Organocatalytic Strategies for the Synthesis of Axially Chiral Compounds

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Abstract: Atropisomers are compounds in which chirality arises from hindered rotation along carbon-carbon or carbon-heteroatom single bond. Recently organocatalysis appeared to be a rapid, valuable and efficient strategy for their preparation in an enantioselective manner. In this report a general overview of the most important organocatalyzed atroposelective transformations will be given pointing out in particular the specific role played by the catalyst.

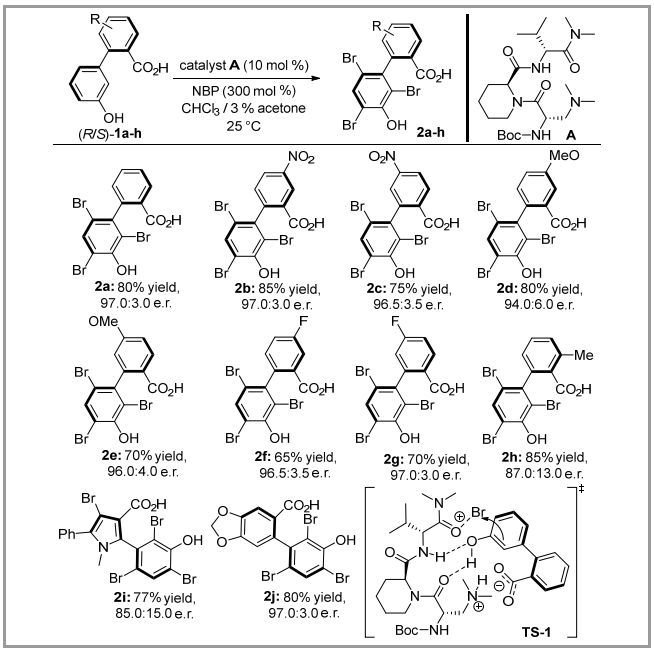
1 Dynamic kinetic resolution
2 Desymmetrization of biaryls
3 Direct synthesis of biaryls
4 Asymmetric Friedel-Crafts amination of naphthols
5 *N*-alkylation via phase transfer catalysis
6 Desymmetrization of *N*-arylmaleimides

Key words: Atropisomers, Organocatalysis, Enantioselective synthesis, Desymmetrization, Dynamic kinetic resolution.

The enantioselective synthesis of axially chiral compounds is a stimulating research field mainly focused for the preparation of biarylic systems. Large number of methodologies have been successfully employed[1] and among all the Suzuki–Miyaura coupling is certainly the most diffuse.[2] The enantioselectivity can be generally induced using chiral auxiliary directly bonded to the substrates or using catalytic strategies in which chiral ligands surrounds the active metal core of the catalyst. Recently organocatalysis[3] has emerged as one of the most versatile and powerful tool for the realization enantioenriched compounds. The recent successfully applications of organocatalysis to the synthesis of atropisomeric compounds[4] confirm the potentiality expressed by small organic molecules to design novel and challenging chemical transformations. It is well known the importance that biaryl atropisomers have as ligands, catalysts or biological active compounds,[5] so it is not strange that most of the organocatalytic synthesis of atropisomers focused on biarylic systems. However, during the last years, the attention of several research groups has been directed also to the enantioselective synthesis of non biaryls atropisomers such as amides, anilides and imides. In this report an overview of the most important organocatalyzed atroposelective transformations is given pointing out in particular the specific role played by the catalyst.

1 Dynamic Kinetic Resolution

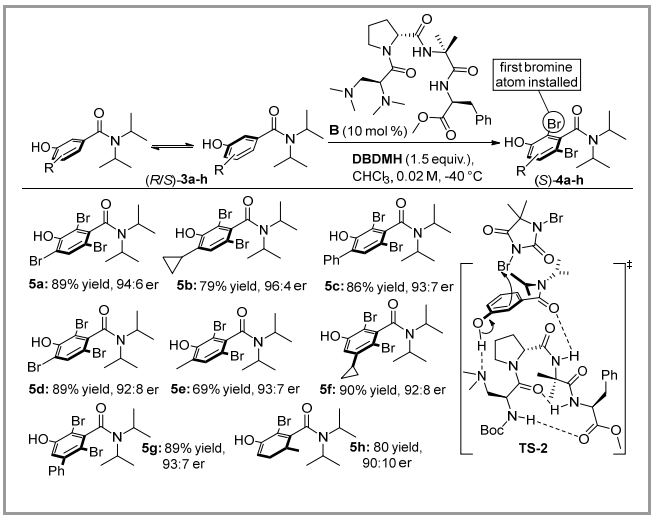
The dynamic kinetic resolution (DKR) is one of the most important techniques to transform racemic axially chiral in biaryls into enantiopure atropisomers. For example in compound **1** the low energy barrier to rotation of the carbon-carbon single bond connecting the two aryl units do not allow the isolation of stable atropisomers. By means of an appropriate regioselective reaction the barrier to racemization can be increased to a sufficiently high value so that the resulting compound can be isolated as stable atropisomer. This strategy was successfully applied by Miller and co-workers[6] using the peptide catalyzed asymmetric bromination of carboxylic acids. Racemic biarylic benzoic acids **1a-h** were converted into non-racemic analogs using a simple bromination strategy employing 3 equivalents of *N*-bromophthalimide (NBP) as brominating agent. It was envisaged that peptidic based organocatalysts could be fundamental for the success of the atroposelective transformation. In particular their β-turn conformation could select the stereogenic axis orientation during the electrophilic aromatic substitution. Various tripeptide catalysts were screened and it was found that catalyst **A**, with an L-pipecolinic acid residue showed an excellent catalytic activity as well as a remarkable ability to control the axial chirality in the products. The reaction was performed using a large number of functional groups, was well tolerated and displayed good reactivity and enantioselectivity, however no mention on the effects of the substituents on the phenol ring was reported. The scope of the reaction is furthermore enriched by the presence of a pyrrole analog **2i** and catechol **2j** as precursors of natural bioactive substructures[7] (scheme 1).



Scheme 1 Atroposelective bromination of carboxylic acids.

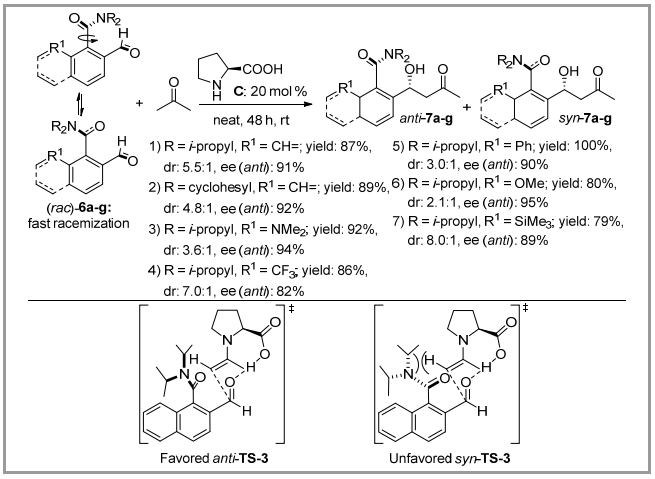
The proposed transition state **TS-1** is governed by several weak interactions involving **A** with the substarte. Thus **A** forms a quaternary ammonium salt with the carboxylic acid and also coordinates with the phenolic aryl unit by H-bonding interactions. The result is a twisted biarylic system which reacts with the bromonium ion activated by the *N,N*-dimethylamide. The increased steric hindrance resulting from the first bromination, probably occurring at the 2′ position, enhanced the barrier to rotation avoiding a rapid racemization of the product. Further bromination at the 6′ position definitely freezes the rotation leading to (*R*)-atropisomer.

Miller and coworkers[8] confirmed the usefulness of a peptidic framework as catalyst for the dynamic kinetic resolution of racemic benzamides **3**. Various *N,N*-diisopropylbenzamides underwent atroposelective bromination in high yields and enantioselectivity with dibromodimethylhydantoin (DBDMH) as the brominating agent. In this transformation catalyst **B** based on a D-prolinic core was employed. Interestingly a different bromination pathway was observed in the presence and in the absence of catalyst that installed the first bromine atom in the most sterically demanding ortho position generating the stable chiral axis at this stage of the reaction. Based on the X-ray structure **TS-2** in which the deprotonation of the phenol by the NMe_2 group of **B** and an intermolecular hydrogen bond with the diisopropyl amide promote the steroselective bromination was proposed (scheme 2).



Scheme 2 Atroposelective bromination of benzamides.

In 2-formyl-*N*,*N*-diisopropyl-1-naphthamide **6** the different orientations of the carbonyl group of the amide with respect to the plane entailed by the naphthyl moiety, reveals the existence of two possible atropisomers. However the orthogonal orientation of the freely rotating trigonal aldehyde substituent and the aryl allows the rapid interconversion of the two atropisomers by fast rotation along the single bond connecting the amidic carbony group and the aryl unit. The result is that **6a-g** exist as racemic compounds (scheme 3). A route to synthesize stable atropisomers is to increase the energy barrier to rotation by transforming the aldehyde from a trigonal-planar to a spherical-tetrahedral subsituent.[9] Walsh and co-workers[10] exploited this concept and developed the first DKR of amides by means of an L-proline **C** catalyzed aldol reaction of acetone on the aldehydic substituent.



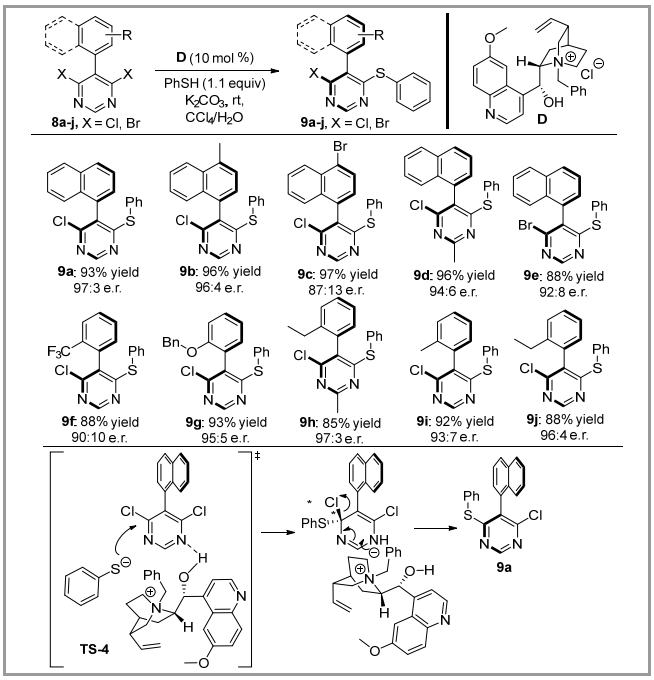
Scheme 3 Atroposelective DKR catalyzed by L-proline.

The reaction proceeded with high enantiocontrol but with moderate *anti*-diastereoselectivity and can be easily applied also to substituted benzamides with similar results. Several experiments revealed that **C** gave high enantiocontrol during the aldol reaction but

it was not so efficient to control of the stereogenic axis. The favored *anti* product is probably the result of a **TS-3** where the interactions of the amide substituents with the axial hydrogen in the Zimmerman-Traxler transition state model[11] are absent.

2 Desymmetrization of biaryls

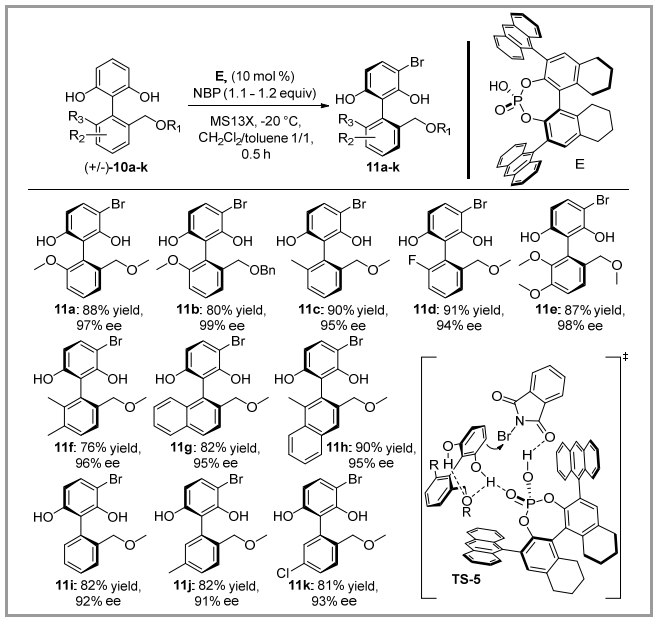
The desymmetrization is a largely investigated strategy for the preparation of chiral biaryls. An interesting example was reported by the group of Smith[12] using phase transfer catalysis (PTC).[13]



Scheme 4 Atroposelective desymmetrization via NAS.

Under the control of commercially available *N*-benzylquininium chloride **D** one enantiotopic chlorine atom of electron poor dichcloropyrimidines **8a-j** was selectively displaced by thiophenol. The nucleophilic aromatic substitution (NAS)[14] was highly efficient and gave high yields and atroposelectivities with a large series of substituents. Using an excess of thiol the atroposelectivity was increased because of a desymmetrization/kinetic resolution that transformed the minor enantiomer to an achiral species after displacement of the second chlorine atom. The chiral ion pair represented by the catalyst cation and the thiophenol anion (**TS-4**) promoted the formation of a Meisenheimer complex[14] in which a chiral axis and a stereogenic center are present.

Akiyama[15] developed an interesting example of desymmetrization/dynamic kinetic resolution (DKR) performing an electrophilic aromatic bromination reaction of *ad-hoc* designed racemic biaryls catalyzed by chiral phosphoric acid **E**.

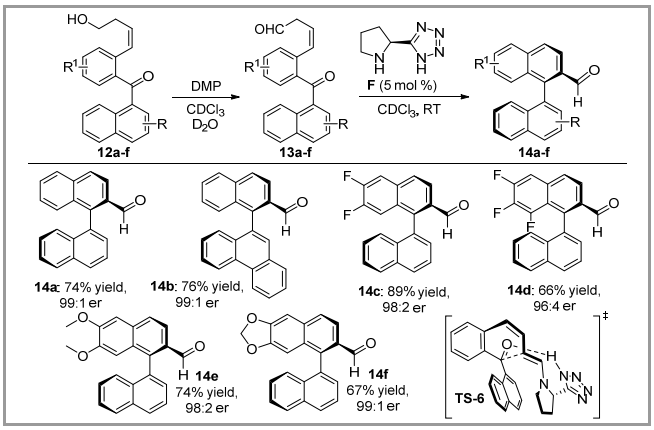


Scheme 5 Desymmetrization catalyzed by chiral phosphoric acid.

The two hydroxy groups could establish a hydrogen bond network made of two concomitant interactions with *N*-bromophthalimide (NBP) and the catalyst and with the etheral substituent of the other aromatic ring. While the first interaction allows the reagents to react under the stereochemical control of **E**, the second gives the required rigidity to the complex during the generation of the chiral axis (TS-5). Using an excess of NBP the reaction proceeded in a desymmetrization/kinetic resolution sequence leading to chiral biaryls in excellent enantioselectivity. The postulated hydrogen bond network was supported by computational calculations that highlighted the role of both hydroxy and CH_2OMe groups (scheme 5).

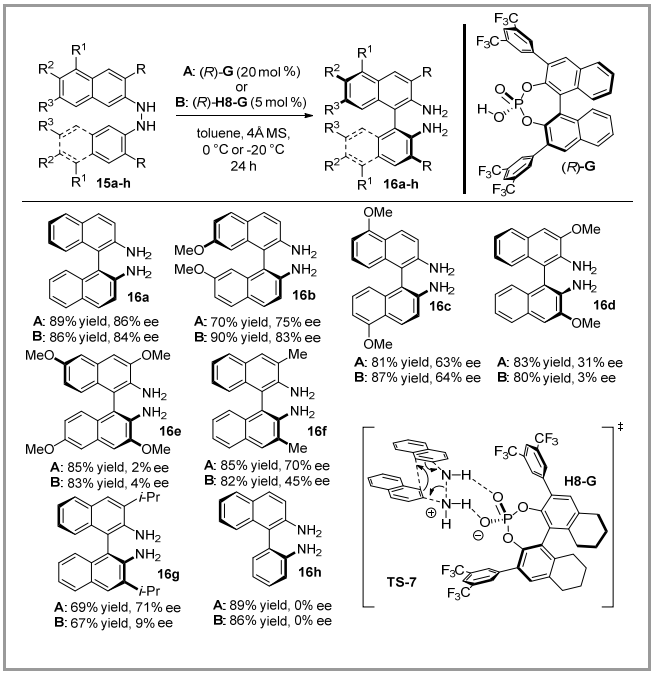
3 Direct synthesis of biaryls

Sparr[16] developed a new atroposelective synthesis of 1,1'-binaphthalene-2-carbaldehydes **14a-f** using an intramolecular aldol condensation of ketoaldehyde of type **13** catalyzed by pyrrolidine-tetrazole **F**. Despite the instability of the starting materials, prepared *in situ* from alcohols **12a-f**, the reaction gave binaphthyles in excellent yields and atroposelectivity with 5 mol% of **F**. The geometry of the substrate places the enamine in a suitable position to react with the ketone. The plausible coordination of the ketone by the NH group of **F** twists the carbonyl and the naphthyl groups out of the plane (TS-6). In this way during the dehydration/aromatization path the stereochemical information is transferred from the catalyst to the chiral axis (scheme 6).



Scheme 6 Atroposelective intramolecular aldol condensation.

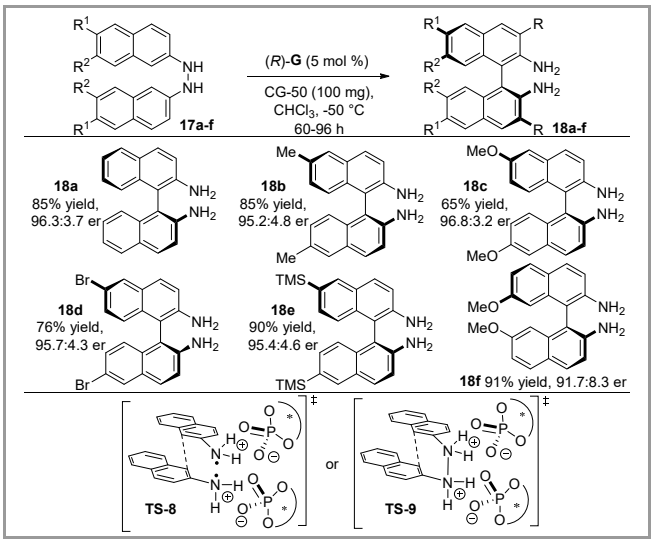
In 2013, Kürti[17] presented the first organocatalytic atroposelective coupling reaction of *N,N'*-biaryl hydrazines **15a-h** for the synthesis of BINAM[18] derivatives **16**.



Scheme 7 [3,3]-Sigmatropic rearrangement of *N,N'*-biaryl hydrazines catalyzed by chiral phosphoric acid.

The strategy of this synthesis exploited the ability of phosphoric acid **G** to promote the [3,3]-sigmatropic rearrangement giving enantioenriched 1,1'-binaphthyls as single regioisomers. The reaction could be catalyzed also by **H8-G** that furnished similar conversions but different enantiocontrol when 3,3'-disubstituted hydrazines were used (scheme 7). A DFT calculated model for the TS-7 is presented. The stereoselectivity is the result of steric and electronic effects. It was observed a complete proton transfer from the catalyst to the nitrogen of the hydrazine with the phosphate counterion that locks the protonated intermediate via H-bonding and π-π aryl interactions into a sole conformation until deprotonation, assisted by the same phosphate occurs.

List et al[19] presented the same reaction using the same catalyst albeit with some differences that lead to an increment of yields and atroposelectivity (scheme 8). Loading of (*R*)-**G** was reduced to 5 mol%, chloroform was used as the solvent and the temperature was reduced to -50 °C. Moreover to ensure complete conversion acidic CG-50 resin was employed. However the scope is limited only to 6,6'- and 7,7'-dinaphthylhydrazines. Based on the study on the nonlinear effects,[20] the authors presented experimental evidences supporting a dicationic or radical cation rather than a monocationic pathway (**TS-8** or **TS-9**).



Scheme 8 Synthesis of BINAM derivatives via dication/ diradical intermediate.

4 Asymmetric Friedel-Crafts amination of naphthols

After the seminal report by Curran,[21] atropisomerism in which axial chirality originates from restricted rotation along carbon-nitrogen single bond became an important topic of asymmetric synthesis. Jørgensen and Bella[22] developed the first organocatalytic atroposelective synthesis of anilides via Friedel-Crafts (FC) amination of 2-naphthols using atropisomeric 5'-aminated dihydrocupreidine-DHQD **H** and dihydrocupreine-DHQ **I** as catalyst (Figure 1).

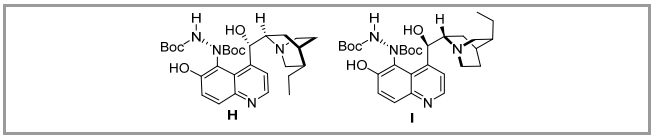
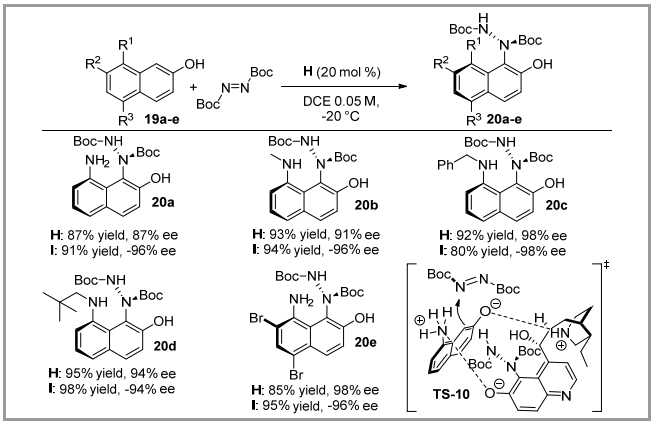


Figure 1 Catalysts for the Friedel-Crafts atroposelective amination.

The reaction was highly enantioselective and various naphthylanilides **20a-e** were prepared. The presence of large substituents in the 8-position of naphthols and at both carbonyl groups of the azodicarboxylate derivative, avoided racemization of the chiral axis

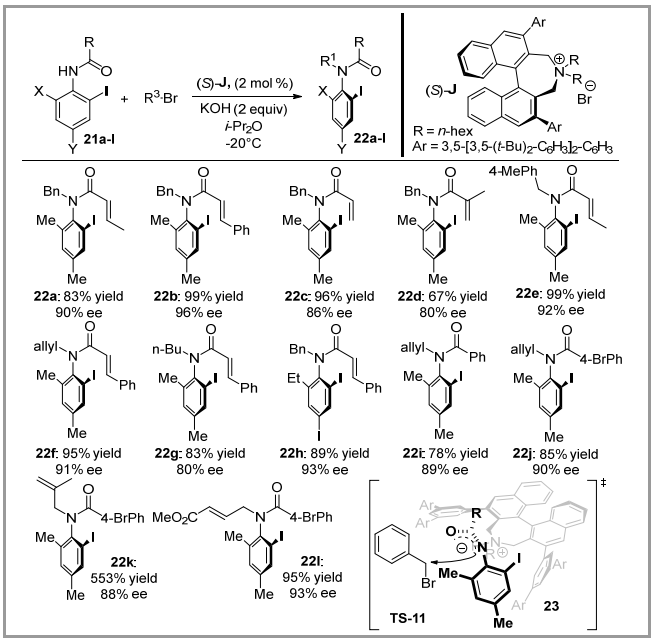
(scheme 9). The reaction mechanism is expected to work through deprotonation of the naphtholic hydroxy group by the quinuclidine ring of **H** followed by the FC amination. However because various substituents, different from amino group at the 8-position of naphthols gave racemic mixtures, a double zwitterionic species closely associated in a two-point contact ion pair, is believed to be the intermediate that undergoes the FC amination **(TS-10)**.[22b]



Scheme 9 Atroposelective Friedel-Crafts amination of naphthols.

5 *N*-alkylation via phase transfer catalysis

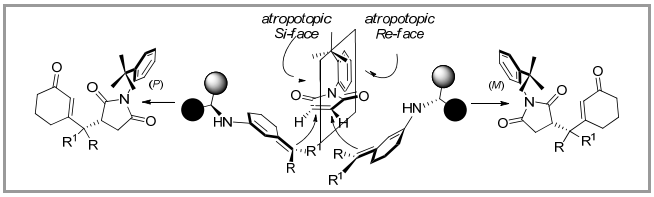
Maruoka[23] realized the first synthesis of axially chiral *o*-iodoanilides using PTC. A chiral binaphthyl-modified ammonium salt (*S*)-**J** promoted the *N*-alkylation reaction of substituted *o*-iodoanilides **21a-l** in excellent enantioselectivity and yields. X-ray analysis on the chiral ammonium anilides **23** elucidates that the alkylation takes place from the opposite side shielded by the catalyst cation **(TS-11)** which recognizes the different steric hindrance between iodide and methyl group in salt **23** giving rise to the observed axial chirality (scheme 10).



Scheme 10 Selected examples for the alkylation of *o*-iodoanilides.

6 Desymmetrization of *N*-arylmaleimides

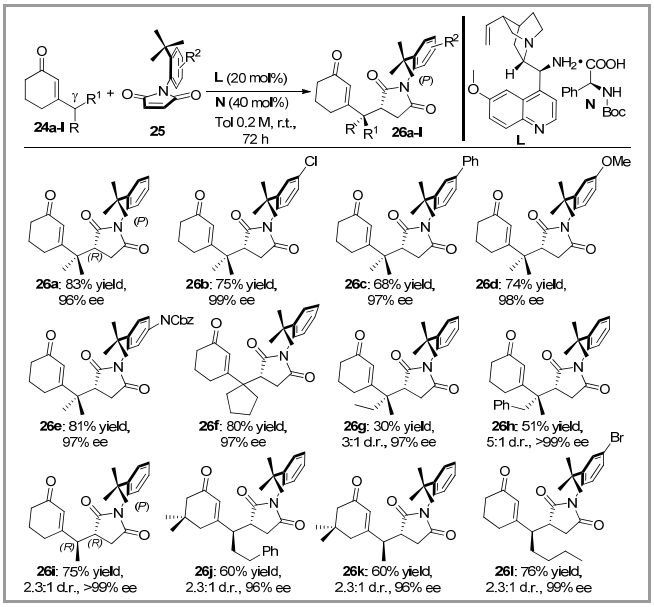
Inspired by the report of Curran on the addition of *tert*-butyl radicals to *N*-arylmaleimides,[21] we realized the atroposelective desymmetrization of *N*-(2-*tert*-butylphenyl)maleimides via vinylogous Michael addition of 3-substituted cyclohexenones.[24] This class of compound has a hindered rotation of the C_{Ar}-N single bond. This implies the existence of a plane of symmetry which can be desymmetrized through nucleophilic addition at one of the two carbon atoms of the double bond, with the consequent generation of a stereogenic axis in the resulting succinimide. The ability of a catalyst to distinguish between the two atropotopic faces of the maleimide and direct the reaction to only one of the two carbon atoms that are at the same time prochiral for central and axial chirality is fundamental (scheme 11).



Scheme 11 Desymmetrization of maleimides via Michael addition.

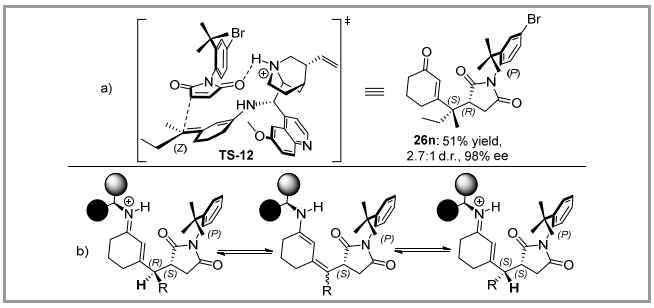
9-Amino(9-deoxy)*epi*-quinine **L** in combination with *N*-Boc-L-Phenylglycine **N** promoted the vinylogous reaction of various substituted cyclohexenones and maleimides with complete remote control over all the elements of chirality (scheme 12). After several experiments and with the absolute configuration in hand, a mechanism based on a hydrogen bonding activation of the carbonyl group lying in the *Re* face of the plane of symmetry of the maleimide was proposed **(TS-12)**. In this way catalyst **L** directed the

approach of enone to the bottom face of the double bond with the control of both the chiral axis and the chiral centers (scheme 13a).



Scheme 12 Selected examples for the desymmetrization of maleimides. Only major diastereoisomers are reported.

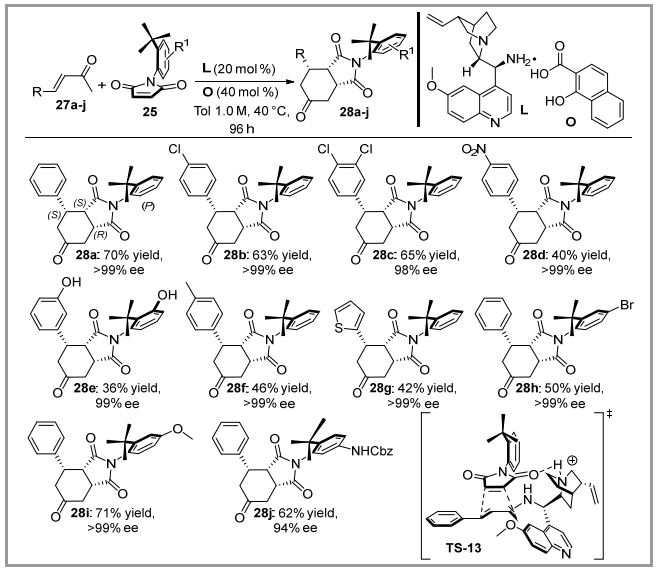
We demonstrated that an equilibrium of epimerization at the exocyclic chiral center accounted for the moderate diastereoselection when γ-monosubstituted enones were employed (scheme 13b).



Scheme 13. a) Proposed TS; b) Epimerization parasitic reaction.

Using a similar strategy we recently studied the formal Diels-Alder reaction of *α,β*-unsaturated ketones **27a-j** with *N*-(2-*t*-butylphenyl)maleimides.[25]

Catalyst **L** in combination with 1-hydroxy-2-naphthoic acid **O** catalyzed the cycloaddition process of a large series of *α,β*-unsaturated enamines giving rise only to *endo*-diatereoisomers with complete control of axial and central chirality (scheme 14). The approach of the enamines to the double bond of the maleimide gives rise to an opposite stereochemical outcome at the chiral centers from the non-atroposelective examples reported by Melchiorre.[26] Probably the reaction is strongly influenced by the presence of the *tert*-butyl group which *forces* the chiral enamine to add to a different side of the maleimide leading to a site specific reaction pathway (**TS-13**).



Scheme 14 Selected examples for the atroposelective formal Diels-Alder reaction of α,β-unsaturated ketones with *N*-arylmaleimides.

In summary several methods for the preparation of atropisomers have been developed using diverse organocatalytic strategies. In addition to the well established methodologies mainly focused on the use of metal or chiral auxiliaries, organocatalysis offers different but powerful tools for the enantioselective approach to various classes of atropisomers.

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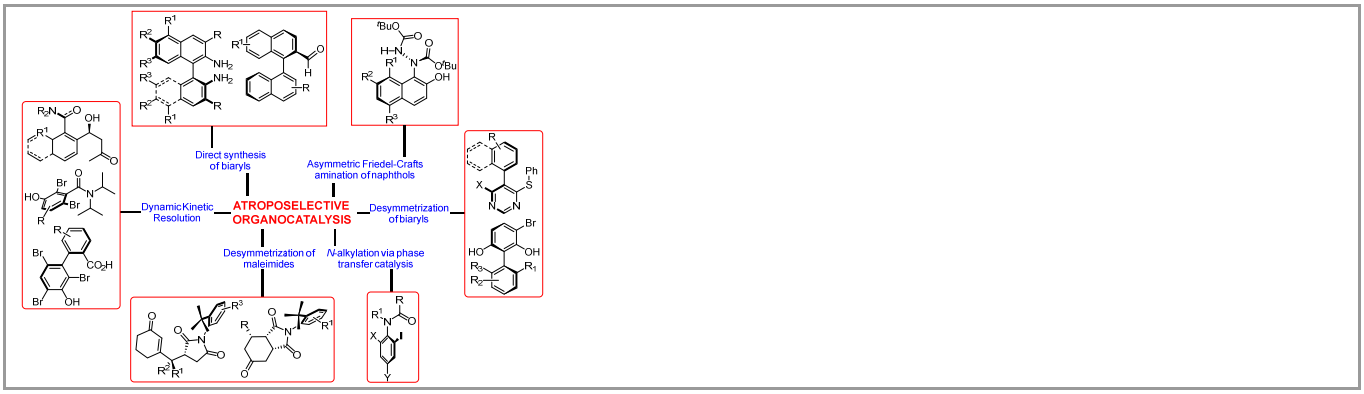

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