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Synthesis of enantiomerically-enriched *N*-aryl amino-amides *via* a Jocic-type reaction

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ABSTRACT

Enantiomerically-enriched secondary trichloromethyl-alcohols react with aryl amines to give enantiomerically-enriched α-*N*-arylamino-acid derivatives. The intermediate acid chlorides can react *in situ* with aryl or, regioselectively, with alkyl amines to give aryl or alkyl α-*N*-arylamino amides.

Introduction

N-Aryl amino acids, amides and other derivatives are common features in biologically active molecules (Fig. 1). The majority of syntheses of these molecules involve the *N*-arylation of an amino acid or a derivative. Aryl halides with electron withdrawing groups react directly with amino acids, for instance during the synthesis of fibrinogen receptor antagonist SB 214857 **1** and NNRTIs talviraline (HBY097) **4** [1–5]. Copper-catalysed coupling of aryl halides [6–11] has also been used in the synthesis of SB-214857 **1** [12] as well as for (−)-indolactam V **2** [13,14], benzolactam-V8 **3** [15], and GW420867X **5** [16]. Catalysis can also occur in mixed copper/ palladium systems [17,18], or with palladium-only catalysts [19–23] sometimes with noticeable racemization. Copper can also mediate arylation with boronic acids [24–28]. Arylation can also be effected with arynes [29–32], or by condensation with carbonyls [33,34].

Control of stereochemistry nucleophilic substitution of aryl amines onto chiral electrophiles has been reported in an alternative synthesis of (−)-by the direct indolactam V by S_N2 reaction of a chiral triflate [35–37]. Jocic [38] and Bargellini [39] reactions that occur *via* ∝-trichloromethylalcohols and dichloroepoxides are also very useful methods for the introduction of nucleophiles at the ∝-carbon of acid derivatives, often with excellent stereocontrol [40–53]. Previously, we reported the enantioselective reduction of trichloromethyl ketones using ruthenium asymmetric transfer hydrogenation (ATH) catalysts [54–59] and the subsequent Jocic-type reactions of the products to give enantiomerically enriched amino-amides (Scheme 1) [60,61]. In these reactions we noted that the primary alkyl amine component of a diamine generally reacts with the epoxide intermediate preferentially, before subsequent intra- or inter molecular amidation of the intermediate acid chloride. The Bargellini-type reaction of primary aryl amines with achiral tertiary alcohol derived dichloroepoxides has previously been reported by Lai [62]. These results raised the question of whether primary aryl amines can open the dichloroepoxide

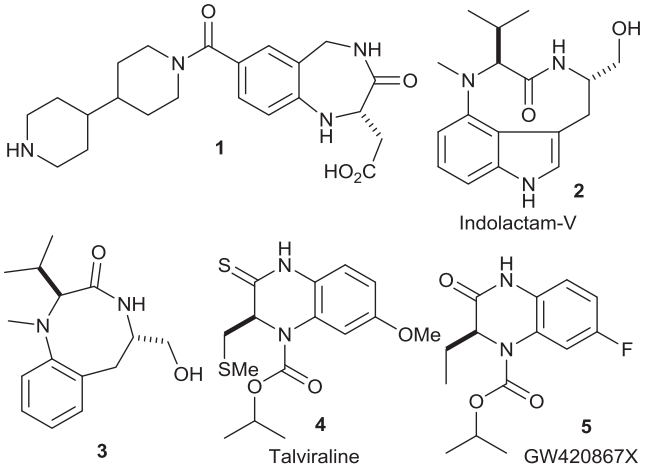

Fig. 1. *N*-Aryl amino amide derivatised drugs.

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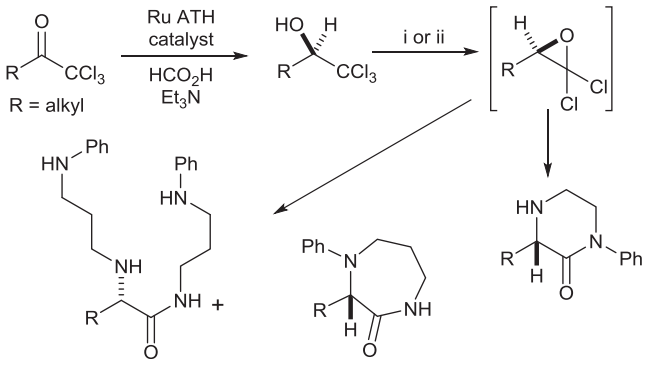


Scheme 1. Previous work. Reagents and conditions: (i) $PhNHCH_2CH_2NH_2$, NaOH, $BnNEt_3Cl$, CH_2Cl_2, H_2O; (ii) $PhNHCH_2CH_2CH_2NH_2$, NaOH, $BnNEt_3Cl$, CH_2Cl_2, H_2O.

intermediates, derived from enantiomerically-enriched secondary trichloromethyl alcohols, with control of stereochemistry.

Results and Discussion

The synthesis of known alcohol (*R*)-**6** (95% e.e.) [60] as well as new enantiomerically enriched alcohols (*R*)-**7** (95% e.e.) and (*R*)-**8** (95% e.e.) was followed by their reactions with an excess amount of four *para*-substituted anilines (Table 1). The stereochemical purity of the starting material is maintained during the Jocic-type reactions. The formation of the (*S*)-*N*-aryl amide (X-ray crystallography) from the (*R*)-alcohol demonstrates the inversion of stereochemistry typical for such reactions (Fig. 2). We assume that all of the reactions in Table 1 occur *via* the same inversion of stereochemistry.

Jocic-type reactions can also be performed in alcohol solvents instead of chlorinated solvents [46,47,52,63,64]. The related formation of *N*-aryl amino acids from achiral trichloromethyl-alcohols using a single equivalent of aniline in methanol has been reported [65], and we wished to test these reaction conditions with the

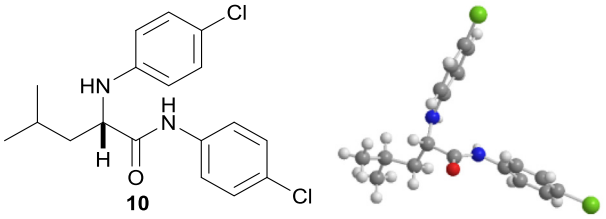
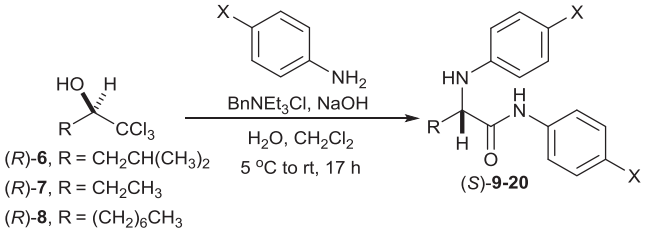


Fig. 2. Crystal structure of (*S*)-**10**.

enantiomerically enriched secondary alcohols. Conversions were however very low (results not shown) and changing the solvent to acetone improved the yields (Table 2). The importance of the original biphasic reaction medium (Table 1) on maintaining the stereospecificity of the reaction, presumably separating the organically soluble product from the aqueous base, was demonstrated as the products, isolated as their methyl esters, had lost stereochemical integrity during the Jocic process (Table 2). We have previously shown that stereochemical integrity can be lost in the Jocic reactions of amines with trichloromethyl secondary alcohols when using methanol as a single phase solvent [61]. By analogy with the formation of compound (*S*)-**10** we have assigned the major enantiomer of the ester products to have the (*S*)-configuration (See Table 3).

Chiral *N*-alkyl-*N*-aryl-aminoamides are fragments of drug compounds **1**–**3**. Direct Jocic-type synthesis of amino amides with different nitrogen substituents requires the selective *in situ* reaction of two different amines, an aryl amine to open the intermediate epoxide, and an alkyl amine to capture the acid chloride. Such a strategy is known [62] but again only on achiral tertiary alcohol-derived epoxides. Table 3 shows the results of the reaction of 10 equivalents of an aryl amine and two of an alkyl secondary amine with chiral alcohol (*R*)-**8** in biphasic conditions. In most cases the major product is the ∝-*N*-aryl tertiary amide, but with the most nucleophilic aniline (4-methoxyaniline) the secondary aryl amide **19** was the major product. Stereochemical integrity was

Table 1
Formation of *N*-aryl amino-amides.



Entry	S. M.	R	X	Yield %[a]	e.e. %[b]	Product
1	(*R*)-**6**	$CH_2CH(CH_3)_2$	H	82	98	**9**
2	(*R*)-**6**	$CH_2CH(CH_3)_2$	Cl	61	97	**10**
3	(*R*)-**6**	$CH_2CH(CH_3)_2$	OCH_3	78	97	**11**
4	(*R*)-**6**	$CH_2CH(CH_3)_2$	CH_3	74	96	**12**
5	(*R*)-**7**	CH_2CH_3	H	73	96	**13**
6	(*R*)-**7**	CH_2CH_3	Cl	61	97	**14**
7	(*R*)-**7**	CH_2CH_3	OCH_3	69	97	**15**
8	(*R*)-**7**	CH_2CH_3	CH_3	62	95	**16**
9	(*R*)-**8**	$(CH_2)_6CH_3$	H	73	96	**17**
10	(*R*)-**8**	$(CH_2)_6CH_3$	Cl	56	95	**18**
11	(*R*)-**8**	$(CH_2)_6CH_3$	OCH_3	63	95	**19**
12	(*R*)-**8**	$(CH_2)_6CH_3$	CH_3	61	96	**20**

[a] Isolated yield.
[b] By chiral HPLC analysis.

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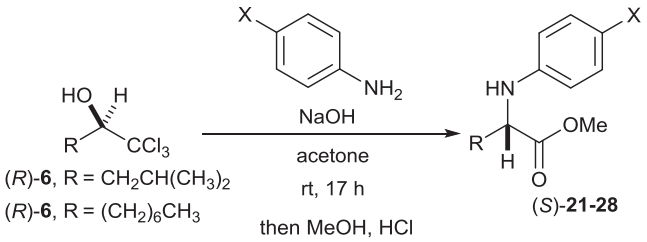
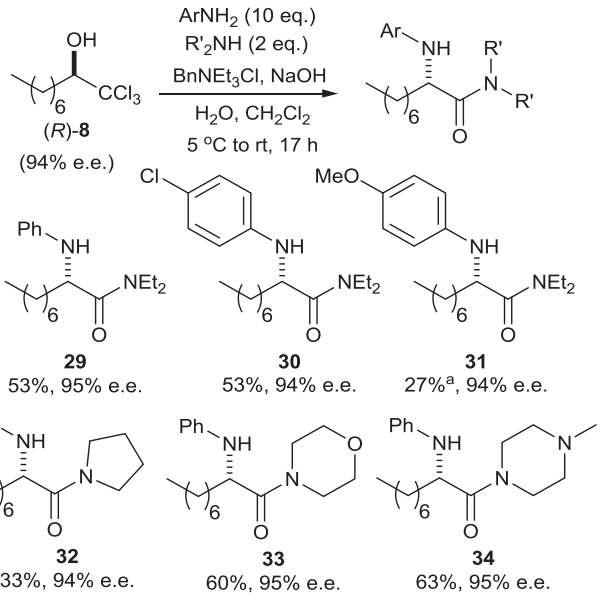
Table 2
Jocic-type reactions with arylamines.



Entry	S. M.	R	X	Yield %[a]	e.e. %[b]	Product
1	(*R*)-**6**	$CH_2CH(CH_3)_2$	H	65	76	**21**
2	(*R*)-**6**	$CH_2CH(CH_3)_2$	Cl	65	73	**22**
3	(*R*)-**6**	$CH_2CH(CH_3)_2$	OCH_3	53	82	**23**
4	(*R*)-**6**	$CH_2CH(CH_3)_2$	CH_3	59	79	**24**
5	(*R*)-**8**	$(CH_2)_6CH_3$	H	69	33	**25**
6	(*R*)-**8**	$(CH_2)_6CH_3$	Cl	58	49	**26**
7	(*R*)-**8**	$(CH_2)_6CH_3$	OCH_3	61	52	**27**
8	(*R*)-**8**	$(CH_2)_6CH_3$	CH_3	64	65	**28**

[a] Isolated yield.
[b] By chiral HPLC analysis.

Table 3
Formation of *N*-aryl amino-amides.



[a] 36% of amide **19** was also produced in this reaction

maintained during the reactions (chiral HPLC). Again we assume that the stereochemical inversion demonstrated in the synthesis of amide **10** also occurs for these closely related reactions. The issue of competitive nucleophilic chemoselectivity in such reactions is a complex one, however our results here and previously [60,61], as well as those of others [66,67], do tend to indicate that primary amines (either alkyl or aryl) are preferred for the epoxide opening step, while alkyl amines (either primary or secondary) are preferred for reaction with the acid chloride. This synthesis of enantiomerically enriched ∝-*N*-aryl tertiary amides, when coupled to asymmetric syntheses of secondary trichloromethyl alcohols [40,60] has potential use in drug libraries, especially if it can be extended to heteroarylamines.

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Appendix A. Supplementary data

Supplementary data (Synthesis details, NMR spectra, chiral HPLC chromatograms and crystallographic details. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and assigned the deposition number CCDC 1568159) to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.09.046.

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