Tetrahedron: *Asymmetry* 20 (2009) 2193–2199

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Tetrahedron: *Asymmetry* Report Number 118

Routes toward enantiopure 2-substituted indolines: an overview

Saithalavi Anas, Henri B. Kagan *

Laboratoire de Catalyse Moléculaire, Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR 8182), Université Paris-Sud, 91405 Orsay, France

ARTICLE INFO

Article history:
Received 27 July 2009
Accepted 6 August 2009

ABSTRACT

Chiral-2-substituted indolines are an important class of compounds with numerous applications in organic synthesis and as constituents of a number of biologically active molecules. Consequently, there has been a continued interest in the development of efficient methods for the syntheses of this class of chiral compounds. In this review, a detailed survey of the important efforts toward the synthesis of enantioenriched 2-substituted indolines by means of the kinetic resolution or the use of a chiral auxiliary in stoichiometric or catalytic processes is provided. The resolution of racemic mixtures through diastereomeric separation is not considered in the article.

© 2009 Elsevier Ltd. All rights reserved.

Contents

1. Introduction

The indoline skeleton is a ubiquitous scaffold found in a range of biologically active alkaloid natural products[1–3] and pharmaceutically active compounds.[4] Indolines have also been successfully employed as chiral auxiliaries in asymmetric synthesis.[5] Among the various classes of chiral indolines, 2-substituted indolines[6] enjoy a coverted status due to their prevalence in Nature associated with diverse biological activities as found in many compounds such as *Benzastatin* E (Fig. 1).[7] The structural component of pharmaceutical small molecule *Pentopril*[8] (angiotensin converting enzyme (ACE) inhibitor) is largely built upon (*S*)-indoline-2-carboxylic acid.[9] With such a wide range of potential uses, chiral-2-substituted indolines are an important class of compounds drawing increased synthetic interest. It has driven the development of methods to construct or, more commonly, to functionalize the indoline backbone. Consequently, a number of efficient strategies have been

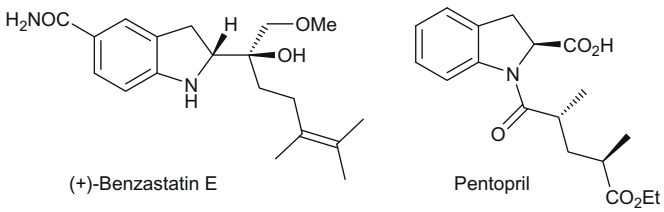


Figure 1. Some biologically active 2-substituted indoline compounds.

* Corresponding author. Tel.: +33 1 69 157895.
E-mail address: kagan@icmo.u-psud.fr (H.B. Kagan).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.008

developed for synthesizing these chiral compounds. To date there is no systematic review available on this topic.

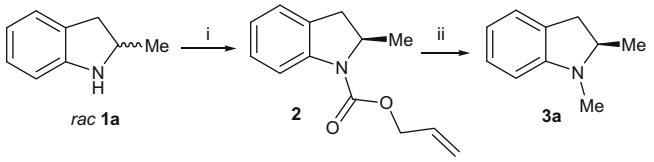
The present review is intended to be a resource for organic chemists, providing a collection of the important efforts toward the synthesis of enantioenriched 2-substituted indolines by means of the kinetic resolution or the use of a chiral auxiliary in stoichiometric or catalytic processes. In Section 2, the approaches by kinetic resolution of racemic 2-substituted indolines is discussed first. In Section 3, the asymmetric synthesis by the stoichiometric use of the chiral auxiliary is considered. In Section 4, the asymmetric catalysis leading to chiral-2-substituted indolines is dealt with. The later part of this review focuses on the methods based on the synthetic transformations of a chiral starting material. It should be noted that the resolution of racemic mixtures by diastereomeric separation is outside the scope of this article.

2. Kinetic resolution of 2-substituted indolines

Kinetic resolution is an interesting protocol to afford the individual enantiomers from various racemic mixtures.[10] This is one of the most widely adopted methodology for the asymmetric entry into 2-substituted indolines. Both enzymatic and non-enzymatic approaches have been established for the resolution of these substrates.

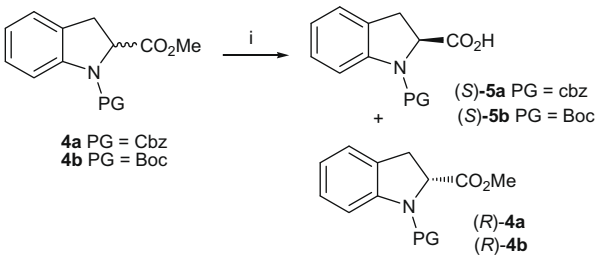
2.1. Enzymatic kinetic resolution

The enzymatic resolution of racemic indolines has been limited to only a couple of examples in which good enantiomeric excesses are obtained, but low conversions were achieved using subtilisin as the biocatalyst.[11] The chemoenzymatic resolution of 2-alkyl indoline was first described by Wong et al. in 1996.[12] They used a novel enzymatic method (lipase and protease) for the enantioselective acylation of various amines. This process was applied for the resolution of racemic 2-methyl indoline **1a**. The enzymatic reaction was carried out for 92 h with subtilisin BPN and diallyl carbonate to give carbamate **2** with 93% ee and in 6% yield (Scheme 1). Carbamate **2** was subsequently reduced to the *N*-methyl derivative **3a** using $LiAlH_4$.



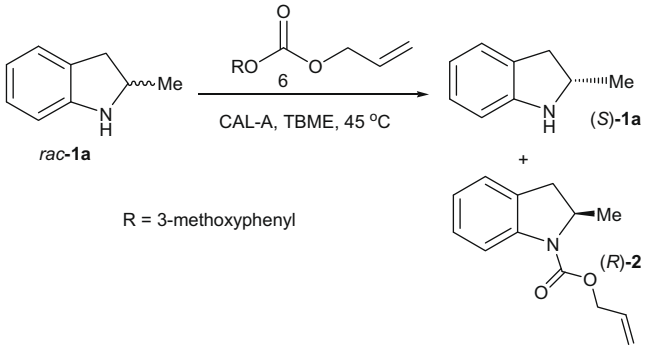
Scheme 1. Enantioselective acylation of 2-methyl indoline with diallyl carbonate. Reagents and conditions: (i) diallyl carbonate (1.5 mmol), phosphate buffer (0.1 M, pH 8.0, 10 mL), subtilisin BPN (50 mg), rt, 92 h, 6% yield, 93% ee; (ii) $LiAlH_4$ (8.7 equiv), ether, 0 °C, 2 h, 93%.

Sugai et al. reported a novel method for the enantioselective hydrolysis of N-protected indoline-2-carboxylic acid methyl ester **4** catalyzed by *Candida antarctica* in good yield (Scheme 2).[13] The enzyme-catalyzed hydrolysis of cbz-protected indoline 2-carboxylic acid ester **4a** at 85 °C proceeded with an *E*-value of 120, at a conversion of 30% to give the product (*S*)-**5a** (97.2% ee) and the unreacted substrate (*R*)-**4a** (41.4% ee). The reaction of the Boc-protected indoline-2-carboxylic acid ester *rac*-**4b** proceeded efficiently at a lower temperature (60 °C), with a conversion of 49.9% and an *E*-value over 1000. In this case, the (*S*)-carboxylic acid **5b** was obtained with >99:9% ee and the unreacted (*R*)-ester **4b** was resolved with 99.6% ee.



Scheme 2. Enzyme catalyzed hydrolysis of N-protected indoline-2-carboxylic acid methyl ester. Reagents and conditions: (i) *Candida antarctica*, 0.1 M phosphate buffer (pH 7), 60 °C.

In 2006, Gotor-Fernandez et al. developed an efficient chemoenzymatic route for the production of enantiomerically pure indolines.[14] *C. antarctica lipase A* (CAL-A) proved to be an excellent enzyme for the kinetic resolution of 2-substituted-indolines, while *C. antarctica lipase B* (CAL-B) showed greater efficiency in the kinetic resolution of 3-methylindoline. Different parameters such as the alkoxycarbonylating agent, temperature, solvent, and the amount of enzyme, amine, and carbonate were studied in order to establish the optimal reaction conditions. The combination of lipase with allylcarbonate **6** in TBME as a solvent at 45 °C has allowed the isolation of the carbamate **2** and (*S*)-2-methyl indoline **1a** with a high level of enantiopurity (Scheme 3).



Scheme 3. Enzymatic kinetic resolution of **1** with allyl carbonate **6**.

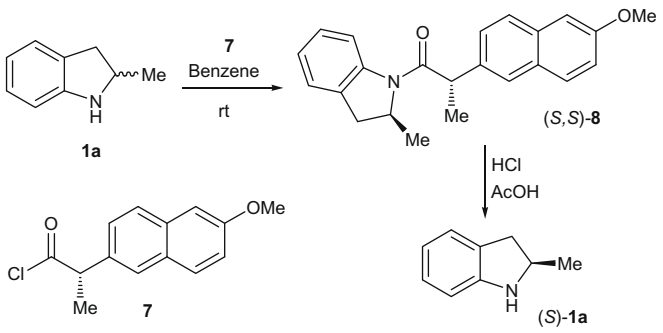
2.2. Non-enzymatic kinetic resolution

It is only relatively recently that the widespread application of non-enzymatic kinetic resolution (or dynamic kinetic resolution) has gained popularity within the synthetic community.[15] In this context, both chiral reagents and chiral catalysts are utilized for the non-enzymatic resolutions of 2-alkyl indolines.

2.2.1. Chiral reagents

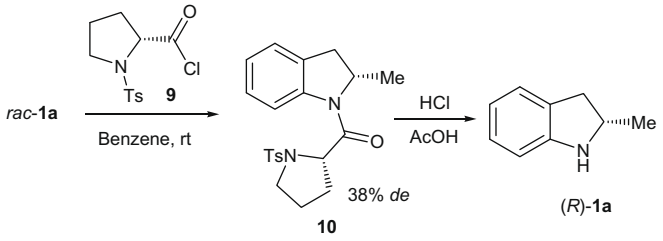
Krasnov et al. reported a non-enzymatic kinetic resolution of 2-methyl indoline leading to the (*S*)-enantiomer by using (*S*)-naproxen acyl chloride **7** as the resolving agent.[16] The reaction is depicted in Scheme 4. The acylation of racemic 2-methyl indoline **1a** with 0.5 equiv of (*S*)-naproxen chloride in the absence of any tertiary amine resulted in the kinetic resolution with predominant formation of (*S,S*)-diastereoisomeric amide **8** (76% de). The recrystallization of **8** followed by acid hydrolysis gave (*S*)-methylindoline **1a** in 27% yield relative to the starting racemic amine. The (*R*)-isomer of **1a** can be isolated from acidic solutions in 76% ee.

The same authors have developed a complementary method for obtaining the (*R*)-enantiomer of **1a** in high enantiomeric excess by using another chiral agent, *N*-tosyl-(*S*)-prolyl chloride **9**.[17] The interaction of **9** with racemic indoline **1a** in a 1:2 molar ratio re-



Scheme 4. Non-enzymatic kinetic resolution of 2-methyl indoline using (*S*)-naproxen acyl chloride **7**.

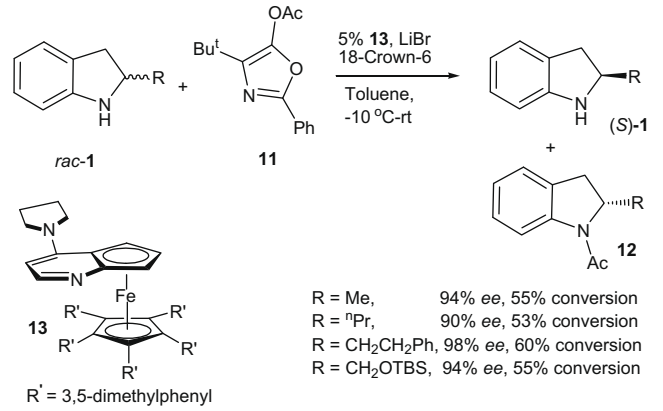
sulted in the predominant formation of corresponding (*R*,*S*)-amide **10**. Further acid hydrolysis of the latter made it possible to obtain the (*R*)-methyl indoline in 38% ee (Scheme 5).



Scheme 5. Non-enzymatic kinetic resolution of 2-methyl indoline using *N*-tosyl-(*S*)-prolyl chloride **9**.

2.2.2. Chiral catalysts in kinetic resolution

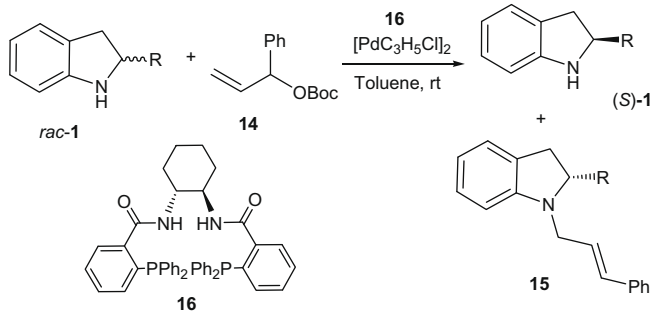
In 2006, Fu et al. reported a non-enzymatic kinetic resolution of indolines through catalytic N-acylation by using a chiral catalyst **13**, which is a ferrocene analogue of DMAP (Scheme 6).[18]



Scheme 6. Non-enzymatic kinetic resolution of indolines through catalytic N-acylation by using chiral catalyst **13**.

After considerable studies on the effect of various reaction parameters on the efficiency of the kinetic resolution of 2-methylindoline **1a**, they found that the addition of LiBr in the presence of 18-crown-6 was essential for obtaining highest selectivity (*s* value 23). To further improve the selectivity factor ($s = k_R/k_S$), a new planar-chiral PPY derivative **13** was designed wherein the chiral environment was tuned through the use of a more bulky cyclopentadienyl group. They have established that an array of 2-substituted indolines (R = Me, ^{n}Pr, CH_2CH_2Ph, CH_2OTBS) can be kinetically resolved with good selectivity factors (14–26) under these optimized reaction conditions.

Recently, Hou et al. realized the kinetic resolution of 2-substituted indolines via a Pd-catalyzed allylic amination in high yields and high enantioselectivities with an *s* factor of up to 59.[19] Among the various chiral ligands investigated, the Trost's ligand **16** showed its superiority for this transformation. High enantioselectivities were obtained when 2-arylindolines were used, independent of the electronic nature of the aryl substituent at the 2-position of the indolines. For example, the kinetic resolution of 2-phenyl indoline (*rac*-**1b**) through the Pd-catalyzed allylic amination with branched allylic carbonate **14** provided the N-allylated indolines **15** in 42% yield and 89% ee, accompanied by the recovered indoline (*S*)-**1b** in 50% yield and 83%, ee with an *s* factor of 44 (Scheme 7).



Scheme 7. Kinetic resolution of 2-substituted indolines via Pd-catalyzed allylic amination.

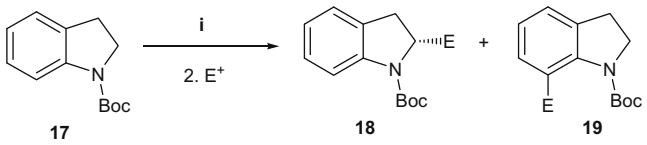
In the case of alkyl or allyl groups at the 2-position of the indoline, good ee's were obtained, but the *s* value was lower (Table 1). This methodology provided the first example for the kinetic resolution of nucleophiles via a transition-metal-catalyzed allylic substitution reaction.

Table 1
Kinetic resolution of indolines **1**

Entry	R		15		1		*s*
			Yie ld%	ee%	Yield%	ee%	
1	Ph	**1b**	42	89	50	83	44
2	Allyl	**1c**	48	65	47	43	7
3	^{i}Pr	**1d**	49	65	48	58	8
4	^{n}Pr	**1e**	40	61	48	36	6
5	*p*-$MeOC_6H_4$	**1f**	38	92	46	80	59
6	*p*-FC_6H_4	**1g**	34	90	40	82	48
7	*p*-ClC_6H_4	**1h**	38	86	43	94	47

3. Stoichiometric asymmetric synthesis

A few stoichiometric approaches have been described for the asymmetric synthesis of 2-indolines. As part of the studies on asymmetric synthesis using circularly polarized light, in 1976, Nicoud and Kagan succeeded in the synthesis of *N*-methyl 2-phenyl indoline by asymmetric photocyclization of *N*-methyl *N*-phenyl enamine, but with very low enantiomeric excess.[20] The first synthetically useful stoichiometric approach for the preparation of enantiopure 2-substituted indolines was developed by Beak et al. in 1997 by utilizing the asymmetric lithiation-substitution strategy. They found that *N*-Boc indoline **17** can be deprotonated regioselectively at the 2-position with *s*-BuLi/(−)-sparteine and allowed to react with various electrophiles to afford 2-substituted *N*-Boc indolines **18**, along with traces of *N*-Boc-7-substituted indolines **19**, in excellent enantioselectivity and in variable yields (Scheme 8).[21]



Scheme 8. Asymmetric deprotonation/substitution of *N*-boc indolines. Reagents and conditions: (i) *s*-BuLi/(−)-sparteine, −78 °C, 6 h, cumene.

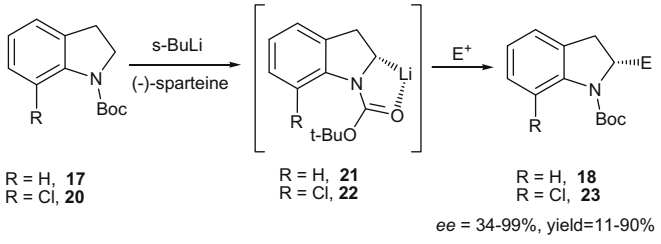
The regioselectivity of this lithiation-substitution was found to be significantly influenced by the choice of ligand and solvent, a 20:1 regioselectivity was observed with (−)-sparteine in cumene at −78 °C. The scope of this lithiation-substitution was investigated with various electrophiles and the details are summarized in Table 2.

Table 2
Electrophiles used for asymmetric deprotonation of indoline **17**

Electrophile	E	Yield%	er[a]
Me_3SnCl	$SnMe_3$	**18a** 70	99:1
CO_2	CO_2Me	**18b** 65	99:1
PhCHO	CH(OHPh	**18c** 61, 13	98:2, 91:9[b]
Me_2SO_4	Me	**18d** 52	98.5:1.5
TMSCl	TMS	**18e** 57	97.5:2.5
PH_2CO	$C(OH)Ph_2$	**18f** 11	92.5:7.5
C_3H_5Br	$CH_2CH{=}CH_2$	**18g** 28	68:32
C_3H_5Cl	$CH_2CH{=}CH_2$	**18h** 18	65:35
C_3H_5Cl/DMPU	$CH_2CH{=}CH_2$	**18i** 15	99:1

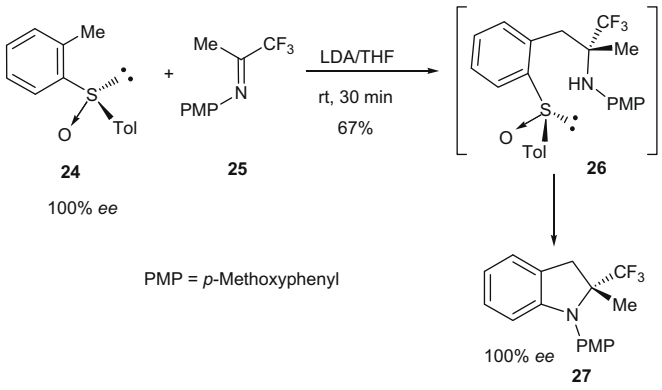
[a] er = enantiomeric ratio.
[b] Ratio of the diastereomers.

When the 7-position of the *N*-Boc indoline was blocked by a chloro substituent **20**, the lithiation-substitution can be carried out at the 2-position to provide 2,7-disubstituted indolines with good yields and ees. It is noteworthy that, the organolithium intermediates (*S*)-**21** and (*S*)-**22** formed in these reactions (Scheme 9) are configurationally stable and react stereoselectively with a variety of electrophiles.



Scheme 9. Formation of configurationally stable organolithium intermediates (*S*)-**21** and (*S*)-**22**.

In a recent report, Ruano et al. outlined an interesting strategy for the preparation of enantiopure fluorinated indolines **27** from 2-*p*-tolylsulfinyl alkylbenzenes through anionic–anionic asymmetric tandem reactions.[22] This approach involves the direct reaction of *N*-PMP-fluorinated imine **25** with 2-(*p*-toluenesulfinyl) alkylbenzene **24** in the presence of LDA (Scheme 10). Almost complete stereoselectivity and mild conditions are the key features of these tandem processes, which include the unusual intramolecular nucleophilic aromatic substitution of a *p*-tolylsulfinyl group by the amide anion as the key reaction.



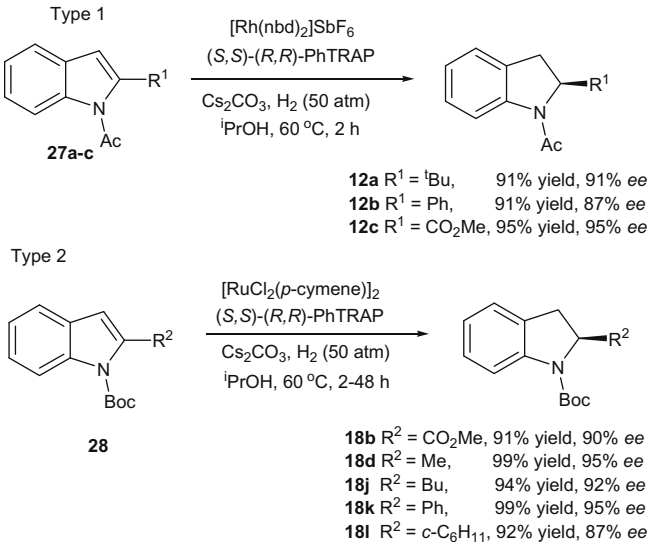
Scheme 10. Synthesis of enantiopure fluorinated indolines through anionic–anionic asymmetric tandem reactions.

4. Catalytic enantioselective reactions

The synthesis of enantiopure products by asymmetric catalysis represents one of the most important areas in modern synthetic chemistry. Unsurprisingly, a number of catalytic approaches have been employed for the asymmetric synthesis of 2-substituted indolines.

4.1. Asymmetric hydrogenation reaction

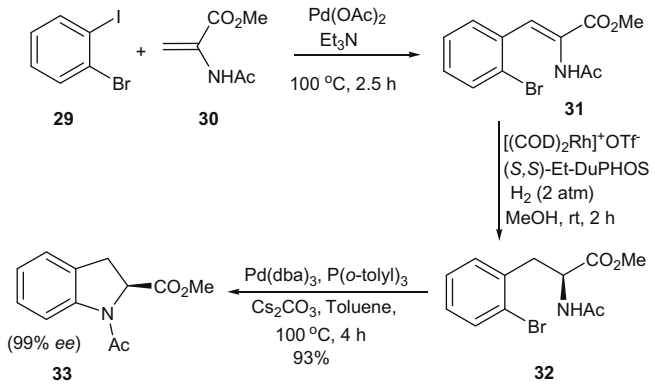
Kuwano et al. succeeded in the synthesis of enantioenriched 2-alkyl indolines **12** with up to 95% ee via the catalytic asymmetric hydrogenation of *N*-acetyl indoles by using a rhodium catalyst.[23] This was the first example of highly enantioselective hydrogenation of five-membered heteroaromatic compounds using asymmetric catalysis. The enantioselective hydrogenation of N-protected indoles was successfully carried out by the use of the rhodium catalyst generated in situ from $[Rh(nbd)_2]SbF_6$ and the chiral bisphosphine PhTRAP, which can form a *trans*-chelate complex with a transition metal atom. The PhTRAP–rhodium catalyst required a base (e.g., Cs_2CO_3) for the achievement of high enantioselectivity. Various 2-substituted *N*-acetylindoles **28** were converted into the corresponding chiral indolines **12** with up to 95% ee. The enantioselectivity of this reaction was significantly affected by the substituent on the nitrogen of the substrate (Scheme 11, Type 1).[23b]



Scheme 11. Catalytic asymmetric hydrogenation of indoles.

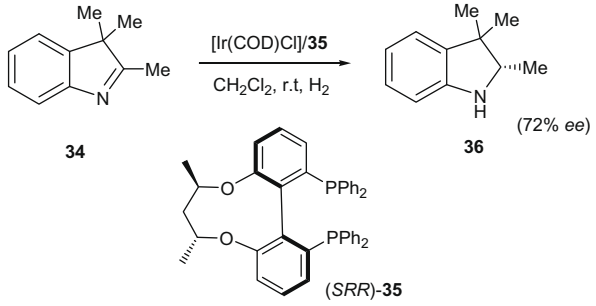
The same authors have also developed a chiral ruthenium-based catalyst for the asymmetric hydrogenation of various *N*-Boc-protected indoles.[24] For example, in the presence of the ruthenium complex generated from an appropriate ruthenium precursor and the chiral bisphosphine PhTRAP ligand, they have successfully carried out the enantioselective hydrogenation of *N*-Boc-2-substitiuted indoles **28**. When the PhTRAP was replaced by other phosphines, the ruthenium catalyst failed to deliver indoline **18** (Scheme 11, Type 2).

Buchwald et al. have utilized the catalytic asymmetric hydrogenation reaction toward the synthesis of chiral-2-substituted indolines.[25] They offered the prospect for the preparation of (*S*)-*N*-acetylindoline-2-carboxylate methyl ester **33** in 99% ee through an asymmetric hydrogenation of the dehydro aminoester **31** followed by the palladium-catalyzed intramolecular coupling of the resulting enantiomerically enriched amine **32** (Scheme 12). Here, enamide **31** was prepared by a Heck coupling reaction of *o*-bromoiodobenzene **29** with methyl-2-acetamidoacrylate **30**.



Scheme 12. Catalytic asymmetric hydrogenation of enamide **31** toward the synthesis of chiral 2-indoline **33**.

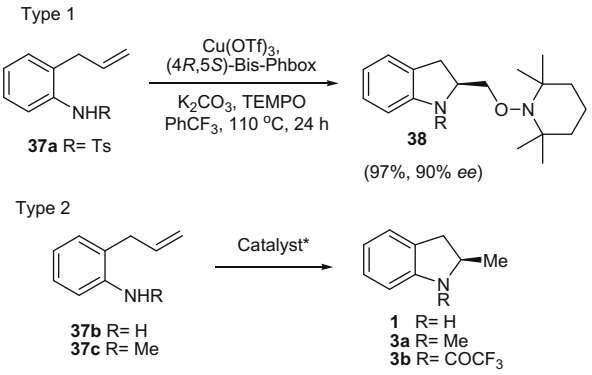
Chan et al. provided an isolated example for the generation of the chiral 2,3,3-indoline **36** by an iridium-catalyzed asymmetric hydrogenation of 2,3,3-trimethylindolenine **34** in the presence of chiral ligand **35** (Scheme 13).[26]



Scheme 13. Iridium-catalyzed asymmetric hydrogenation of **34**.

4.2. Intramolecular amination reaction

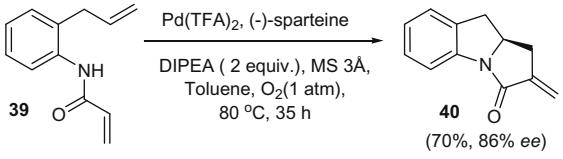
Chemler et al. disclosed a novel and mechanistically distinct copper-catalyzed enantioselective intramolecular aminooxygenation of olefins in the presence of TEMPO leading to the synthesis of chiral 2-indolines and pyrrolidines. After a detailed ligand screening study for the asymmetric induction, they noticed that both enantiomers of the 4,5-*cis*-diphenyl bisoxazoline ligands are optimal for this transformation. Under these conditions, the *N*-tosyl-2-allyl aniline **37a** cyclized in 97% yield providing 2-substituted indoline **38** in high ee (Scheme 14, Type 1).[27]



Scheme 14. Catalytic intramolecular amination of **37**.

As part of the investigation on the hydroamination reactions catalyzed by chiral lanthanide amide ate complexes, Collin et al. attempted the asymmetric synthesis of 2-methyl indoline **1** from 2-allyl aniline **37b** (Scheme 14, Type 2). The targeted cyclization occurred slowly at 110 °C over four days and the chiral ytterbiumate catalyst failed to induce any enantioselectivity for this transformation.[28] The asymmetric hydroamination of this kind of substrate was first achieved by Scott et al. in the presence of a zirconium catalyst.[29] Although the enantioselectivity obtained was modest (20% ee), the *N*-methyl-2-allylaniline **37c** cyclized efficiently to give **3a**. The most promising result in this category of transformation was reported by Bergman et al. in 2006, by utilizing a novel zirconium bis(amido)complex generated by the combination of diphosphinic amide ligand and $Zr(NMe_2)_4$ catalyst.[30] They have demonstrated the asymmetric hydroamination of 2-allylaniline **37b** to afford *N*-trifluoroacetyl-2-methyl indoline **3b** in 70% ee and 93% yield (Scheme 14, Type 2).

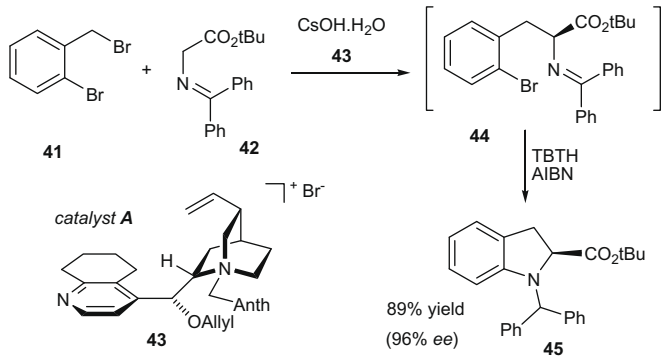
Yang et al. developed an interesting methodology for the direct access to enantioenriched and structurally versatile indolines, by a Pd(II)-catalyzed enantioselective oxidative tandem cyclization reactions (Scheme 15). For example, the reaction of the substrate **39** using (−)-sparteine as the chiral ligand and molecular oxygen as the oxidant provided the chiral-2-indoline derivative **40** in 70% yield and 86% ee.[31]



Scheme 15. Enantioselective oxidative tandem cyclization of **39**.

4.3. Phase-transfer catalysis

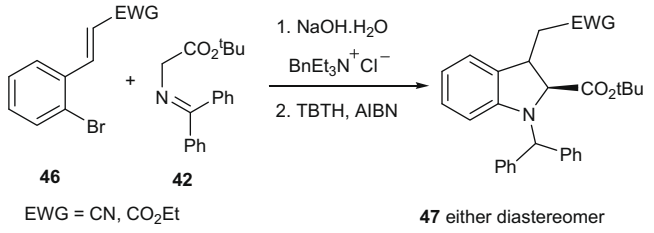
Johnston et al. recently reported enantioselective indoline annulations in two steps, leading to enantioenriched 2-substituted indolines starting from an aromatic dibromide (Scheme 16). The sequence involves an enantioselective phase-transfer-catalyzed glycine Schiff base alkylation with *o*-bromo benzylbromide **41** followed by free radical-mediated aryl amination to deliver either



Scheme 16. Phase-transfer-catalyzed alkylation and free radical-mediated aryl amination.

enantiomer of indoline amino ester **45** with high ee.[32] Using the Corey protocol for alkylation, they found that the cinchonidinium salt **43** provided the (*S*)-phenylalanine derivative **44** in good yield and with high enantiomeric excess. Exposure of the resulting aryl halide to tri-*n*-butyltin hydride in the presence of AIBN furnished the cyclization product **45** in excellent yield.

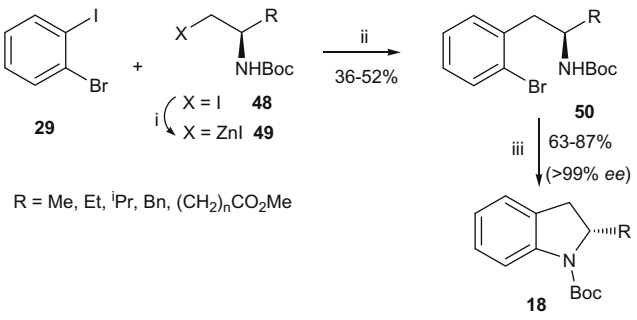
The same authors recently pursued a variation on this theme that targeted the 2,3-disubstituted indoline ring system, by retaining the convergency offered by the basic modular assembly beginning from a protected glycine Schiff base **42**.[33] The phase-transfer-catalyzed Michael addition of **42** to activated styrene derivatives **46** and subsequent free radical-mediated aryl amination provided various 2,3-disubstituted indolines **47** (Scheme 17). The asymmetric version of this reaction remains unexplored.



Scheme 17. Phase-transfer-catalyzed Michael addition/free radical-mediated aryl amination.

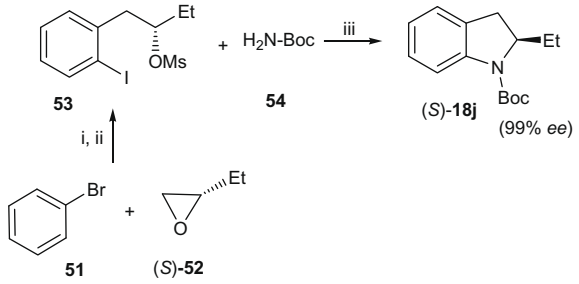
5. Chiral synthons strategy

In addition to the aforementioned routes, some synthetic transformations of a chiral starting material are available, which may lead to the synthesis of enantioenriched 2- or 2,3-substituted indolines. Jackson et al. presented a simple and effective access to enantiomerically pure 2-substituted indolines using a sequential palladium-catalyzed processes (Scheme 18).[34] The chemistry involved in this protocol was the application of the Pd-catalyzed coupling of a chiral amino organozinc reagent **49** with 2-bromoiodobenzene **29**, followed by Buchwald's palladium-catalyzed intramolecular amination of the resulting amine **50**. The organozinc reagents **49** were prepared by the treatment of iodide **48** with activated zinc dust in DMF at 0 °C. The yields in the initial coupling were modest (36–52%), but the cyclization yields were satisfactory (63–87%). The cyclization occurs without any racemization of amine derivatives **50**, and all the products **18** were enantiomerically pure.



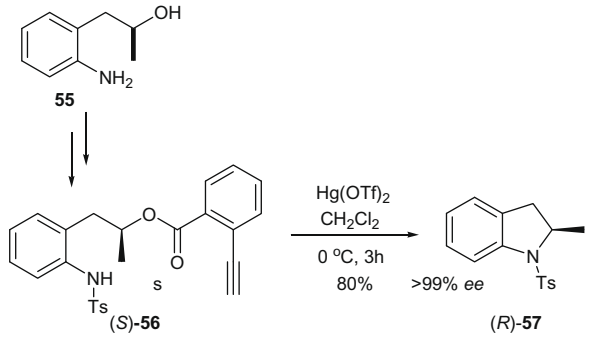
Scheme 18. Sequential palladium-catalyzed coupling reactions toward the synthesis of **18**. Reagents and conditions: (i) Zn, DMF, 0 °C; (ii) $Pd_2(dba)_3$,P(*o*-tolyl)$_3$, rt, 4 h; (iii) $Pd_2(dba)_3$,P(*o*-tolyl)$_3$, Cs_2CO_3, toluene, 100 °C, 15 h.

Buchwald et al. reported an efficient one-pot procedure for the synthesis of chiral 2-ethylindolines based on a domino Cu-catalyzed amidation/nucleophilic substitution reaction (Scheme 19). The copper-catalyzed reaction of (2*S*)-iodophenethyl mesylate **53** with carbamate **54** in THF resulted in the formation of (2*S*)-ethyl indoline **18j** in excellent yield.[35] The enantiomerically pure mesylate **53** was obtained by *n*-BuLi mediated-ring opening of (*S*)-1,2-epoxy butane **52** with bromobenzene **51** in the presence of $BF_3{\cdot}Et_2O$ followed by the subsequent treatment with $AgCO_2CF_3$ and powdered iodine.



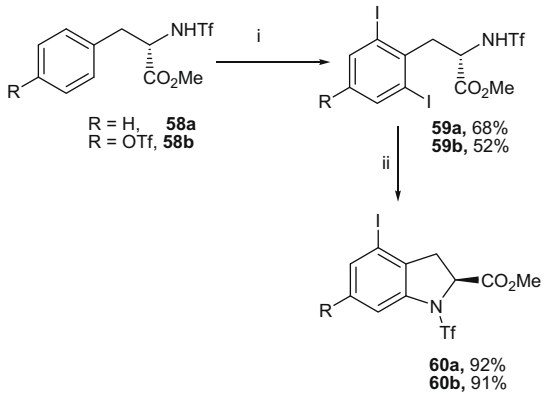
Scheme 19. Domino Cu-catalyzed amidation/nucleophilic substitution reaction. Reagents and conditions: (i) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C–rt, 1 h; (ii) $AgCO_2CF_3$, I_2, $CHCl_3$, rt, 1.5 h; (iii) CuI, DMEDA, THF, 80 °C, 16 h, 94%.

An efficient access to enantiopure 2-methyl indoline by a novel catalytic activation of the leaving group in a S_N2 reaction has been described by Nishizawa et al. The (2*S*)-anilinopropyl-ethynyl benzoate **56** (100% ee) prepared from the corresponding amino alcohol **55**, reacted smoothly with catalytic amounts of $Hg(OTf)_2$ to give (*R*)-2-methyl indoline derivative **57** in 80% yield and 98% ee.[36] It should be noted that, the reaction on enantiomerically pure secondary alcohol derivative resulted in inversion of stereochemistry (Scheme 20).



Scheme 20. Catalytic activation of the leaving group in a S_N2 reaction.

Yu et al. recently developed a promising C–H bond iodination/intramolecular amination route for the synthesis of the enantiopure indoline 2-carboxylic esters from natural amino acids phenyl alanine and tyrosine (Scheme 21).[37] The Pd^{II}-catalyzed iodination of the aminoacid derivative **58** in presence of $PhI(OAc)_2$ and I_2 followed by CuI mediated intramolecular amination of the diiodo-product **59** resulted in the formation of indoline 2-carboxylic acid derivative in excellent yields.



Scheme 21. Pd^{II}-catalyzed iodination and CuI mediated intramolecular amination. Reagents and conditions: (i) $Pd(OAc)_2$, $PhI(OAC)_2$, I_2, $NaHCO_3$, DMF, 130 °C, 72 h; (ii) CuI, 1 equiv $NaHCO_3$, DMF, 130 °C, 24 h.

6. Conclusions

The widespread occurrence and interesting biological activities of enantiopure 2-substituted indolines make them important targets for synthesis. Consequently, a number of useful methodologies have been developed for the asymmetric entry into this class of compounds. This review article revealed that only a few examples of catalytic processes are described for the generation of 2-substituted indolines in high enantiomeric excess. Therefore the search for novel and efficient methods involving easily available starting materials and convenient reaction remains to be explored.

Acknowledgments

We thank Université Paris-Sud and CNRS for financial support. One of us (S.A.) acknowledges the Servier Company for post-doctoral fellowship. We thank Dr. A. Cordi and Dr. J.-L. Péglion for fruitful discussions.

References

1. (a) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (c) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Mura, S. O.; Smith, A. B., III *J. Am. Chem. Soc.* **2000**, *122*, 2122.
2. (a) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366; (b) Dounay, Z. A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186; (c) Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753.
3. (a) Gueritte, F.; Fahy, J. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, 2005; pp 123–135; (b) Dewick, P. M. *Medicinal Natural Products. A Biosynthetic Approach*, 2nd ed.; John Wiley and Sons, Ltd: New York, 2002.
4. (a) Bromidge, S. M.; Duckworth, M.; Forbes, I. T.; Ham, P.; King, F. D.; Thewlis, K. M.; Blaney, F. E.; Naylor, C. B.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D.; Clarke, S. E. *J. Med. Chem.* **1997**, *40*, 3494; (b) Hobson, L. A.; Nugent, W. A.; Anderson, S. R.; Deshmukh, S. S.; Haley, J. J.; Liu, P.; Magnus, N. A.; Sheeran, P.; Sherbine, J. P.; Stone, B. R. P.; Zhu, J. *Org. Process Res. Dev.* **2007**, *11*, 985.
5. Andersson, F.; Hedenstrom, E. *Tetrahedron: Asymmetry* **1952**, *2006*, 17 and references cited therein.
6. (a) Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625; (b) Corey, E. J.; Harbans, S. S.; Gougoutas, J. Z.; Saenger, W. *J. Am. Chem. Soc.* **1970**, *92*, 2488; (c) Choi, J. Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 7795.
7. Kim, W. G.; Kim, J.-P.; Koshino, H.; Shin-Ya, K.; Seto, H.; Yoo, I.-D. *Tetrahedron* **1997**, *53*, 4309.
8. (a) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277; (b) Natesh, R.; Schwager, S. L. U.; Evans, H. R.; Sturrock, E. D.; Acharya, K. R. *Biochemistry* **2004**, *43*, 8718.
9. Sato, S.; Watanabe, H.; Asami, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4329.
10. (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249; (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5; Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407; (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.
11. Wong, C.-H.; Orsat, B.; Moree, W. J.; Takayama, S. US-5981267.
12. Orsat, B.; Alper, P. B.; Moree, W.; Mak, C.-P.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 712.
13. Kurokawa, M.; Takeshi Sugai, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1021.
14. Gotor-Fernandez, V.; Fernandez-Torres, P.; Gotor, V. *Tetrahedron: Asymmetry* **2006**, *17*, 2558.
15. (a) Keith, M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5; (b) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869; (c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.
16. Krasnov, V. P.; Levit, G. L.; Andreeva, I. N.; Grishakov, A. N.; Charushin, V. N.; Chupakhin, O. N. *Mendeleev Commun.* **2002**, *12*, 27.
17. Krasnov, V. P.; Levit, G. L.; Bukrina, I. M.; Andreeva, I. N.; Sadretdinova, L. S.; Korolyova, M. A.; Kodess, M. I.; Charushin, V. N.; Chupakhin, O. N. *Tetrahedron: Asymmetry* **2003**, *14*, 1985.
18. Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.
19. Hou, X. L.; Zheng, B. H. *Org. Lett.* **2009**, *11*, 1789.
20. Nicoud, J. F.; Kagan, H. B. *Israel J. Chem.* **1976/1977**, *15*, 78.
21. Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.
22. Ruano, J. L. G.; Aleman, J.; Catalan, S.; Marcos, V.; Monteagudo, S.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941.
23. (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614; (b) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521.
24. Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653.
25. Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
26. Qiu, L.; Chan, A. S. C., et al *J. Am. Chem. Soc.* **2006**, *128*, 5955.
27. Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638.
28. Aillaud, I.; Collin, J.; Duhayon, C.; Guillot, R.; Lyubov, D.; Schulz, E.; Trifonov, A. *Chem. Eur. J.* **2008**, *14*, 2189.
29. Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894l.
30. Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.
31. Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N. Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130.
32. Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.
33. Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040.
34. Deboves, H. J. C.; Hunter, C.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 733.
35. Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721.
36. Yamamoto, H.; Pandey, G.; Asai, Y.; Nakano, M.; Kinoshita, A.; Namba, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 4029.
37. Li, J.-Q.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.