[a008]

Université des **S**ciences et **T**echnologies de **L**ille		**UMR CNRS 8009 COM** **S**ynthèse **O**rganique, **R**éactivité, **F**onctionnalisation

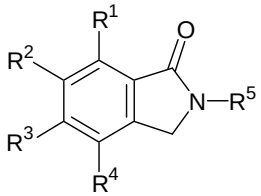
A Versatile Method for the Elaboration of Diversely Substituted *N*-Alkylated and Free-NH Isoindolinones. Application to the Asymmetric Synthesis of the C3-Substituted Models

Axel Couture,* Eric Deniau, Magali Lorion, Marc Lamblin, Pierre Grandclaudon,

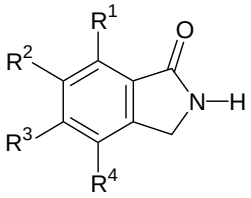
UMR 8009 "Chimie Organique et Macromoléculaire", associée à l'ENSCL,
Laboratoire de Chimie Organique Physique,
Bâtiment C3(2), Université des Sciences et Technologies de Lille 1,
F-59655 Villeneuve d'Ascq Cédex, France
**Axel.Couture@univ-lille1.fr*

Introduction

Isoindolinones and their derivatives of generic structure **1, 2** have gained considerable attention due to their diverse physiological and chemotherapeutic activities [1] and for their importance as key intermediates for the construction of various drugs, biologically active compounds [2] and naturally occurring alkaloids [3].

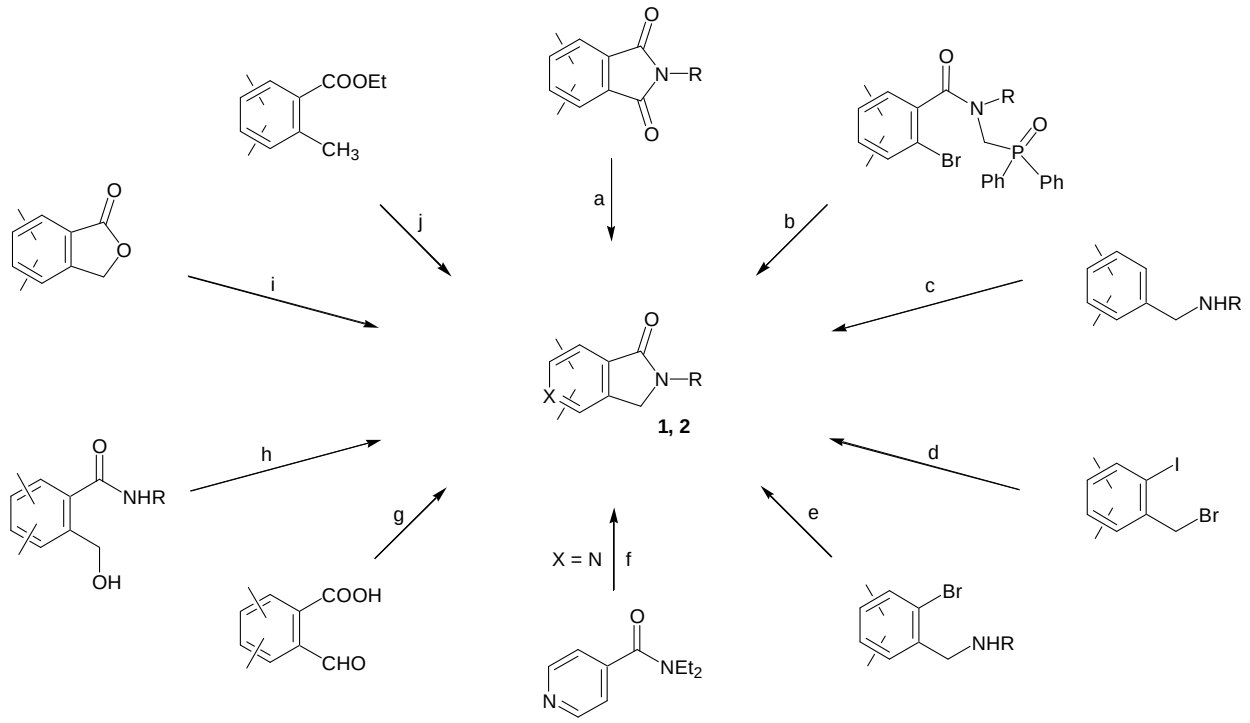


1



2

The most common synthetic routes to these benzolactams are portrayed in Scheme 1. They are generally of procedural simplicity and proceed in satisfactory yields but the reported methods suffer from several drawbacks and particularly from restrictions in the choice of substituents in their nature, their number and their specific position on the basic aromatic nucleus. Furthermore the elaboration of free-NH models **2** requires an additional and somewhat erratic deprotection step [4].



Entry	Reagents and Conditions	Ref.
a	Zn , AcOH , reflux	[5]
b	KHMDS , -78 ℃ to rt , then H_2O , OH^- , reflux	[6]
c	$Pd(OAc)_2$ – $Cu(OAc)_2$, air , CO (1 atm) , toluene , reflux	[7]
d	Pd Cys , CO (1 atm) , RNH_2 , K_2CO_3 , DMF	[8]
e	PPh_3 , *n*-Bu_3N , CO (1 atm)	[9]
f	LTMP , RCH_2CN , aq. NH_4Cl	[10]
g	RNH_2 , AcOH, reflux	[11]
h	*i*PrMgCl , DMI , Cl-P(O)$(NMe_2)_2$	[12]
i	RNH_2 , reflux	[13]
j	NBS , AIBN , CCl_4 , then RNH_2 , MeOH	[14]

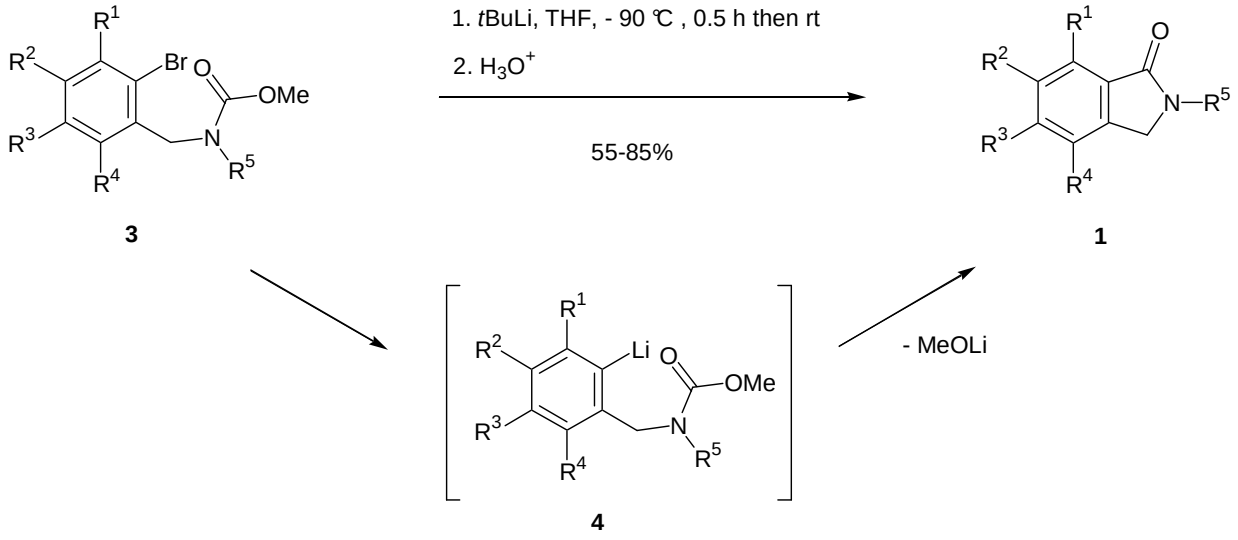
Scheme 1. Synthetic Routes to *N*-alkylated isoindolin-1-ones **1**, **2**.

Results and Discussion

A new synthetic approach to these bicyclic lactams **1, 2** that is based on the Parham cyclization protocol [15], *i.e.* creation of an aryllithiated species by halogen/metal exchange and subsequent trapping by an internal electrophile, has then been developed.

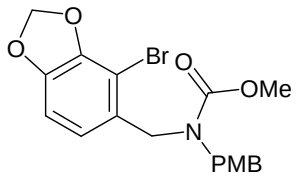
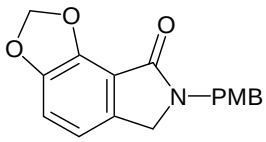
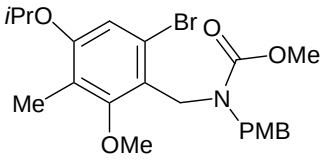
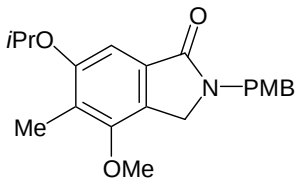
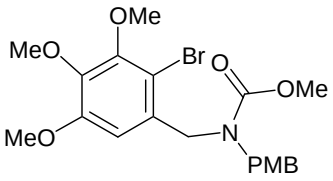
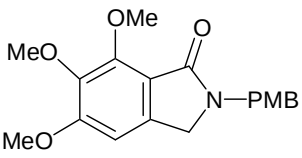
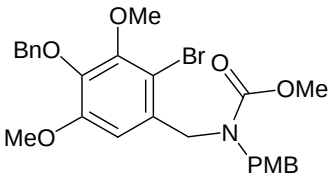
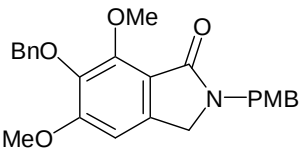
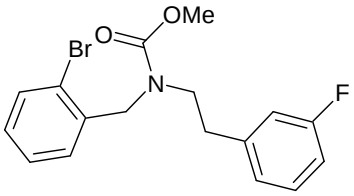
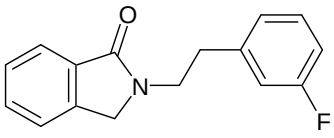
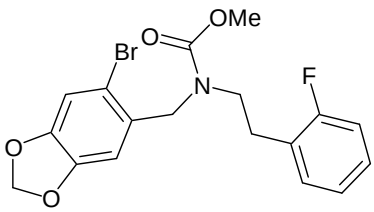
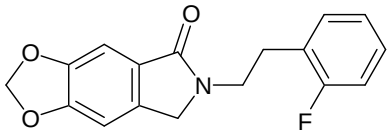
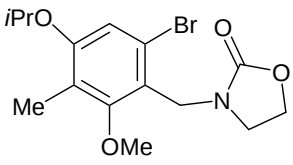
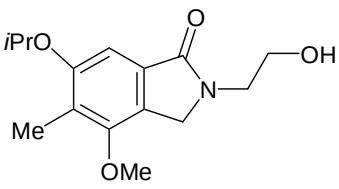
1. Synthesis of the N*-alkylated isoindolin-1-ones* (1)

For the assembly of the *N*-substituted models **1** a variety of poly and diversely substituted *N*-alkyl-halobenzylcarbamates **3a-g** were initially synthesized and subsequently exposed to *t*BuLi at –90 °C followed by gentle warming to rt. This technique ensured the optimal formation of the transient aryllithiated species **4** (Scheme 2). With the carbamate function acting as the internal electrophile the targeted annulated compounds **1a-f** were solely obtained with very satisfactory yields (Table 1). The method tolerates the presence of fluorinated substituents that survive the halogen/metal interconversion reaction (Table 1, entries 5, 6). This process can also be applied to model compound where the carbamate function is embedded in an oxazolinone ring system, e.g. **3g**, as exemplified by the assembling of the benzolactam **1g** equipped with an hydroxyalkyl chain which may serve as a handle for further synthetic development (Table 1, entry 7).



Scheme 2.

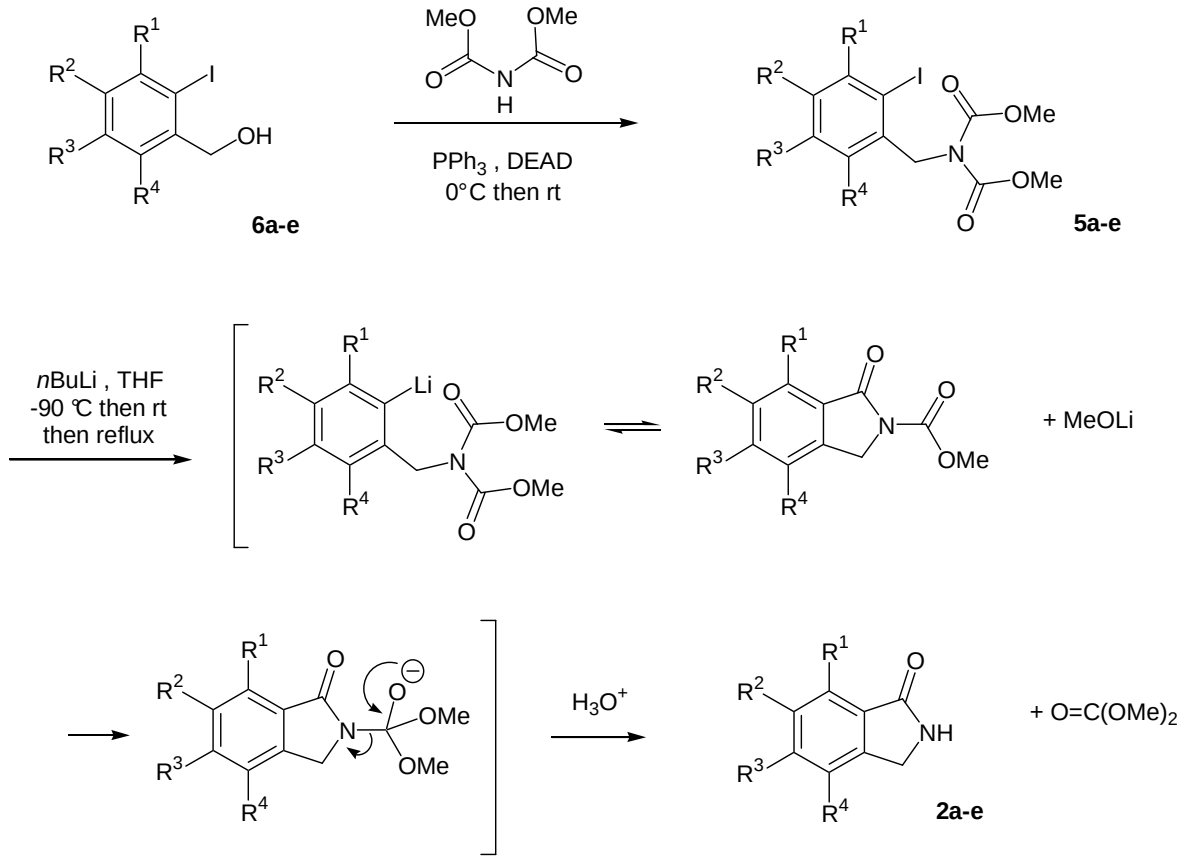
Table 1. Isoindolin-1-ones **1** Prepared

Entry	Carbamate **3**		Product **1**		Yield (%)	Ref.
1		**3a**[a]		**1a**[a]	63	[16]
2		**3b**[a]		**1b**[a]	55	[17]
3		**3c**[a]		**1c**[a]	85	[18]
4		**3d**[a]		**1d**[a]	82	[18]
5		**3e**		**1e**	70	[18]
6		**3f**		**1f**	69	[19]
7		**3g**		**1g**	69	[20]

[a] PMB = *para*-methoxybenzyl

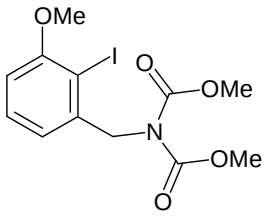
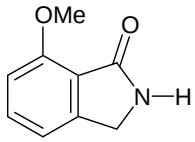
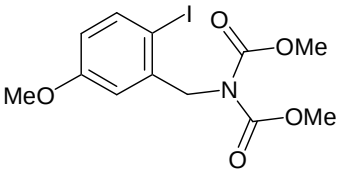
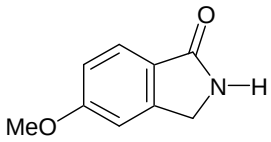
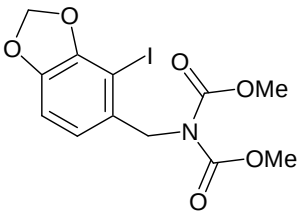
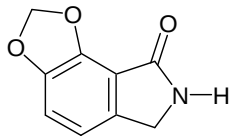
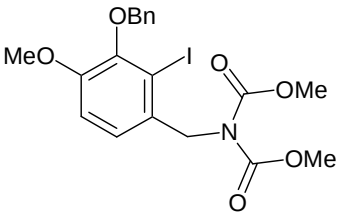
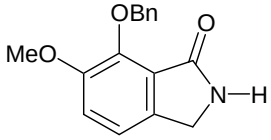
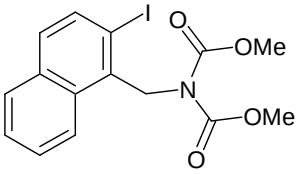
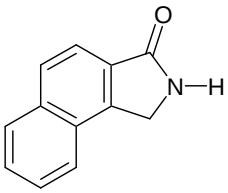
*2. Synthesis of the free-*NH *isoindolin-1-ones* (2)

Since an alkoxide species was released upon the anionic cyclization of carbamate **3a-g** (see Scheme 2) we reasoned that incorporation in the annulated compounds **1** of a temporary protecting group R^5 highly sensitive to nucleophile attacks would conceivably deliver the free-NH models **2** (R^5 = H) in a straightforward manner. The choice of the alkoxycarbonyl group (R^5 = COOMe) originated from the following premises: (i) the carbamate group is endowed with a remarkable propensity to react with basic and nucleophilic reagents, in particular with alkoxy moieties, inter and intramolecularly [21] and (ii) the presence of a symmetrical *N*-diacyl functionality in the parent models **5** should not alter the annulation process leading to the fused benzolactams **2**.
A range of iodinated benzyldicarbamates **5a-e** which are liable to favor halogen/metal interconversion upon treatment with organolithiated reagents while sparing the diacyl functionality were initially assembled by a Mitsonobu reaction between the benzylic alcohols **6a-e** and dimethyl iminodicarboxylate (Scheme 3). They were subsequently exposed to *n*BuLi at –90 ℃ followed by warming to rt and reflux ing for a short period. This protocol delivered a variety of free-NH annulated products **2a-e** (Table 2) upon acidic workup following the anticipated mechanistic pathway depicted in Scheme 3.



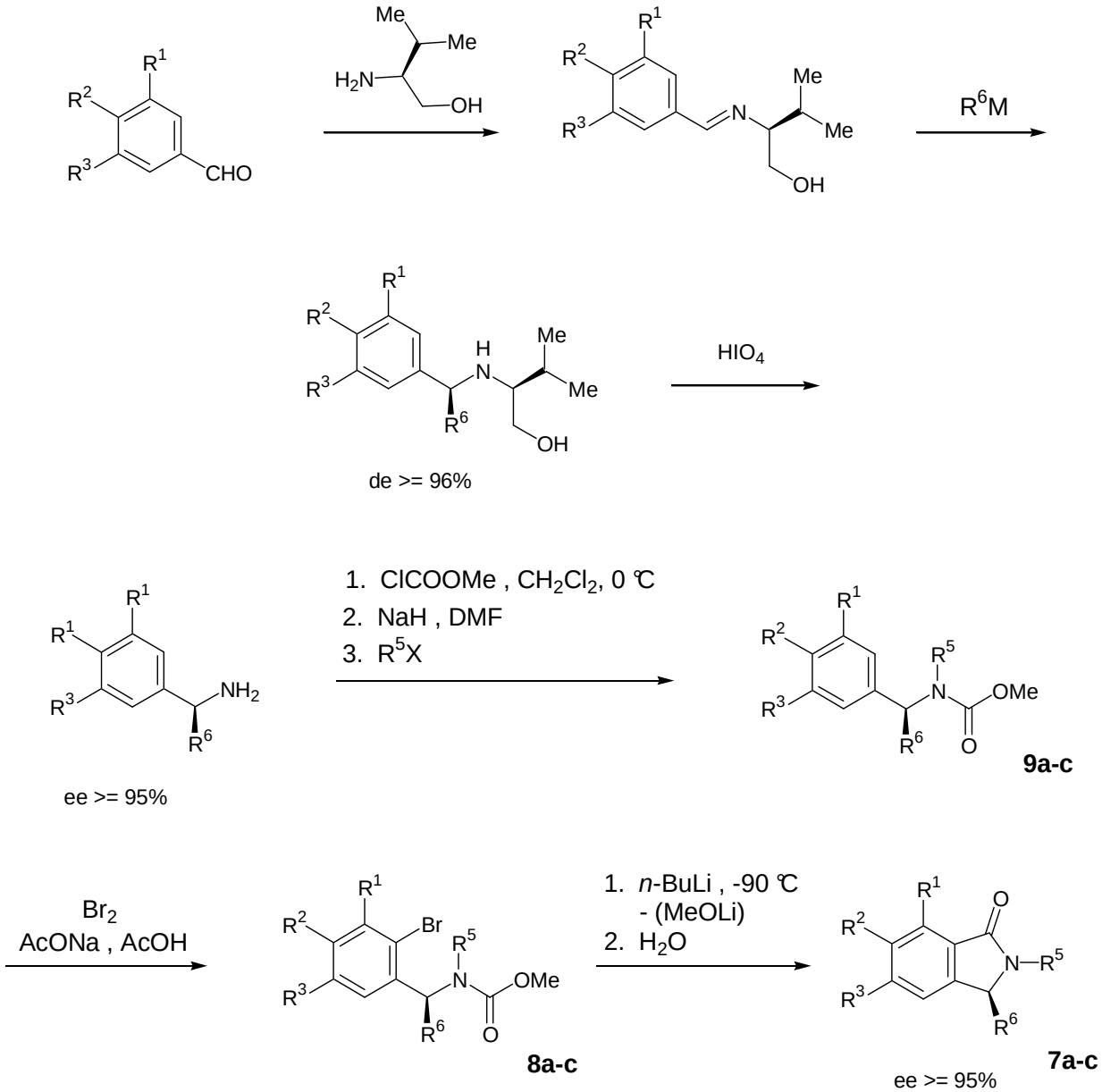
Scheme 3.

Table 2. Free-NH Isoindolin-1-ones **2** Prepared [22]

Entry	Dicarbamate **5**	Yield (%)	Product **2**	Yield (%)
1	 **5a**	71	 **2a**	55
2	 **5b**	69	 **2b**	51
3	 **5c**	81	 **2c**	52
4	 **5d**	79	 **2d**	64
5	 **5e**	76	 **2e**	65

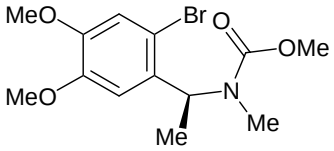
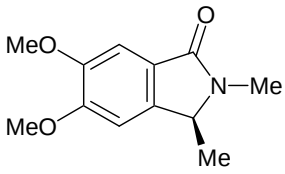
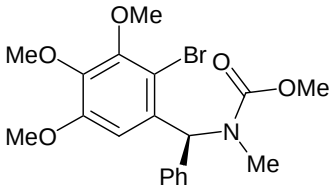
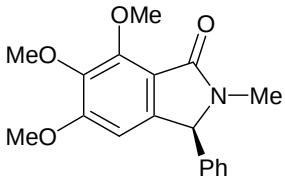
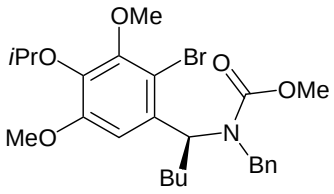
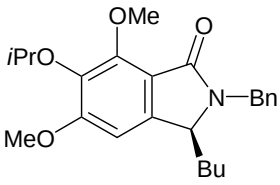
3. Application to the asymmetric synthesis of the C3-substituted isoindolin-1-ones (7a-c)

The key step of the synthetic approach is based upon the construction of the C3-substituted isoindolinone template by the Parham type cyclization of chiral haloarylcarbamates **8a-c** as depicted in Scheme 4 (Table 3). Noteworthy the alkoxy groups on the basic benzene nucleus were prone to force and facilitate the regioselective bromination of the opened carbamate **9a-c** and installation of the bromine atom at the in between site could be readily secured under standard conditions.



Scheme 4.

Table 3. Chiral C3-Substitued Isoindolin-1-ones **7** Prepared

Entry	Chiral carbamate **8**	Yield (%)	Product **7**	Yield (%)
1	 **8a**	73	 **7a**	76
2	 **8b**	82	 **7b**	72
3	 **8c**	78	 **7c**	74

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