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Diastereoselective addition of metalated isoindolin-1-ones to aldehydes. Stereoselective preparation of (*E*)-3-arylideneisoindolin-1-ones

Axel Couture,* Eric Deniau, Pierre Grandclaudon, Christophe Hoarau and Véronique Rys

Laboratoire de Chimie Organique Physique, UPRESA 8009, Université des Sciences et Technologies de Lille, F-59655 Villeneuve d'Ascq Cedex, France

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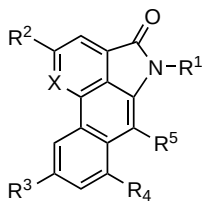
Abstract—Lithiated isoindolinones react with aromatic aldehydes to afford 3-hydroxybenzyl derivatives with high diastereoselectivity. Dehydration of *erythro* and *threo* adducts through an E1cb mechanism gives rise indiscriminately to the (*E*)-arylideneisoindolinones.

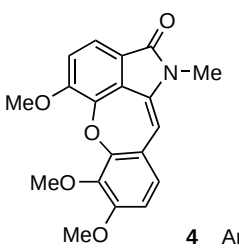
The 3-ylideneisoindolin-1-one ring system has featured in recent years as a desirable synthetic target in view of its presence in both natural products and synthetic pharmaceuticals with biological activity. This highly conjugated system is indeed present in a group of natural products as exemplified by aristolactam alkaloids[1] enterocarpam II **1**, velutinam **2** and eupolauramine **3**. It also represents the main structural subunit of architecturally sophisticated alkaloids like aristoyagonine **4** and fumaridine **5**. On the other hand, some phenolic derivatives **6** have been shown to possess inhibitory activity for thromboxan A_2 analogue (U-46619)-induced vasoconstriction.[2]



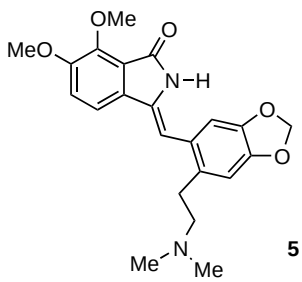
1 $R^1 = R^3 = R^5 = H$; $R^2 = OH$; $R^4 = OMe$; X = C-OMe Enterocarpam II

2 $R^1 = R^3 = R^5 = H$; $R^4 = OH$; $R^2 = OMe$; X = C-OMe Velutinam

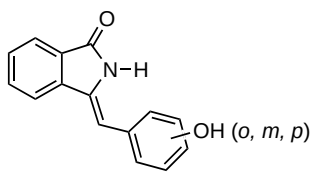
3 $R^1 =$ Me; $R^2 = R^3 = R^4 = H$; $R^5 = OMe$; X = N Eupolauramine



4 Aristoyagonine



5 Fumaridine



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Keywords: metalation; diastereoselection; stereochemistry; enamides.

* Corresponding author. Fax: +33 (0)3 20 33 63 09; e-mail: axel.couture@univ-lille1.fr

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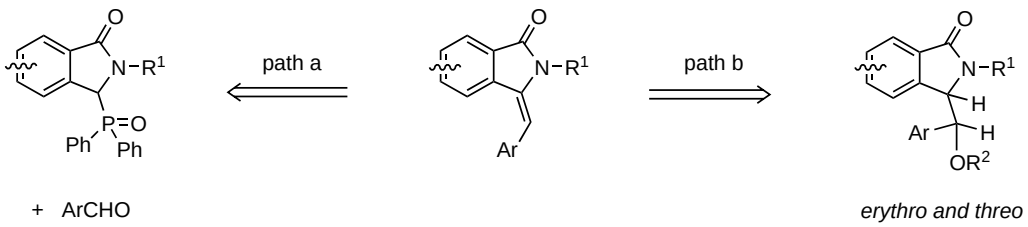
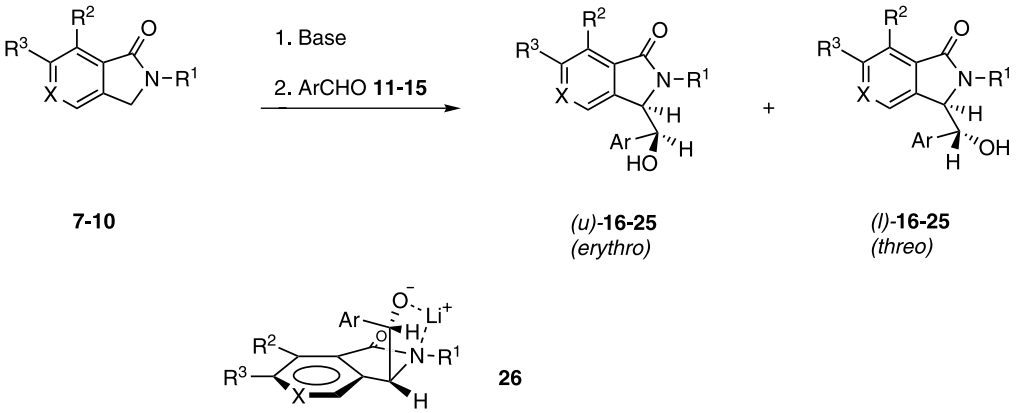
As a part of a program aimed at the synthesis of **1**–**5**[3,4] we were interested in the development of a stereoselective method for the preparation of (*Z*)- and (*E*)-3-arylideneisoindolin-1-ones in order to facilitate access to the above-mentioned natural products and synthetic bioactive compounds. In previous papers[3–5] we have observed that the configuration of the exocyclic double bond in models elaborated under the agency of the Horner process (Retrosynthetic Scheme 1, path a) was precisely governed by the presence of bulky substituent connected to the lactam nitrogen. In all cases variable mixtures of (*E*) and (*Z*) isomers were obtained. We then anticipated that isoindolinone benzylic deprotonation of *O*-substituted alcohol derivatives (Scheme 1, path b) through an E1cb mechanism could ensure the stereoselective formation of (*E*) and (*Z*) isomers. Consequently we embarked on a program aimed at the stereoselective synthesis of the parent *erythro* (*u*) and *threo* (*l*) alcohols[6] (Scheme 1, $R_2=H$). Synthetic methodology for C–C bond formation at the isoindolinone benzylic position has been dominated by procedures based on the nucleophilic interception of iminium ions,[7] while radical and carbanionic approaches have received far less attention.[8] We recently reported on the synthesis of a variety of 3-substituted isoindolinones by quenching with alkyl halides isoindolinones regioselectively metalated by weak nucleophilic metalating reagent sparing the lactam unit.[9] We therefore decided to adopt the same strategy for the installation of the hydroxybenzyl appendage.

For this purpose we examined the metalation of a variety of isoindolin-1-ones **7**–**10** with amidic bases differing by the metal counterion, and their subsequent reaction with a range of aromatic aldehydes **11**–**15** (Scheme 2, Table 1). All reactions were carried out in THF at −78°C. Dropwise addition of the base gave a deep orange solution of benzylic anions deriving from **7**–**10**, the colour of which was discharged on addition of the appropriate aromatic aldehydes **11**–**15**. A series of compounds which have been prepared by this method are presented in Table 1, where it may be seen that this simple procedure affords good yields of the hydroxybenzyl adducts **16**–**25**. It is worth noting that the reaction performed with sodium and potassium amidic bases gave invariably a mixture of *erythro* and *threo* isomers. The major diastereomer was shown to possess an (*u*)-configuration based on the ^1H NMR observed vicinal coupling constant $J_{3\text{-}1'}=2.7$ Hz (value given for **16**),[10–12] whereas $J_{3\text{-}1'}=4.2$ Hz for the minor diastereomer with (*l*)-configuration. Furthermore, the relative configuration of the major isomers was determined unequivocally by X-ray crystallography.[13] The highest diastereoselectivity was obtained with lithiated base LHMDS (Table 1). Interestingly it has been shown that addition of aromatic aldehydes to related metalated species such as lithiated tetrahydroisoquinoline pivalamide[11] and isoquinolyloxazoline[12] gave a mixture of both *erythro* and *threo* isomers, whereas the majority formation of the *erythro* isomer required transmetalation with magnesium bromide prior to addition. We did not find the same trend with lithiated isoindolinones since whatever the structure of the parent models and the aromatic carboxaldehyde derivatives, the *erythro* adducts were always predominant by a large margin. These were easily obtained in pure form (>99%) by simple recrystallization from ethanol. Replacement of the *N*-methyl



Scheme 1.



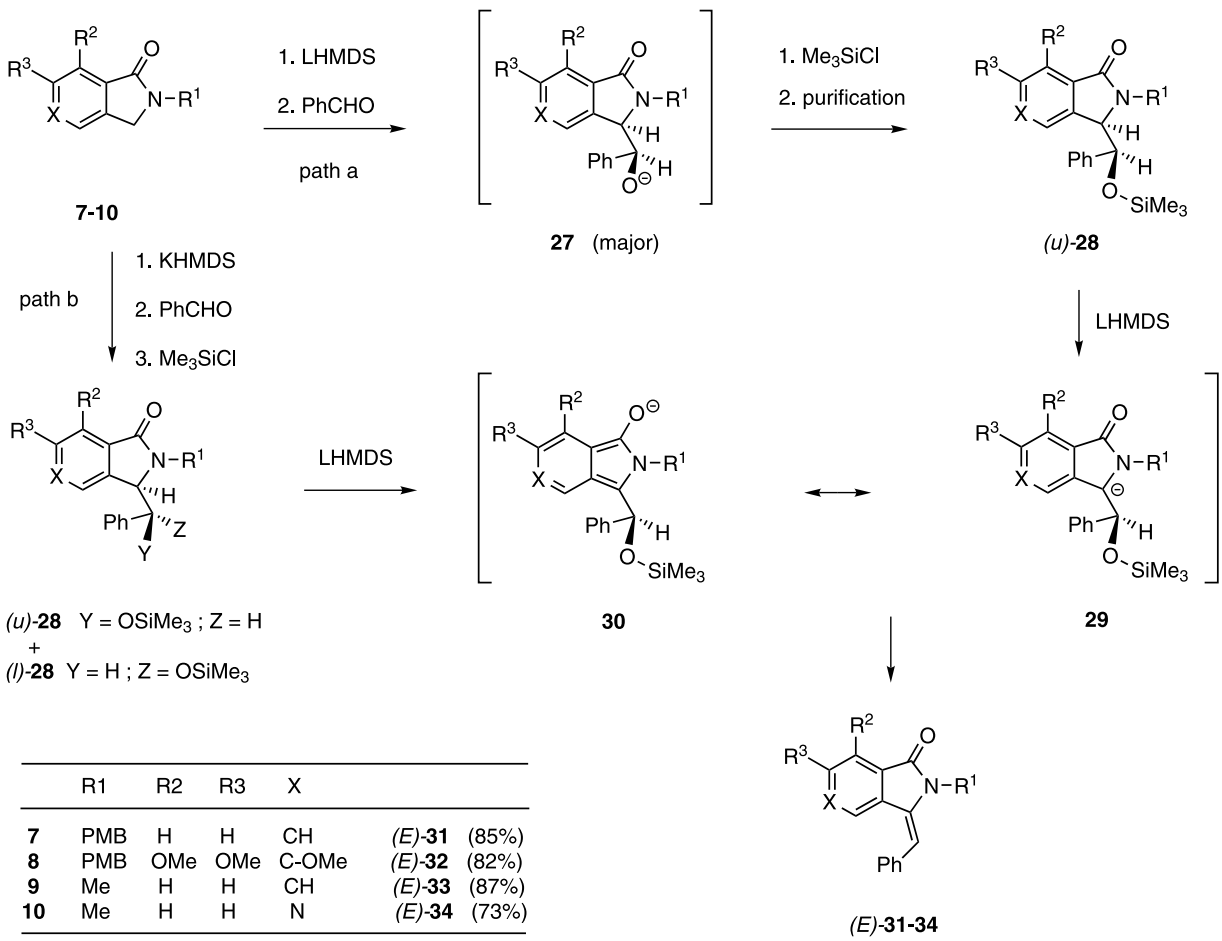
Scheme 2.

Table 1. Ratio of diastereomers produced by reaction of metalated **7–10** with **11–15**

Entry	Compounds **7–10**					Aldehydes **11–15** (ArCHO)			Diastereomeric ratio *erythro*:*threo* (yield %)		
		R^1	R^2	R^3	X		Ar		KHMDS[a]	NaHMDS[b]	LHMDS[c]
1	**7**	PMB[d]	H	H	CH	**11**	C_6H_5	**16**	55:45 (88)	50:50 (80)	90:10 (82)
2	″	″	″	″	″	**12**	1-Naphthyl	**17**	55:45 (83)		85:15 (78)
3	″	″	″	″	″	**13**	3,4,5-Trimethoxy-C_6H_2	**18**	80:20 (91)		85:15 (74)
4	″	″	″	″	″	**14**	2,3,4-Trimethoxy-C_6H_2	**19**	45:55 (76)		65:35 (71)
5	**8**	″	OMe	OMe	COMe	**11**	C_6H_5	**20**	75:25 (88)		65:35 (78)
6	**9**	Me	H	H	CH	**11**	″	**21**	50:50 (92)	65:35 (83)	90:10 (90)
7	″	″	″	″	″	**12**	1-Naphthyl	**22**	50:50 (89)		90:10 (82)
8	″	″	″	″	″	**14**	2,3,4-Trimethoxy-C_6H_2	**23**	80:20 (81)		95:5 (75)
9	″	″	″	″	″	**15**	2-Iodo-C_6H_4	**24**	55:45 (90)	60:40 (80)	90:10 (88)
10	**10**	″	″	″	N	**11**	C_6H_5	**25**	95:5 (87)		>95:5 (86)

[a] KHMDS: potassium bis(trimethylsilyl)amide.
[b] NaHMDS: sodium bis(trimethylsilyl)amide.
[c] LHMDS: lithium bis(trimethylsilyl)amide.
[d] PMB: *para*-methoxybenzyl.

group by the larger benzyl group had no effect, as shown in entries 1–5. A slight decrease of stereoselectivity was, however, observed with the trimethoxy parent compound (entry 5), but results obtained with trimethoxybenzaldehydes (entries 3 and 4) suggest that steric effects predominate over electronic effects. The high degree of diastereoselectivity observed with LHMDS may be tentatively rationalized by stabilization of the alkoxide by chelation of the lithium counterion embedded in a five-membered heteroring system in the primary adduct **26**. π-Donor–acceptor interactions may also account for the highest diastereoselectivity observed with the π-deficient pyridine model **10**.



	R1	R2	R3	X		
7	PMB	H	H	CH	*(E)*-**31**	(85%)
8	PMB	OMe	OMe	C-OMe	*(E)*-**32**	(82%)
9	Me	H	H	CH	*(E)*-**33**	(87%)
10	Me	H	H	N	*(E)*-**34**	(73%)

Scheme 3.

The stereoselective preparation of the *erythro* hydroxybenzyl derivatives (*u*)-**16**–**25** allowed us to envisage the development of a stereoselective method for the preparation of the 3-arylidene derivatives (*E*)-**31**–**34**. For this purpose we opted to perform the hydroxyalkylation and elimination reactions a single one-pot reaction. Metalation of the parent isoindolinones **7**–**10** and stereoselective connection of the hydroxyalkyl appendage was then carried out as described above (Scheme 3, path a). *O*-Silylation in situ of the transient oxanion **27** with TMSCl and subsequent treatment with LHMDS in the sequel ensured completion of the elimination reaction and gratifyingly this protocol delivered the (*E*)-isomers **31**–**34** in yields ranging from 73 to 87%. The stereochemistry of the exocyclic double bond of (*E*)-**31**–**34** follows unambiguously from the ^{1}H NMR data[14] and has also been related by characteristic chemical shift data to known arylideneisoindolinones.[15] We were also surprised to note that the same geometrical isomers were obtained exclusively by applying the same reaction sequence to a mixture of *erythro* (*u*) and *threo* (*l*) isomers **28** obtained by making use of KHMDS as the base (Scheme 3, path b). It is then likely that deprotonation of the *O*-silylated derivatives **28** (*l*+*u*) leads to the metalated species **29** which can adopt the *o*-quinodimethane structure **30** owing to electronic delocalization. Consequently once formed **29** and **30** collapse to (*E*)-**31**–**34** stereospecifically through the E1cb mechanism.[16] Interestingly such a phenomenon may also strengthen the hypothesis of π-donor–acceptor interactions in the adduct **26**.

In the course of this work we have then shown that lithiated isoindolinones react with aromatic aldehydes at the C-3 position of the lactam ring to afford hydroxyalkyl derivatives in good yields and with high diastereoselectivity. We have further demonstrated that the dehydration leading solely to the (*E*)-isomer could be indiscriminately performed on *erythro* and *threo* adducts.

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