Asymmetric photoinduced electrocyclic ring closure of chiral aromatic enehydrazides. Application to the asymmetric synthesis of 3-aryl dihydroisoquinolones and tetrahydroisoquinolines.

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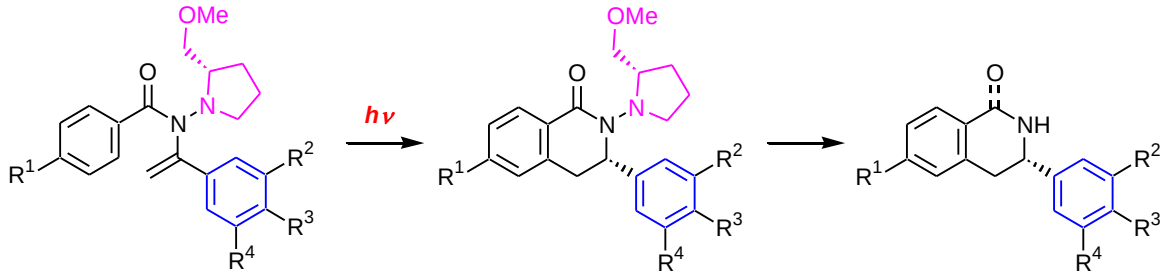
Abstract: A flexible route for the stereoselective synthesis of a variety of 3-aryl dihydroisoquinolones and tetrahydroisoquinolines has been developed. The key step is a diastereoselective photoinduced 6π-electrocyclic ring closure of enantiopure aromatic enehydrazides via a 1,4-remote asymmetric induction. N-N bond cleavage to release the chiral appendage from the preliminary annulated compounds and/or concomitant reduction of the lactam carbonyl group completed the synthesis of the title compounds.



Keywords: Asymmetric synthesis, enol phosphates, cross-coupling, chiral enehydrazides, photocyclization, 3-arylisoquinolones

Introduction

The isoquinoline core is one of Nature's most popular structural motif and this ring system lies at the heart of a large number of natural and synthetic bioactive compounds. [1] In particular those in which the azaheterocycle unit is partially hydrogenated occupy a noticeable place in this class of interesting alkaloids because of their manifold pharmacological properties, e.g. fibrinolytic, antiviral, tranquilizing, muscle relaxant, hypotensive and positive inotropic effects. [1,2] Isoquinolinones are somewhat less prominent but very often they serve a key role as advanced intermediates prior to their conversion to isoquinolines. Consequently the development of general methodologies leading to molecular diversity in a highly efficient stereo and enantioselective manner is a permanent challenging task for organic chemists and interest in this field continues unabated. [3,5] While much effort has been devoted to the asymmetric synthesis of 1-substituted models, [5m,6] the stereoselective elaboration of 3-substituted dihydroisoquinolones and tetrahydroisoquinolines has much less precedent in the literature. The 3-arylated models fall into this category and are of particular interest since they are known as a relevant class of compounds among the isoquinoline alkaloids. [1] They can be regarded as important synthetic intermediates for the construction of structurally related alkaloids like protoberberines e.g. xylopinine, pavines e.g. (-)-argemonine, and benzo[*c*]phenanthridines e.g. chelerythrine (Fig. 1). [1,7] They are also enjoying considerable attention as potential therapeutic agents [8] as evinced by bombesin-2 (BB2) receptor antagonist [9] and MDM2-p53 interaction inhibitors [10] (Fig. 1).

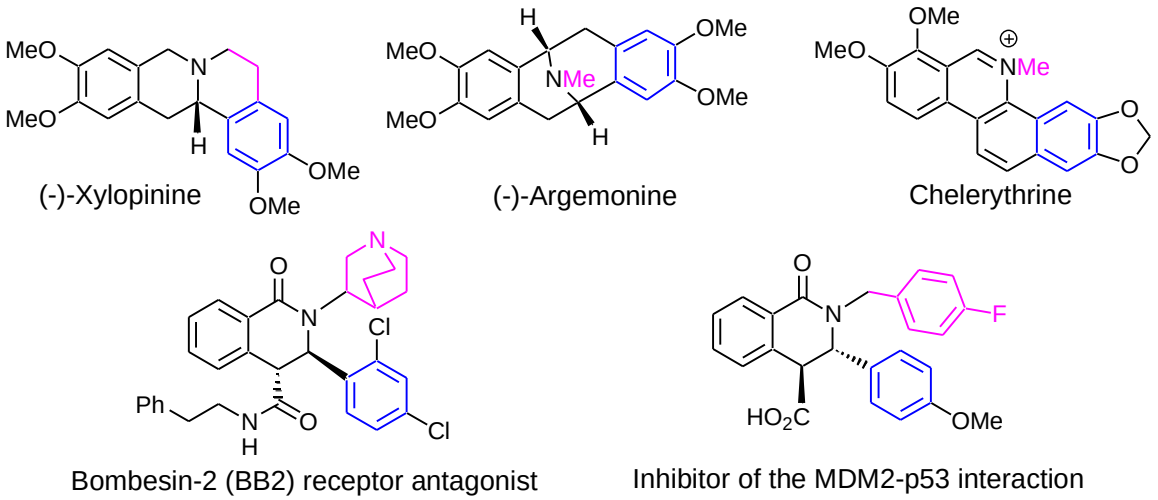
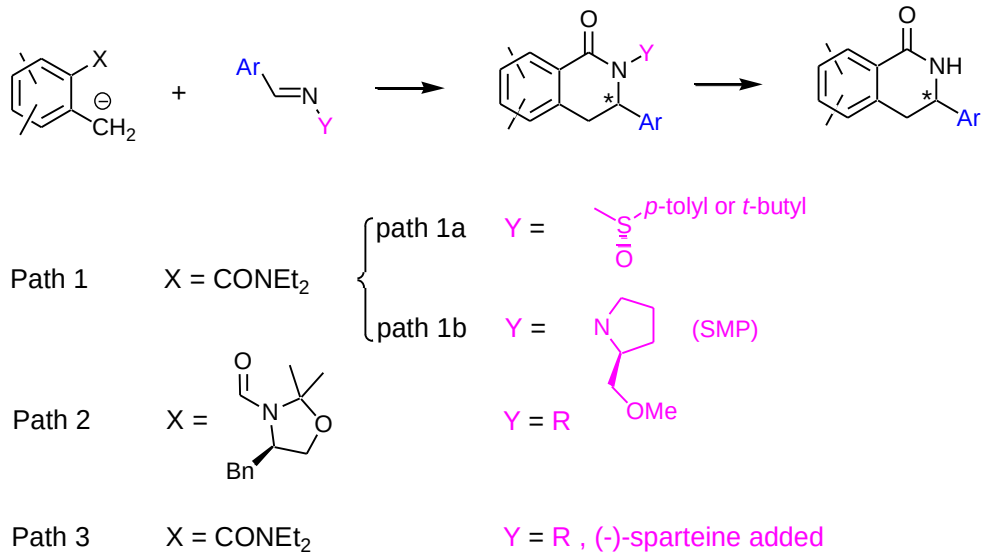


Figure 1. Natural and synthetic bioactive compounds incorporating the 3-arylisoquinolin(one) skeleton

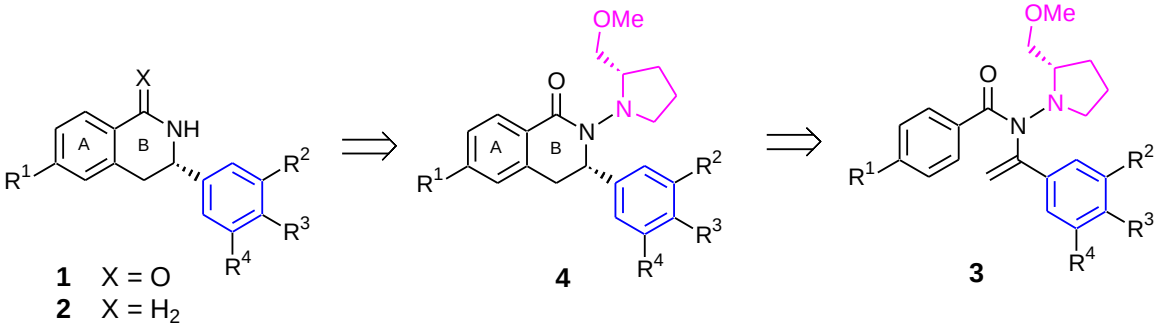
The asymmetric synthetic methods for the elaboration of 3-arylated dihydroisoquinolones can be cursorily classified into three main categories whose fundamental tenets come within the scope of the lateral metalation methodology pioneered by Clark and coll [11] (Scheme 1). The first one hinges upon a tandem addition/cyclization of lithiated 2-methylbenzamides to imine appended chiral auxiliary, such as sulfinyl imines developed by Davies [5b,e,l,12] and Chrzanowska [4a,b] (path 1a) or SAMP hydrazones exploited by Enders [13] (path 1b).For the second one (path 2) enantioinduction is secured by making use of achiral imines and laterally lithiated (*S*) or (*R*)-*o*-toluamides equipped with a chiral auxiliary derived from (*S*) or (*R*) phenylalaninol. At last the same synthetic approach was skillfully developed by Snieckus [5a] and Liu [4c] starting from achiral substrates and enantioinduction was achieved this time via addition of the chiral ligand (-)-sparteine (path 3). It is also worth noting that a stereocontrolled synthesis of 3-aryltetrahydroisoquinoline by a Pictet Spengler heterocyclization reaction of optically active 1,2-diarylethylamines has been developed but the resulting compounds were invariably alkylated at the C1 position. [5] The same unsubstituted models could also be obtained by deoxygenation of isoquinolinols prepared from chiral arylglycines under ionic hydrogenation conditions. [4d] All these methods are generally efficient and of procedural simplicity but they have also been claimed to proceed with varying degrees of success with regard to their enantioselectivities.

Consequently the development of alternative and efficient methodologies which may find generality for constructing polyhydroisoquinolones and isoquinolines with aryl appendage at C3 in a stereoselective manner is currently the object of synthetic endeavor. [4,13]



Scheme 1. Synthetic strategies for the stereoselective synthesis of 3-arylated dihydroisoquinolones.

We wish to delineate a novel route to a variety of diversely substituted 3-aryl polyhydroisoquinolones and quinolines, **1** and **2** respectively, that is based upon the use of chiral aromatic enehydrazides **3** as substrates for photoinduced ring closure to secure the formation of the lactam unit, that is ring B in the title compounds (Scheme 2). Ensuing deprotection by N-N cleavage of the hydrazide bond of the preliminary annulated compounds **4** possibly associated with reduction of the carbonyl function then should provide an entry to the targeted optically active compounds **1,2**.



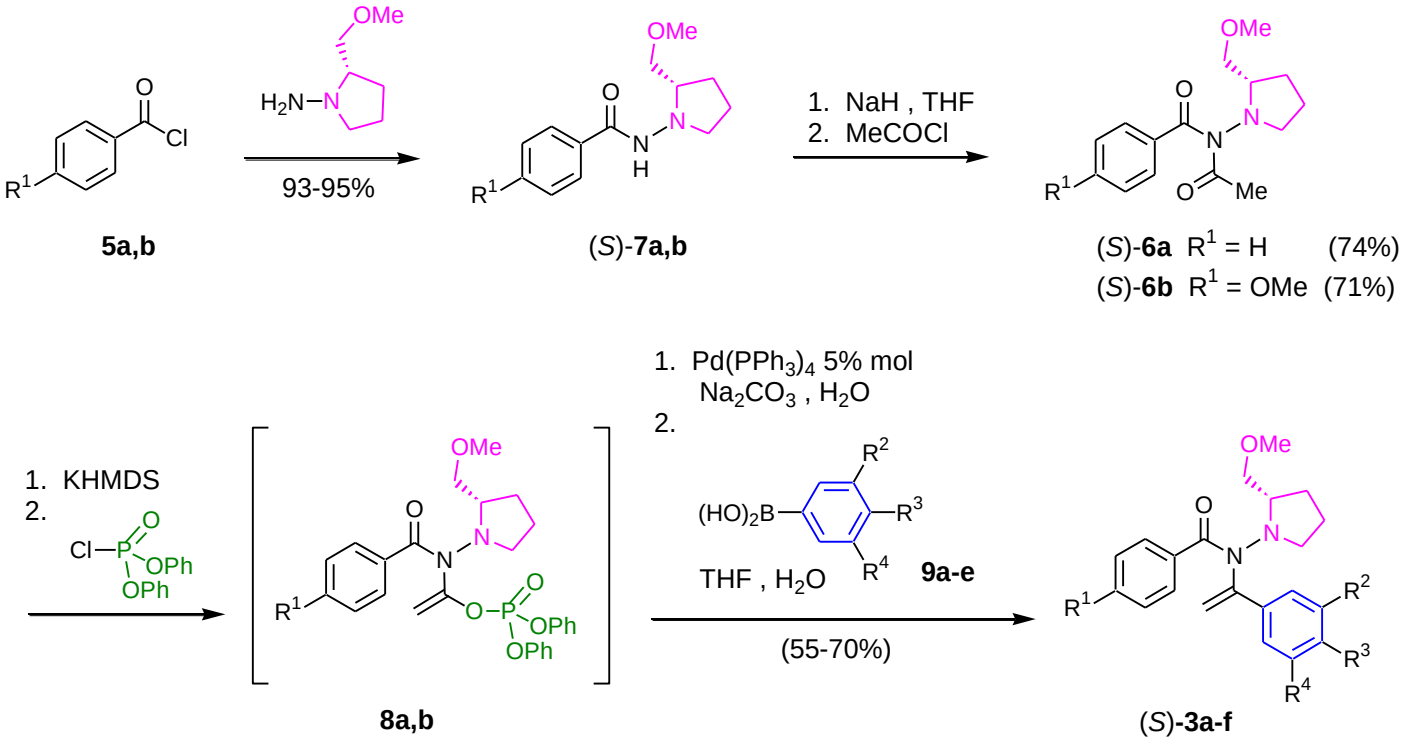
Scheme 2 Retrosynthetic analysis.

The photocyclization of enamides has been developed as an efficient synthetic route toward six-membered azaheterocycles and a wide range of alkaloids has been synthesized in this way. [14] Although a number of possibilities exist for inducing stereoselectivities in photochemical reactions [15] little attention has been paid to the development of photocyclization processes that could ensure the control of the stereogenic center α to the nitrogen atom, a challenging task in alkaloid total synthesis. In a few early reports reductive photocyclization of enamides was carried out in the presence of chiral metal hydride complex but both the chemical yields and enantioselectivities were rather modest. [16] Methodologies based upon the photoinduced cyclization of chiral aromatic enamides are rather scarce. These photochemical studies have been indeed confined to aliphatic dienamides [17] and to structurally sophisticated models that require additional tedious chemical transformation to access the targeted compounds, [18] both with moderate selectivities.

Results and Discussion

Our new synthetic approach hinges upon the photoinduced cyclization of aromatic enehydrazides **3** equipped with a temporary activating auxiliary issued from the chiral pool, that is (*S*)-*O*-methylprolinol (Scheme 2). We speculated that upon photoinduced ring closure under anaerobic conditions, the presence of this rather bulky appendage could have a marked impact on the [1,5]-H shift from intermediate structurally related to B and then force and favor the privileged formation of diastereomerically enriched annulated models **4**.

The first facet of the synthesis which is depicted in Scheme 3 was then the elaboration of the enehydrazides **3**. The construction of these unsaturated compounds revealed to be more problematic that we had anticipated. All attempts to access the desired precursors following the classical method usually employed for the synthesis of styrenic enamides, [19] met with no success. We then set out to achieve an alternative strategy to secure the creation of the styrene unit tailed to the aromatic hydrazide moiety. We surmised that the acetylated hydrazides **8** would possess the appropriate functionalities required for the installation of the mandatory styrene unit through a palladium-mediated cross-coupling reaction. Since the pioneering work of Oshima et coll. [20] several group have successfully and elegantly used constitutionally diverse enol phosphates in a variety of $Pd(PPh_3)_4$ catalyzed cross-coupling reaction. [21] It has been notably demonstrated that enol phosphates deriving from *N*-alkylamides are effective substrates for such coupling reaction provided that the model compounds are further equipped with electron withdrawing groups on nitrogen atom. Despite the fact that to the best of our knowledge such studies have not been performed with N-substituted hydrazides we were reasonably optimistic about the chances of success for this approach since the diacylated hydrazines **8** fulfill these stringent structural criterions. Initially the benzoyl chlorides **5a,b** were efficiently converted into the corresponding hydrazides (*S*)-**7a,b** under standard conditions. Deprotonation of (*S*)-**7a,b** with NaH in THF and subsequent capture of the transient sodium salt with acetyl chloride delivered quite satisfactory yields of the chiral N-acetylated hydrazides (*S*)-**6a,b**. With rapid access to these diacylated models the focus of the research shifted to the use of these compounds as advanced intermediates for the concise and efficient conversion of the acetyl moiety into a styrene unit.

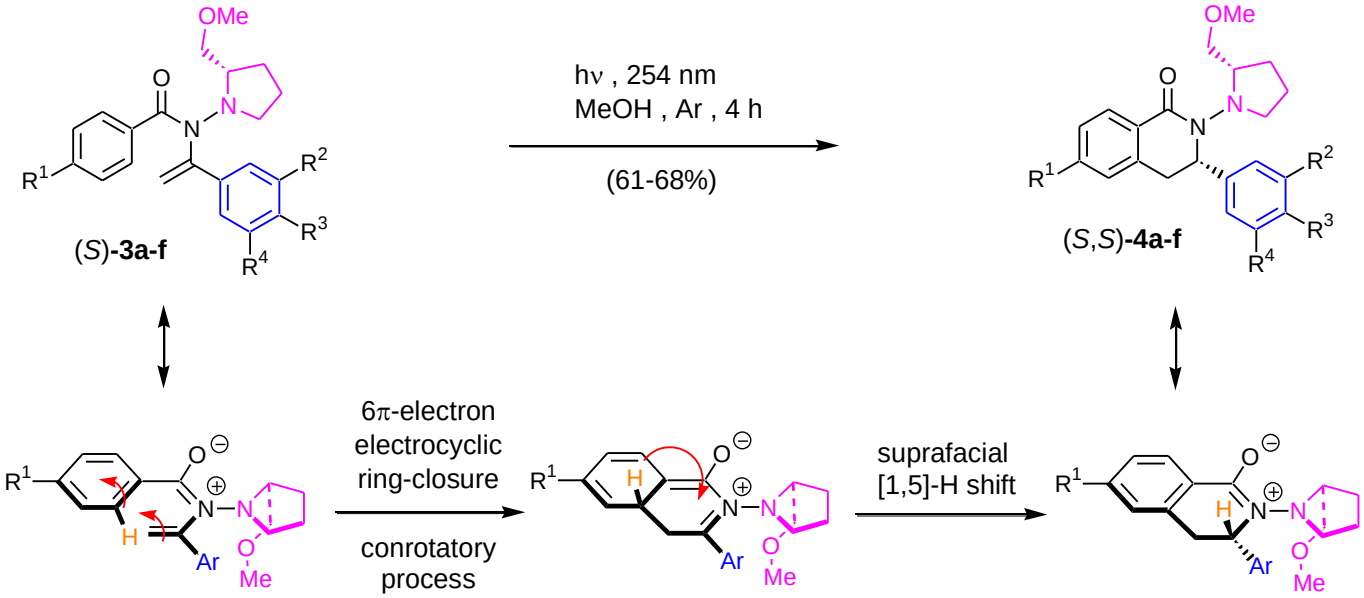


Scheme 3 Synthesis of the parent aromatic enehydrazides **3a-f**.

We were then pleased to observe that exposure of compounds (*S*)-**6a,b** to KHMDS in THF at -78 °C provided a potassium enolate which was intercepted with diphenyl chlorophosphate to afford the sensitive vinyl phosphate **8a,b**. Subsequent Pd-catalyzed Suzuki-Miyaura coupling reaction was then applied under well-defined conditions. The vinyl phosphate thus obtained **8a,b**, a suitably aromatic boronic acid **9a-e**, $Pd(PPh_3)_4$ as the catalyst, aqueous Na_2CO_3 (2 M), a few drops of EtOH were refluxed in THF.

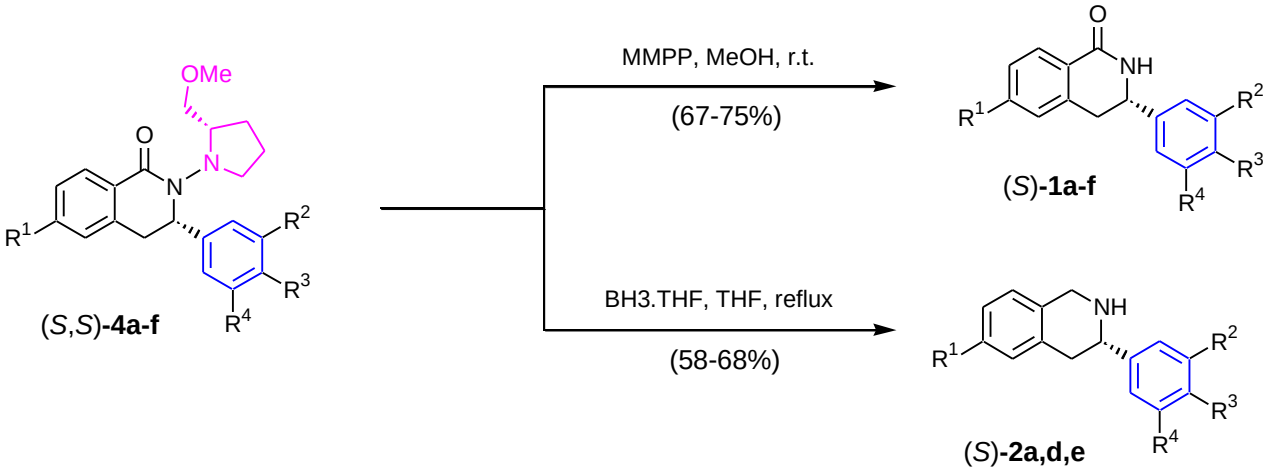
Under these conditions the expected enantiopure styrene hydrazides (*S*)-**3a-f**, candidates for the planned photoinduced ring-closure, were isolated in very satisfactory yields (Scheme 4, Table 1). As far as we are aware such reactions performed in the hydrazide series are unprecedented and should be of interest for alternative synthetic planning. For the crucial photocyclization process a carefully degassed methanolic solution of chiral enehydrazides (*S*)-**3a-f** ($4\ 10^{-3}$ M; λ_{max} = 205, 260, 300 nm) was placed in a quartz vessel and irradiated under Ar in a Rayonet RPR photoreactor equipped with eight 254 nm lamps for 4 h. Subsequent removal of the solvent and flash column chromatography delivered very satisfactory yields of the requisite annulated (*S,S*)-**4a-f** (Scheme 5, Table 1).

To our delight these lactamic compounds were obtained essentially as single diastereomers detectable by NMR (de ≥ 98% after chromatographic treatment) [22] making evident the high selectivity of the initial diastereofacial [1,5]-hydrogen shift process allowing introduction of the absolute stereochemistry at the newly created benzylic carbon center. From a mechanistic point of view one can tentatively assume that the chiral auxiliary is blocking the lower face of the plane of the hexatriene mesomeric form of (*S*)-**3a-f**. Upon the 6π-electrocyclization process the two terminal vinyl and aromatic strands rotate in a conrotatory manner away from the pendant methoxymethyl group of the pyrrolidine auxiliary which may sterically interacts with the styrene unit (Scheme 5). The suprafacial [1,5]-H shift from the transient hydrazinium species then occurs exclusively on the less hindered diastereotopic face and this highly diastereoselective electrocyclization is actually achieved via an unusual 1,4-remote asymmetric induction. These results are in good agreement with the stereoselective 6π-electron cyclic ring-closure of structurally related amidotrienes. [23]



Scheme 4. Synthesis and mechanistic rationalization for the stereoselective construction of 3-arylated isoquinolones **4a-f**.

Ultimate treatment of (*S,S*)-**4a-f** with magnesium monoperoxyphthalate (MMPP) [24] triggered off the exclusive cleavage of the chiral appendage and this operation delivered very satisfactory yields of the virtually enantiopure 3-aryl-1(2*H*)-dihydroisoquinolones (*S*)-**1a-f** (Scheme 5, Table 1). Finally treatment with the borane-THF complex of (*S,S*)-**4a-f** followed by aqueous alkaline work up effected reductive N-N bond cleavage with the concomitant reduction of the lactam carbonyl group to afford the targeted 3-aryltetrahydroisoquinolines (*S*)-**2a,d,e**. The absolute configuration of the newly created stereogenic center in **1** and **2** that was confirmed to be (*S*) as well as the enantiopurity of our synthetic compounds were clearly established from the sign and value of the optical rotation that matched those reported from authentic sample assembled by conceptually different synthetic approaches, e.g. {(*S*)-**1a**: mp 130-131 °C, $[\alpha]_D^{20}$ -198.3 (*c* 0.97, $CHCl_3$); lit.:[5e] mp 130-131 °C, $[\alpha]_D^{20}$ -203.4 (*c* 1.03, $CHCl_3$)} and {(*S*)-**2a**: $[\alpha]_D^{20}$ -125.5 (*c* 0.48, CH_2Cl_2); lit.: [25] (*R*)-enantiomer $[\alpha]_D^{20}$ +125.0 (*c* 0.55, CH_2Cl_2)}.



Scheme 5. Synthesis of enantiopure 3-substituted isoquinolones **1a-f** and isoquinolines **2a,d,e**.

Table 1. Compounds **3a-f**, **4a-f**, **1a-f** and **2a,d,e** prepared

	R^1		R^2	R^3	R^4							
6a	H	**9a**	H	H	H	**6a** + **9a** → **3a**	65%	**4a**	68%	**1a**	75%	**2a**	63%
6a	H	**9b**	OMe	OMe	H	**6a** + **9b** → **3b**	70%	**4b**	63%	**1b**	70%	**-**	-
6a	H	**9c**	OMe	OMe	OMe	**6a** + **9c** → **3c**	58%	**4c**	67%	**1c**	74%	**-**	-
6a	H	**9d**	H	OMe	H	**6a** + **9d** → **3d**	62%	**4d**	62%	**1d**	72%	**2d**	68%
6a	H	**9e**	OCH_2O		H	**6a** + **9e** → **3e**	68%	**4e**	65%	**1e**	73%	**2e**	58%
6b	OMe	**9b**	OMe	OMe	H	**6b** + **9b** → **3f**	55%	**4f**	61%	**1f**	67%	**-**	-

Conclusion

In conclusion we have devised a new, convenient and flexible method for the enantioselective synthesis of 3-aryl isoquinolones and isoquinolines. The key step is the highly diastereoselective photoinduced electrocyclization of enantiopure aromatic enehydrazides to generate the six-membered azaheterocyclic ring system via a 1,4-remote asymmetric induction. The main advantages of this synthetic approach lie in the small number of synthetic steps and the ready accessibility to the chiral SAMP hydrazides which are easily assembled through a newly developed Suzuki-Miyaura cross-coupling reaction involving tailor-made enol phosphates. Owing to the availability of the RAMP chiral auxiliary we believe that this synthetic strategy should also allow for the construction of both antipodes of these 3-arylated isoquinolones and isoquinolines.

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