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Asymmetric synthesis of 3,3-disubstituted isoindolinones

Daniel L. Comins* and Anne-Cécile Hiebel

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA

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Abstract—An anionic chiral auxiliary-mediated asymmetric alkylation of carbamate **2** affords 3,3-disubstituted isoindolinones **3** in moderate to high de. The chiral auxiliary can be removed and recovered under mild conditions, and the resulting enantiopure lactams further elaborated.

Over the past few years, the isoindolinone ring system has emerged as a valuable pharmacophore exhibiting a wide range of therapeutic activities.[1] In addition, antiangiogenic activities[2] and TNFα inhibition[3] by various isoindolone analogs of thalidomide have been investigated. On numerous occasions, the phthalimidine core was shown to possess improved metabolic stability while retaining functionality.[2–4] Antihypercholesterolemic properties have been observed as well.[5] Unnatural bases containing the isoindolinone moiety were shown to have promise at biomolecular recognition.[6] This class of structure was also involved in the design of a redox-mediated molecular brake.[7]

Recently, an increasing number of publications have appeared on the stereoselective synthesis of C-3 substituted isoindolinones.[1a] One of the latest methodologies was published by Hunter and Richards involves the intramolecular radical cyclization of an α-sulfanyl phthalimidine on a chiral enoate ester appendage.[8] Clayden and Menet reported a stereocontrolled synthesis via cyclization and rearomatization of lithiated benzamides formed using a chiral base.[9] Few studies have succeeded at using an easily removable chiral auxiliary or chiral appendage. A chiral auxiliary-mediated asymmetric synthesis involving cleavage of the hydrazide bond between phthalimidine and (*S*)-2-methoxymethylpyrrolidine has been reported by Deniau et al.[10] Huang and co-workers developed the use of (*R*)-*p*-benzyloxyphenylglycinol as a more useful alternative to (*R*)-phenylglycinol for the enantioselective synthesis of 3-alkylisoindolinones.[11]

Our efforts in this area have been recently published[1a] and involves the use of readily available (+)- or (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC)[12] as the chiral auxiliary. A highly selective and high yielding alkylation at the C-3 position of isoindolinone **1** was obtained. It was established by single-crystal X-ray analysis that the use of (−)-TCC leads to the (*R*) configuration as shown in Scheme 1. The methodology was applied toward the first asymmetric synthesis of (+)-lennoxamine.[1a]

In hope of broadening the scope of this methodology, we investigated the selective formation of quaternary centers at the C-3 position via a second asymmetric alkylation reaction. To our knowledge, there have been only a few reports on the introduction of quaternary centers at the C-3 position of isoindolinones.[1e,9,13] Clayden and Menet reported an asymmetric synthesis of a 3-methyl-3-arylisoindolinone, but they were unable to assess the enantiomeric excess.[9] Shim and co-workers published a racemic synthesis of 3,3-disubstituted isoindolinones via palladium-catalyzed intermolecular coupling and heteroannulation.[13] Very recently, Hardcastle et al. reported the synthesis of a series of racemic 3-aryl-3-alkoxyisoindolinones for evaluation as potential antitumor agents.[1e] Our goal was to develop a practical asymmetric synthesis of C-3 disubstituted isoindolinones and to utilize the products as chiral building blocks. Our preliminary results are summarized below.

Treatment of isoindolinone **2a**[1a] with NaHMDS at temperatures ranging between −100 °C and −115 °C (liquid N_2/Et_2O) followed by the addition of various electrophiles gave the 3,3-disubstituted derivatives **3** (Scheme 1, Table 1).

Keywords: Isoindolinones; Asymmetric synthesis; Chiral auxiliary.
* Corresponding author. Tel.: +1 919 515 2911; fax: +1 919 515 9371; e-mail: Dan_Comins@ncsu.edu

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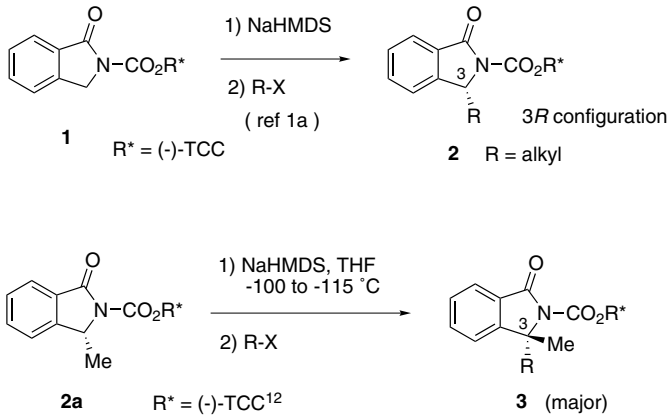


Scheme 1.

Table 1. Stereocontrolled synthesis of isoindolinones **3** from **2a**

Entry	R–X	3	Yield[a,b] (%)	dr[d]
1	CH_2CHCH_2I	**3a**	45	65:35
2	$CH_2C(Me)CH_2CH_2Br$	**3b**	38	55:45
3	CF_3CH_2OCHO	**3c**	(62)	91:9
4	PhCOCl	**3d**	(68)	91:9
5	*t*-$BuOCOCH_2Br$	**3e**	66	94:6
6	BnBr	**3f**	(50)[c]	79:21

[a] Yield is for mixture of diastereomers isolated by chromatography.
[b] Yield in ( ) is for the isolated major diastereoisomer.
[c] The major isomer was isolated by crystallization.
[d] The dr was determined by ^1H NMR analysis of the crude product. R* = (−)-TCC in all examples.

Interestingly, non chelating and/or non π-stacking electrophiles such as allyl iodide and 4-bromo-2-methyl-1-butene (entries 1 and 2) gave poor yields and diastereoselectivities. On the other hand, reaction with electrophiles exhibiting the potential to chelate via a carbonyl group or π-stack via an aromatic ring provided higher yields and showed moderate to high levels of stereoinduction independent of the mechanism of formation of the C–C bond (Fig. 1).

Alkylations proceeding by the addition–elimination (entries 3 and 4) or the S_N2 mechanism (entries 5 and 6) afford comparable levels of selectivity. The stereochemical outcome of these conversions was established by single-crystal X-ray analysis of the products **3d** and **f** (Fig. 2). The preferred direction of attack by the electrophile on the chiral enolate was observed to be the same as in the corresponding mono alkylation.[1a] The attack of the electrophile occurred on the bottom face of the anion containing the (−)-TCC auxiliary (Fig. 1),

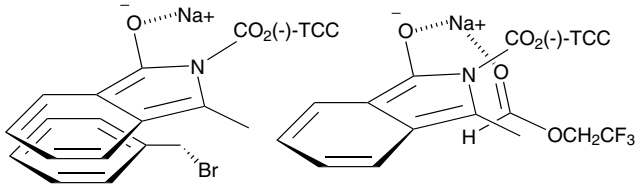


Figure 1. π-Stacking and chelation controlled facial selectivity.

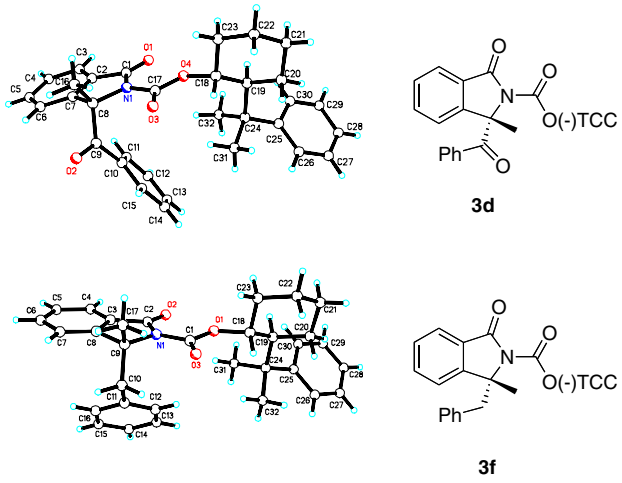
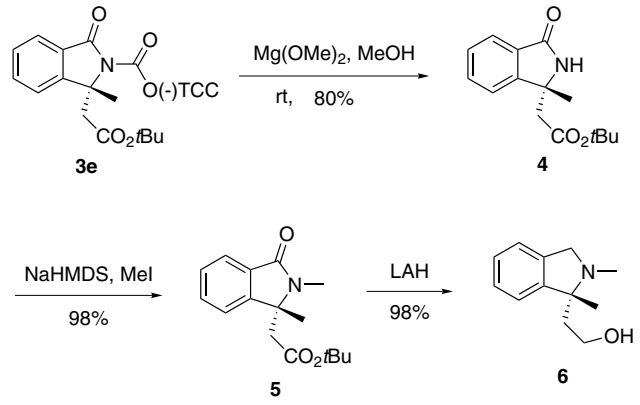


Figure 2. X-ray crystal structures of **3d** and **f**.

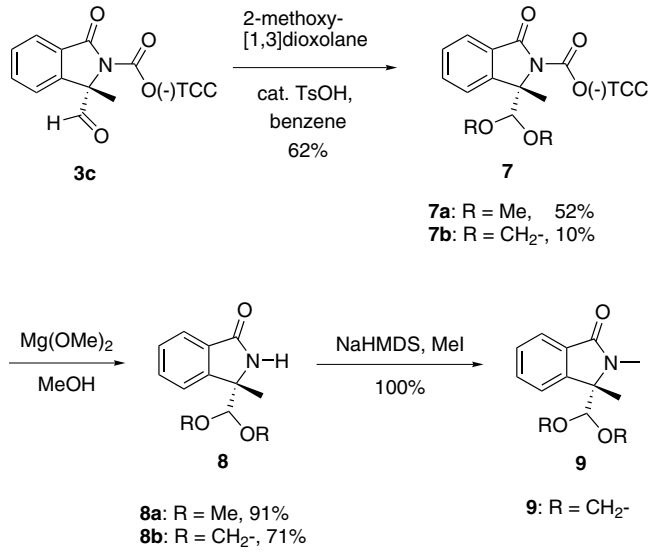
leading to the 3*S* configuration for compounds **3c** and **d** and the 3*R* configuration for compounds **3e** and **f**.

Having successfully introduced a quaternary center at the C-3 position of isoindolinones **2** in a stereocontrolled fashion, we explored subsequent synthetic conversions of the products. Like the corresponding monosubstituted 3-alkylisoindolinones, removal of the chiral auxiliary from the C-3 dialkylated derivatives is easily accomplished under mild conditions with $Mg(OMe)_2$ in methanol. For example, the ester-containing derivative **3e** was converted to lactam **4** in 80% yield with 95% recovery of the auxiliary, (−)-TCC alcohol (Scheme 2).

Methylation of the lactam nitrogen occurred smoothly to afford **5** in near quantitative yield. Reduction of **5** with LAH gave a 98% yield of the aminoalcohol **6**. In the case of aldehyde **3c**, protection of the reactive aldehyde as the acetal **7** was needed in order to achieve carbamate cleavage to isoindolinone **8** and recovery of the chiral auxiliary (Scheme 3). Deprotonation and methylation of **8b** gave the *N*-methyl derivative **9** in quantitative yield.



Scheme 2.



Scheme 3.

In summary, a facile and efficient asymmetric synthesis of 3,3-disubstituted isoindolinones was achieved with moderate to high levels of diastereoselectivity. Since TCC alcohols are readily available as either antipode,[12] both enantiomers of the isoindolinone products are available via this methodology. The chiral auxiliary can be effectively removed and recovered under mild conditions, and the resulting enantiopure lactams further manipulated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.06.105. Experimental for the preparation of **3c–f**, **4**, and **5**, characterization data for compounds **3–9**, and ORTEP plots for **3d** and **f**. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallograpic Data Centre as supplementary publication numbers CCDC 272733 and 272734. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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