31.2 g, 98%, after the weight of Bu_2SnCl_2 was subtracted). The material was used immediately or was cooled (−78 °C) and stored under an argon atmosphere until needed: ^{1}H NMR ($CDCl_3$) 1.12 (t, 3H, J = 7.1 Hz), 2.43 (m, 1H), 2.62 (m, 1H), 3.35 (dt, 2H, J = 5.3,7.1 Hz), 3.43 (m, 1H), 4.91−4.97 (m, 2H), 5.61 (m, 1H), 6.98 (dd, 1H, J = 2.1,8.3 Hz), 7.23 (d, 1H, J = 2.1 Hz), 7.32 (d, 1H, J = 8.3 Hz), 7.57 (d, 1H, J = 5.3 Hz); MS (m/z) = 256 (100)/258 (65) [M + H].

(3*R*)-3-[(1*S*)-1-(3,4-Dichlorophenyl)-3-butenyl]-2-ethyl-2,3-dihydroisoindol-1-one (15). A flask was charged with THF (200 mL) and then cooled to −78 °C. A solution containing freshly-prepared imine **14** (31.2 g, 122 mmol) in dry THF (50 mL) was rapidly added and washed in with additional THF (2 × 25 mL). Methyl *o*-iodobenzoate (19.9 mL, 35.0 g, 133.7 mmol) was added, and the solution was allowed to reequilibrate to −78 °C (internal temperature). $BF_3 \cdot OEt_2$ (16.5 mL, 19.0 g, 134 mmol) was added dropwise, while the internal temperature was maintained below −75 °C. The solution was then cooled to −105 ± 3 °C. Phenyllithium (69.8 mL, 1.92 M in diethyl ether/hexanes, 134 mmol) was then added dropwise over approximately 1 h, during which the internal temperature was maintained between −103 and −106 °C. When the addition was completed, the reaction was cooled to approximately −110 °C and maintained between −110 and −113 °C for 1 h. The low-temperature cooling bath was then replaced with a dry ice−acetone bath, and the reaction was stirred for an additional 1 h. The cooling bath was then removed and the reaction allowed to warm. When the internal temperature reached −25 to −30 °C, ice−water (250 mL) was added. The mixture was allowed to warm slowly to ambient temperature, after which time it was heated at 55−60 °C, with stirring, for 16 h. The mixture was allowed to cool to ambient temperature. The pH of the mixture was adjusted (to pH ∼ 2) with 6 N aqueous hydrochloric acid (∼10 mL) after which diethyl ether (200 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 150 mL). The organic extracts were combined, stirred over anhydrous Na_2SO_4 for 10 min, and then stirred with added anhydrous $MgSO_4$ for an additional 10 min. After standing briefly the combined Na_2SO_4−$MgSO_4$ solids were removed by filtration and washed with additional diethyl ether. The filtrates and washings were combined and concentrated. The red-orange, oily residue (75.2 g) was dissolved in a minimum amount of methylene chloride and then applied to a chromatography column (500 g of silica gel 60) in 3:1 hexane−ethyl acetate. The column was eluted with hexane:

ethyl acetate (3:1). The fractions containing the *syn*-**15** and *anti*-**16** isoindolone diastereoisomers were combined and concentrated. The residue was placed under high vacuum (warming occasionally) until residual solvent was completely removed. The recovered material weighed 30.4 g (69% of theory). Evaluation by HPLC indicated that the ratio of *syn*-**15** to *anti*-**16** diastereoisomers was approximately 18:1. The *syn*-**15** diastereoisomer consisted of >97% of the desired *S*,*R* enantiomer (ca. 94% ee). The material was dissolved in hot methyl *tert*-butyl ether (~90 mL), diluted with an equal volume of hexanes, and briefly reheated to boiling. The solution was stirred and allowed to cool to room temperature. When cool, several "seed" crystals were added, and the mixture was stirred at room temperature overnight. The solid was recovered by suction filtration and was washed twice with hexanes:methyl *tert*-butyl ether (10:1). The recovered solid, mp 77−78 °C, weighed 20.2 g (46%). Reprocessing the mother liquors returned an additional 2.50 g (5.7%) of solid, mp 77−79 °C. The mother liquors (from second crop) were concentrated and rechromatographed using 5%−10% 2-propanol/hexane as the eluent. Fractions containing the lower R_f diastereoisomer were combined and concentrated. The residue was recrystallized (as previously noted) to return an additional 1.10 g (2.5%) of white solid, mp 77−79 °C. Evaluation by HPLC indicated that the recovered solid **15** was >99.6% chemically pure and essentially a single enantiomer (99.4% ee). Total recovery was 23.8 g or 54.2% of theory from acid **12**: TLC, $R_f = 0.20$ (silica, 5:95, 2-propanol:hexane); ^{1}H NMR ($CDCl_3$) 1.20 (t, 3H, J = 7.3 Hz), 2.75 (m, 2H), 3.15 (m, 1H), 3.40 (m, 1H), 4.16 (m, 1H), 4.83 (d, 1H, $J = 3.7$ Hz), 5.10−5.20 (m, 2H), 5.76 (m, 1H), 6.50 (dd, 1H, $J = 2.2$, 8.3 Hz), 6.76 (d, 1H, $J = 2.2$ Hz), 7.09 (d, 1H, $J = 8.3$ Hz), 7.44−7.58 (m, 2H), 7.65 (d, 1H, $J = 7.5$ Hz), 7.70 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) 13.21, 34.66, 35.67, 45.59, 61.24, 117.93, 122.91, 123.75, 127.40, 128.50, 129.63, 130.0, 130.85, 130.89, 131.71, 133.26, 134.90, 137.90, 142.49, 167.61; MS (m/z) = 360 (100)/362 (65) [M + H]; $[\alpha]^{25}_D = +84.4°$ ($c = 1.54 \times 10^{-3}$ g/mL, ethanol). Anal. Calcd for $C_{20}H_{19}Cl_2NO$: C, 66.68; H, 5.32; N, 3.89. Found: C, 66.60; H, 5.41; N, 3.89.

The mother liquors from the first recrystallization were concentrated and chromatographed on silica gel using 2-propanol:hexane (5:95) as the eluent. An analytical sample of the minor diastereomer **(3*S*)-3-[(1*S*)-1-(3,4-dichlorophenyl)-3-butenyl]-2-ethyl-2,3-dihydroisoindol-1-one (16)** was obtained (no yield): TLC, R_f = 0.25 (silica, 5:95/2-propanol:hexane); ^{1}H NMR ($CDCl_3$) 1.36 (t, 3H, $J = 7.2$ Hz), 1.93−2.04 (m, 2H), 3.51 (m, 1H), 4.20 (m, 1H), 4.75 (d, 1H, $J = 3.5$ Hz), 4.90−4.96 (m, 2H), 5.58 (m, 1H), 6.69 (d, 1H, $J = 7.5$ Hz), 7.12 (dd, 1H, J= 8.4, 2.1 Hz), 7.35−7.50 (m, 4H), 7.82 (m, 1H); MS (m/z) = 360 (100)/362 (68) [M + H].

HPLC analysis of the diastereomers was conducted on a Chiracel OD column eluting with 2-propanol:hexane (1:9) at a flow rate of 0.5 mL/min (detector wavelength, 254 nm). Using these conditions, the retention time was 19.8 min for the *R*,*S* enantiomer and 24.1 min for the *S*,*R* enantiomer. The retention time for the *anti* diastereoisomers was 17.4 min (enantiomers not resolved).

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Supporting Information Available: The experimental data for the sample preparation, X-ray diffraction, collection, and solution of the structure of isoindolone **15** are presented (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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