Organic & Biomolecular Chemistry

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 4506

Organocatalytic synthesis of axially chiral atropisomers

P. Renzi

Received 12th April 2017,
Accepted 3rd May 2017

DOI: 10.1039/c7ob00908a

rsc.li/obc

This Review summarises the recent progress made in the organocatalytic synthesis of atropisomeric compounds. Methodologies based on dynamic kinetic resolution and direct access to BINOL-like biaryls are described. A particular emphasis is given to reaction mechanisms and to the development of strategies to obtain stable products by increasing the barrier to atropisomer interconversion during the reaction.

1. Introduction

Despite the fact that axial chirality has been known since the early 20th century,[1] only a few strategies that do not involve transition metal catalysis have been developed to prepare selectively such molecules.[2,3] Coupling reactions mediated by metals frequently require the pre-functionalization of substrates and use of protecting groups. In addition, large-scale production may require the treatment of residual metal waste.[4] The development of new methodologies for the challenging synthesis of atropisomers would lead to potential advances in the preparation of natural products, chiral ligands and asymmetric catalysts bearing a chiral axis (Fig. 1).[5] An emerging

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany. E-mail: polyssena.renzi@chemie.uni-regensburg.de

P. Renzi

Polyssena Renzi was born in Rome, Italy, in 1987. She studied Chemistry at the 'Sapienza' University of Rome where she received her degree in 2011. In 2014, she obtained her Ph.D. at the same institution under the supervision of Professor M. Bella working on the development of new strategies for asymmetric reactions. In 2015, she joined the group of Professor R. M. Gschwind at Regensburg University (Germany) as a post-doctoral researcher, where she is currently working on the mechanistic investigation of organocatalysed reactions by means of NMR-spectroscopy.

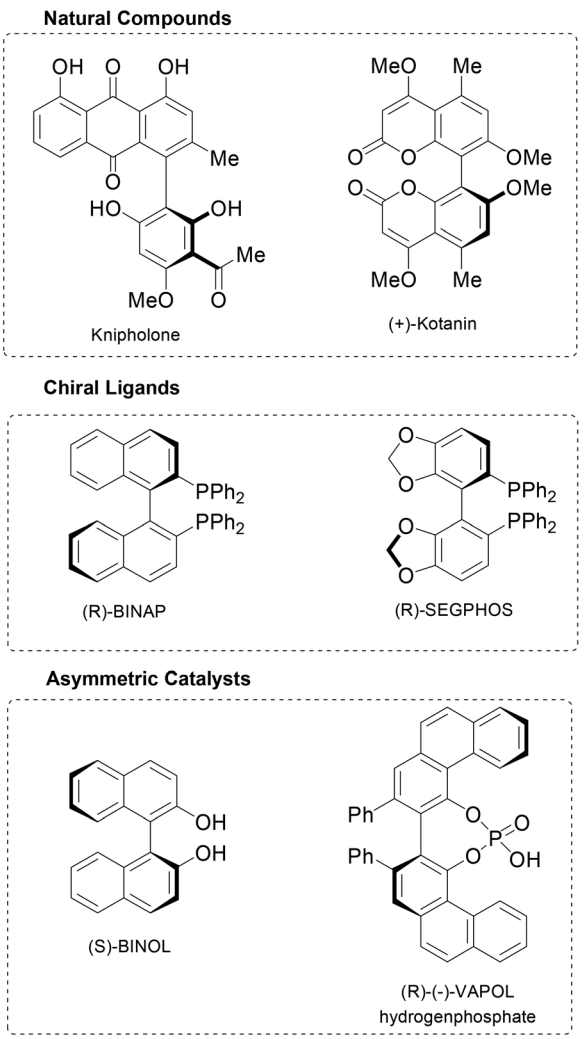


Fig. 1 Examples of natural products, chiral ligands and catalysts containing a stereogenic axis.

strategy is based on the application of organocatalysis. This Minireview describes the recent progress towards the organocatalytic synthesis of atropisomeric compounds and it is divided into two main sections.

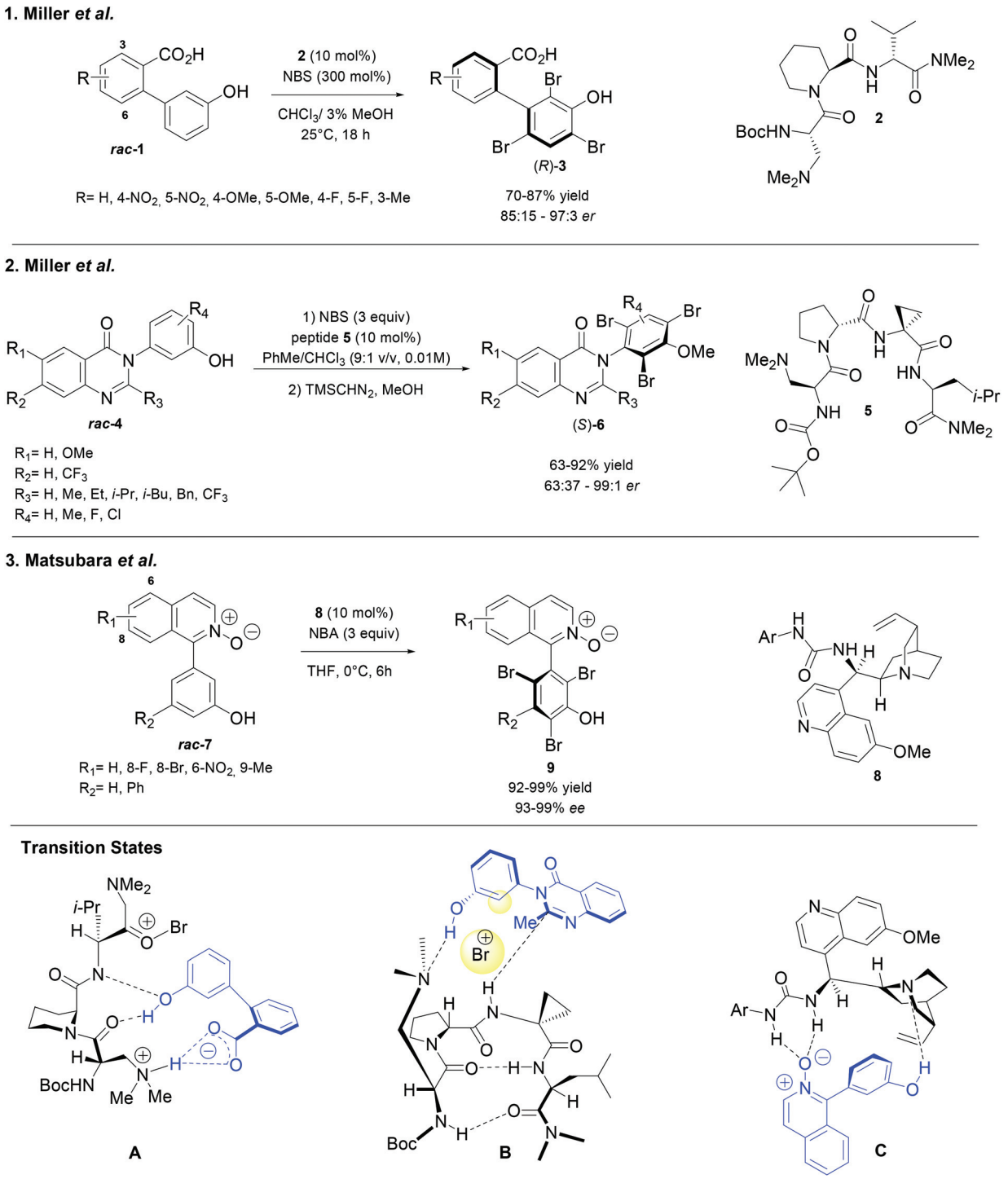
The first part covers the methodologies based on kinetic and dynamic kinetic resolution starting from the pioneering work of Miller published in 2010. The second part is an overview of the most recent methodologies developed for the direct access to BINOL-like structures mediated by acidic or basic catalysts. The synthesis of non-biaryl atropisomers such as anilides and imides mediated by organocatalysis has already been critically reviewed by Bencivenni[6] in 2015 and will not be the subject of this work.

2. Kinetic and dynamic kinetic resolution strategies

2.1. Dynamic kinetic resolution *via* electrophilic aromatic substitutions: asymmetric tribromination as the key step

Kinetic (KR) and dynamic kinetic resolution (DKR) are among the most efficient strategies employed for the synthesis of enantiopure atropisomers starting from racemic axially chiral compounds.[3b] The first example of the DKR of atropisomers was reported by Miller in 2010.[7,8] Chiral biaryls (*R*)-**3** were obtained by dynamic kinetic resolution in the presence of a peptide-based catalyst **2** *via* asymmetric bromination (Scheme 1). The general idea behind Miller's strategy is based on the employment of a starting material with a low barrier to atropisomer interconversion. This low barrier to racemisation increases gradually during sequential electrophilic bromination in the presence of **2**, resulting in tribromide **3** in up to 97 : 3 enantiomeric ratio (er). It is notable that the barrier to racemisation increases from 7 kcal mol^{-1} for *rac*-**1** to *ca.* 30 kcal mol^{-1} for product (*R*)-**3** during the process. In order to enhance the atropisomer selection during the electrophilic aromatic substitution reaction, an optimisation of the tripeptide-based catalyst structure was performed by modifying the peptide β-turn. The optimised structure **2** is shown in Scheme 1. To account for the high selectivity observed, a docking model was proposed (Scheme 1, transition state A). According to this model, the installation of the first bromine atom is guided by the formation of a hydrogen bond between the phenolic proton and the amide groups on the catalyst. The free rotation around the chiral axis is therefore blocked allowing for a selective delivery of all the bromine atoms. A range of substituents on the aryl ring of *rac*-**1** proved to be compatible with excellent results (65–85% yield, 94 : 6–97 : 3 er). Good results were also obtained with pyrrole and catechol analogues proving the validity of this methodology for heteroarene compounds. Following the idea of tribromination as a method to block the rotation around the chiral axis and stabilise the atropisomer, lately Miller[9] and Matsubara[10] reported the synthesis of 3-arylquinazolin-4(3*H*)-ones **6** and axially chiral isoquinoline *N*-oxides **9**. The interest in compounds **6** arose from the possibility of their application in medicinal chemistry after selective dehalogenation or coupling reactions.[9] Also in this case the optimisation of the peptide-based catalyst was reported and it was observed that the slow addition of the brominating reagent (NBS, Fig. 2) was necessary to obtain chiral products **6** in good to high yield with a high level of stereoinduction. The slow addition is, in fact, necessary so that there is sufficient time to let the starting material *rac*-**4** to racemise. In general, substitution on the benzo-moiety of the quinazolinone scaffold was possible. Alkyl substituents at the 2-position of the quinazolinone ring were also well tolerated (75–86% yield; 93 : 7–97 : 3 er) apart for the CF_3 group for which lower yield and enantioselectivity were obtained (63% yield, 63 : 37 er). If on one hand no clear explanation for this observation was given, a rationalisation of the enantioselectivity drop with 2-unsubstituted quinazolinone was proposed. Exploiting DFT calculations, the rotational barrier around the chiral axis of monobrominated products was determined. These compounds are, in fact, considered to be the first species formed during the enantioselective step of tribromination. It was found that this barrier is sufficiently low to permit racemisation on the time scale of NBS addition, thus reducing the enantiomeric ratio. Moreover, the peptide–substrate complex was studied by NMR. The signal shifts in the 1 : 1 complex combined with intermolecular NOE contacts and the (*S*)-absolute configuration of product **6** determined by X-ray were employed to propose a binding model which predicts that the first site of bromination is the *ortho*-position of **4** as shown in transition state B (Scheme 1).[9]

Based on the concept of dual activation of substrates, lately, Matsubara *et al.* reported the synthesis of axially chiral isoquinoline *N*-oxides **9**.[10] In this case, the tripeptide-based catalysts **2** or **5** were substituted with the urea **8** derived from *Cinchona* alkaloids. The hydrogen bond interactions of catalyst **8** with the isoquinoline *N*-oxide (hydrogen bond donor) and the phenol moiety (hydrogen bond acceptor) were expected to twist the molecule in one direction blocking the starting material *rac*-**7** in a fixed position before the delivery of the first bromine atom (Scheme 1, transition state C). Racemic products **9** were obtained employing *ortho*-brominated starting materials proving that, as previously described by Miller, the enantioselective step is the bromination at this position. Once the bromine atom is installed no racemisation can occur by bond rotation. The robustness of the method was proven by the variety of substituents that can be installed on the isoquinoline moiety without affecting the enantiomeric excess and yield (93–99% ee, 92–99% yield). This method was further applied by both Miller[11] and Matsubara[10] groups to the synthesis of axially chiral benzamides **12**. Tripeptide **11** or urea **8** can be used as catalysts employing, respectively, DBDMH or NBA as brominating reagents at −40 °C (Scheme 2, Fig. 2). Racemic mixtures of **12** were obtained employing *rac*-**10** with bromo substituents at the phenol *ortho*- or *para*-position proving also in this case that the *ortho*-bromination is the stereochemistry determining step.



Scheme 1 Asymmetric tribromination as the key step: summary of strategies and proposed transition states.

2.2. Kinetic and dynamic kinetic resolution *via* phase transfer organocatalysis

A different approach based on phase transfer catalysis (PTC) was exploited by Maruoka[12,13] and Smith[14] to access BINOL-derived atropisomers. The kinetic resolution of axially 2-amino-1,1′-biaryls *rac*-**13** was performed by the Maruoka group employing binaphthyl-modified chiral quaternary ammonium salts of type **14** (Scheme 3). The stereoselectivity is controlled after deprotonation with potassium hydroxide by the formation of a chiral ion pair between the phase transfer catalyst and the starting material. A chiral nucleophile is formed and it can attack the allyl iodine thus forming the *N*-allylated chiral product **15**. Biaryl and biphenyl structures

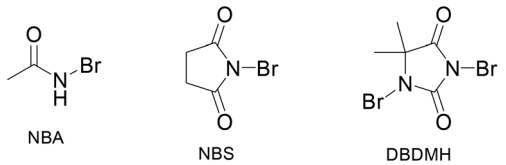
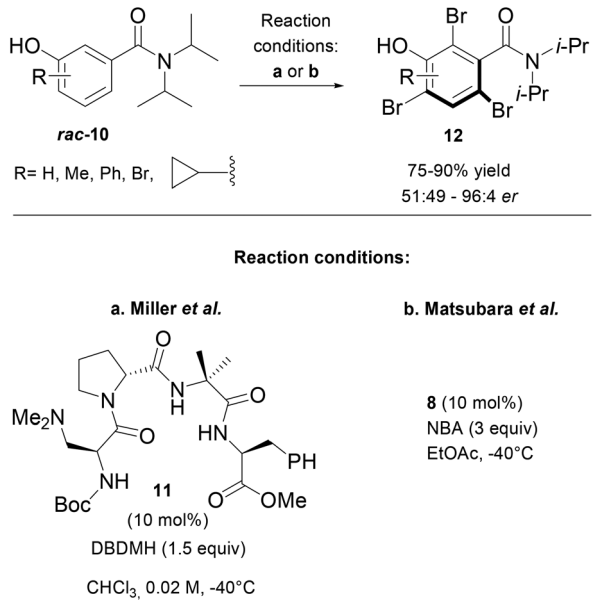


Fig. 2 Brominating reagents.



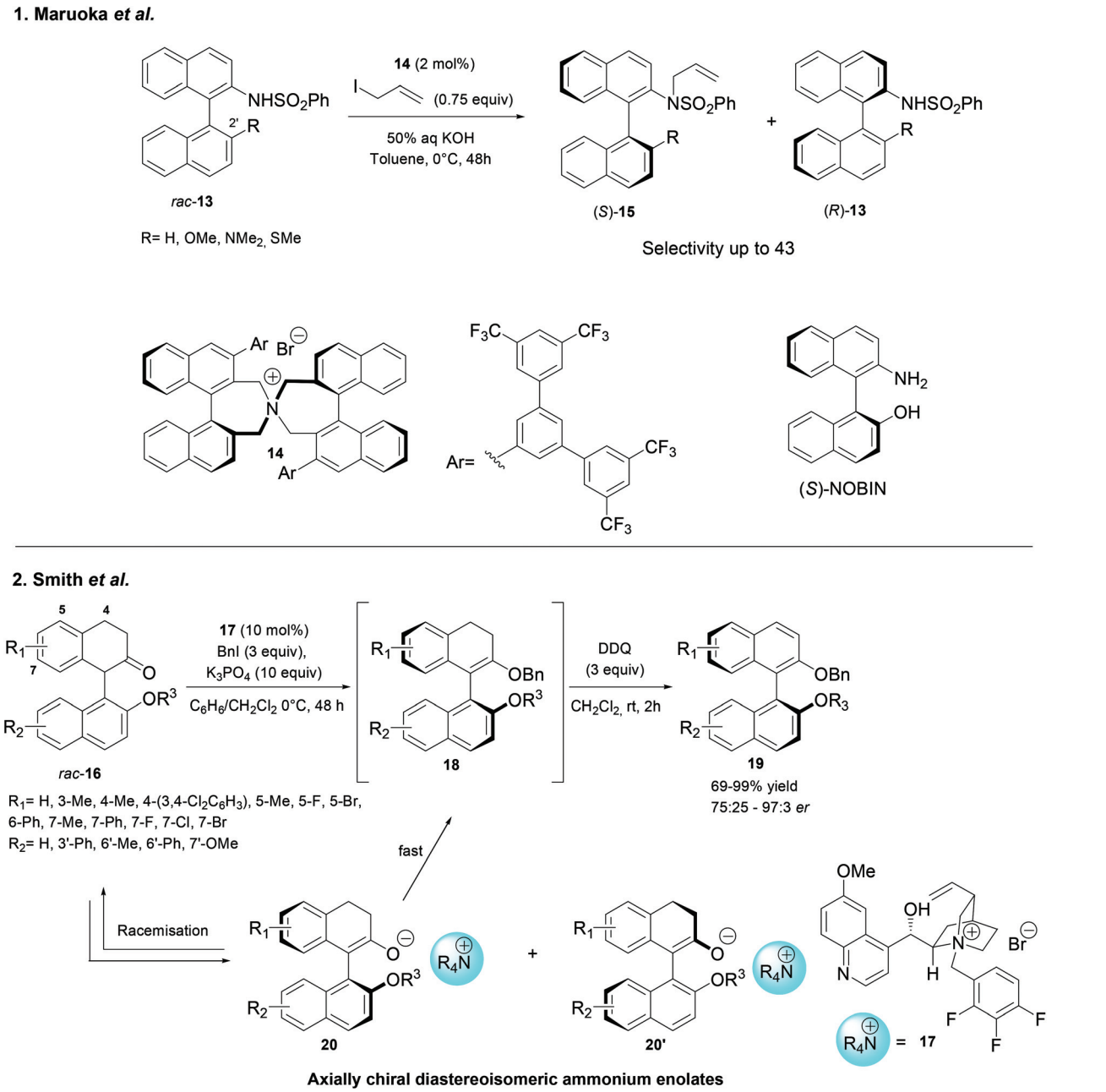
Scheme 2 Asymmetric synthesis of benzamides **12**.

were both well tolerated with good to high selectivities (s = 9.2–43). The substrate scope was then extended to include methylthio- and methylamino-groups at position 2′ of the binaphthyl moiety.[13] The validity of the method was proven by the synthesis of both enantiomers of ligand NOBIN by easy removal of protecting groups on both optically enriched starting material (*R*)-**13** and allylation product (*S*)-**15** without any loss in enantioselectivity.

Very recently, the formation of a chiral counterion by PTC has been exploited by Smith *et al.* to access C_2-symmetric and non-symmetric BINOL derivatives.[14] The concept of *C*-alkylation of enolates during a DKR applied to the synthesis of amino acid derivatives from glycine Schiff bases[15] was further extended to the idea of cation-directed *O*-alkylation. By using a sterically hindered catalyst **17** and a ketone as enolate precursors instead of an ester, it was possible to suppress the *C*-alkylation in favour of *O*-alkylation. This idea was successfully applied to the alkylation of 1-aryl-2-tetralones **16** by a DKR process (Scheme 3). According to the mechanism proposed, the reaction proceeds by a base-mediated deprotonation of racemic tetralone **16** to generate an enolate. The two enolate enantiomers can associate with the chiral catalyst to form the diastereomeric ion pairs **20–20′**. Both axially chiral and racemic potassium enolates exist in solution and they can be rapidly interconverted through protonation and deprotonation allowing the racemisation of tetralone **16**. Then, the *O*-alkylation proceeds at different rates for the two diastereoisomeric ion pairs thus delivering product **18**. This compound is then oxidized *in situ* with DDQ to obtain the BINOL-derivative **19** without any loss in the enantiomeric ratio. The optimised reaction conditions are depicted in Scheme 3. The enantioselectivity is controlled by the catalyst structure, and the type of base and solvent employed. As shown for the optimised catalyst **17** (Scheme 3), the steric hindered *N*-pendant group and the presence of a free OH group on the catalyst are essential to reach high levels of enantioselectivity. A drop in the enantiomeric ratio from 92 : 8 to 66 : 34 is observed when the hydroxyl group of the phase transfer catalyst is benzylated. The reaction scope is quite broad; sterically hindered substituents on position 7 as well as alkylic groups have little influence on the enantioselectivity. On the contrary, the oxygen on the R_3 group has a central role in reactivity and selectivity. If OR_3 is, in fact, substituted with a methyl group, the yield and er decrease drastically (OR_3 = OMe 96 : 4 er, 95% yield; for a Me in that position 75 : 25 er, 30% yield). Changing one hemisphere of the BINOL-core from 2-naphthol to 2-phenantrol has a minor impact on enantioselectivity. The absolute stereochemistry of the product was confirmed by single crystal X-ray diffraction. Moreover, the products obtained can be further functionalized by dealkylation, and selective debenzylation by hydrogenolysis or diastereoselective [1,2]-Wittig rearrangement.

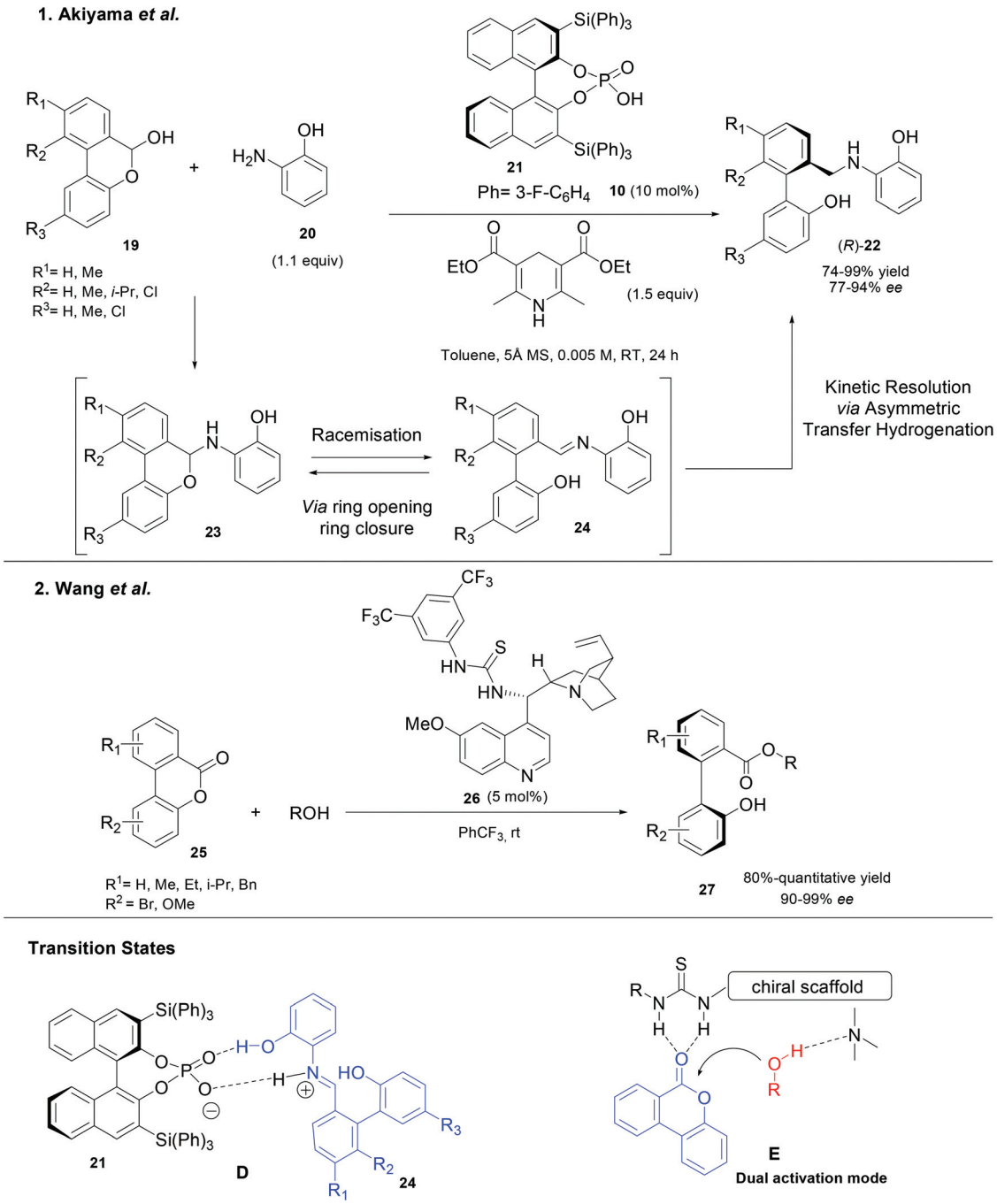
2.3 Dynamic kinetic resolution based on ring-opening reactions or Bringmann's concept

An alternative strategy to realise a dynamic kinetic resolution is based on the ring-opening and ring-closure of the starting material as the racemisation step. The catalytic asymmetric ring opening of biaryl lactones by organocatalytic methods has been realised by the Akiyama group.[16] Biaryl *N*–*O*-acetals **23** proved to be suitable starting materials since they can be easily formed and opened *in situ* (racemisation step). The open form **24**, which is an imine, has a high affinity for the chiral phosphoric acid **21** used as the catalyst and it can be reduced *via* asymmetric transfer hydrogenation in the presence of the Hantzsch ester as a hydride donor (Scheme 4, transition state D). Interestingly, the product atroposelectivity is completely controlled by the choice of the hydroxylamine derivative. When *o*-hydroxylamines **20** are employed the enantioselectivity is in favour of the (*R*)-configured product **22** as shown in Scheme 4. The corresponding (*S*)-isomer is obtained with *m*-hydroxylamine derivatives. To increase the enantioselectivity, the Hantzsch ester has to be added slowly *via* a syringe pump so that the imine has enough time to racemise *via* ring-opening and ring-closure. Good to excellent enantioselectivities (77–94% ee) were obtained in the presence of both electron-donating and electron-withdrawing groups on the upper ring. Substitution on the lower ring is also possible without affecting the reaction outcome. The potential of this transformation was also proven by the enantiodivergent synthesis of chiral *o*-tetrasubstituted biaryls.



Scheme 3 Synthesis of BINOL-like biaryls by (PTC): summary of strategies.

Despite the fact that labile biaryl lactones **25**, known as Bringmann's lactones, have been extensively employed to access chiral biaryl compounds, the development of a catalytic strategy with a broad scope has been reported only recently by the Wang group.[17] The first highly atropo-enantioselective DKR of compounds **25** was realised by employing a chiral bifunctional amine thiourea **26** as the catalyst. A dual activation mode is exploited since catalyst **26** is able to activate at the same time the lactone *via* hydrogen bonding with its thiourea moiety and the alcohol employed as a nucleophile through its amine group (Scheme 4, transition state E). Therefore, the nucleophilic attack is directed in an atropo-enantioselective manner. The bifunctional catalyst is essential to show reactivity since no reaction proceeded when employing triethylamine (used to mimic the quinuclidinic ring of the catalyst) or bis(thiourea). The protocol is very mild and high yields and enantiomeric excess values were obtained with a broad range of alcohols (aliphatic or benzylic alcohols with either electron-withdrawing or electron-donating groups). The use of phenols proved to be more challenging because of their lower nucleophilicity and the tendency of the product to racemise. Good yields with low enantiomeric excess values were in fact obtained with longer reaction times. A compromise between enantioselectivity and yield was found by running the



Scheme 4 Synthesis of chiral biaryls by DKR based on ring-opening reactions or Bringmann's concept.

reaction at −10 °C with short reaction times with both phenols bearing electron-neutral, donating or withdrawing substituents (90–98% ee, 50–76% yield). Regarding the biaryl lactone moiety no influence of substituents was observed for the carbonyl-containing phenyl ring, while yield and enantioselectivity drastically decreased when the 2-methoxy group on the phenolic part was removed, proving that it can potentially offer an additional binding site for the catalyst. The reaction was also run on a gram scale employing a lower catalyst loading and a higher concentration.

3. Organocatalytic synthesis of BINOL-like biaryls: acid or base catalysis?

Despite the fact that the results presented in section 2 represent a major breakthrough in this field, in most cases the preparation of the precursors still requires metal catalysed cross-coupling reactions and generally no direct application to the synthesis of ligands or catalysts has been reported so far. The

lack of an organocatalytic approach, which features mild and operationally simple conditions and, especially, the possibility for a direct access to BINOL-like structures, was addressed by the work of Tan,[18] Bella[19] and Kürti.[20,21] The authors reported independently new organocatalytic routes towards the preparation of non-C_2 symmetrical biaryldiols. The key points of these transformations are: (1) the choice of suitable substrates in order to have hindered rotation around the newly formed chiral axis, thus obtaining configurationally stable binaphthol systems; and (2) the choice of the right catalyst to activate the substrates and transfer the stereocontrol. On one hand, these publications share the application of 2-naphthols **30** and quinone derivatives **28**, **29**, and **33** as starting materials. On the other hand, their activation is achieved by applying different strategies which are based on acidic[18,20,21] or basic organocatalysts.[19] Chiral phosphoric acids, such as 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (TRIP) **31**, were employed by Tan and Kürti, while Bella exploited the unmodified *Cinchona* alkaloid quinine **34**. A different quinone structure was used in each paper and different substitution patterns were exploited to hinder the rotation along the chiral axis. The rotational barrier is, in fact, determined by both the size and the number of substituents present at the positions flanking the aryl–aryl bond (Fig. 3).[22] The determination of the rotational barrier by applying *ab initio* calculation and HPLC on a chiral stationary phase was, therefore, used by Bella and co-workers to rationalise the choice of the quinone structure. A low rotational barrier energy was found for products derived from non-substituted 1,4-benzoquinone (Fig. 3, product **I**). Instead, HPLC separation with the so-called "Batman profile"-peaks was obtained for the corresponding aromatized product **II**. This hinted at the presence of atropisomers with hindered rotation, but with interconversion timescale compatible with the retention time of the HPLC run (Fig. 3).[23] This could also suggest that the low enantiomeric excess reported by Tan for a similar product might be connected to its configurational instability.

Finally, Bella and co-workers obtained configurationally stable products by applying 2,5- or 2,6-dihalogenated 1,4-benzoquinones **33a–b** (for examples of rotational barriers see Fig. 3, compounds **III–IV**), while Tan *et al.* employed quinones bearing a halogen or an ester group at the 2-position (Fig. 4, quinones **28–29**). Quinone and iminoquinone monoacetals were used as arylating agents by Kürti *et al.* In their first report, employing acetals **38** as substrates, only enantiomeric excesses lower than 10% could be obtained after testing the more commonly used chiral phosphoric acid catalysts.[20] It was then observed that the generation of methanol during the catalytic cycle had a detrimental effect on the enantioselectivity. So, in their following paper on the subject, the monoacetal

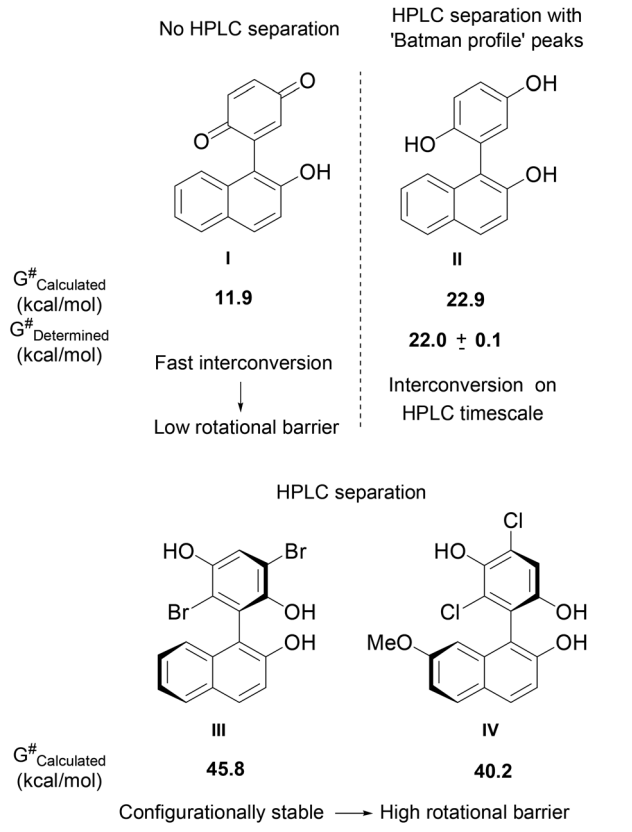


Fig. 3 Modulation of rotational barrier energy by substitution on the quinone moiety: examples of values determined by Bella and co-workers.

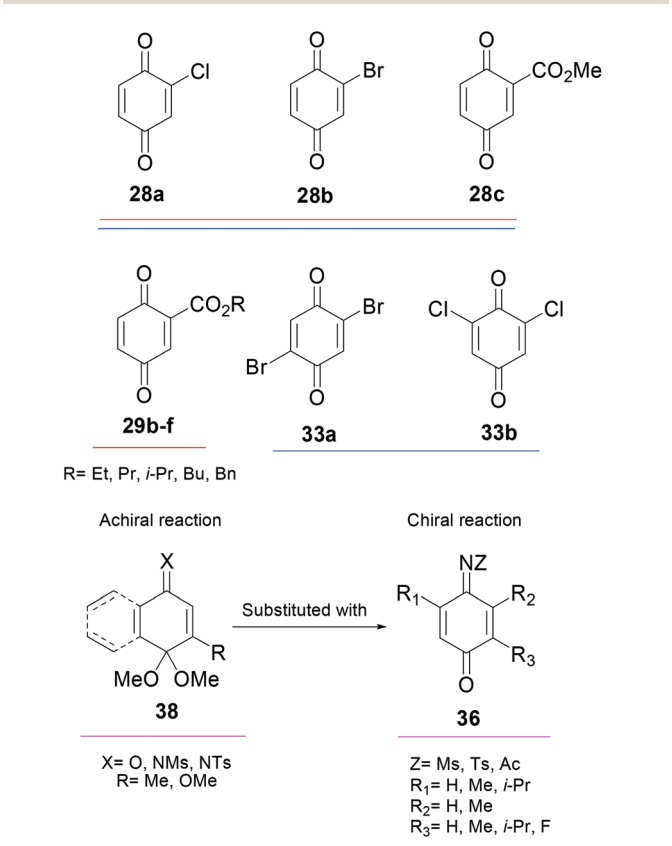


Fig. 4 Examples of quinone structures: — compounds employed by Tan; — quinones employed by Bella and co-workers; — iminoquinones used by Kürti *et al.* in the achiral and chiral version of their reaction.

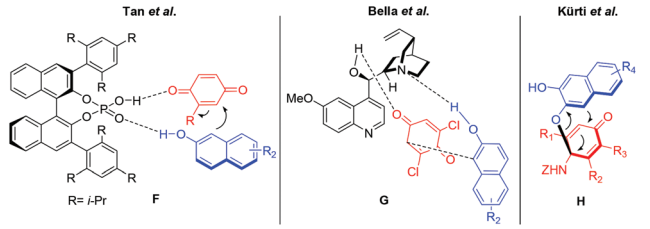
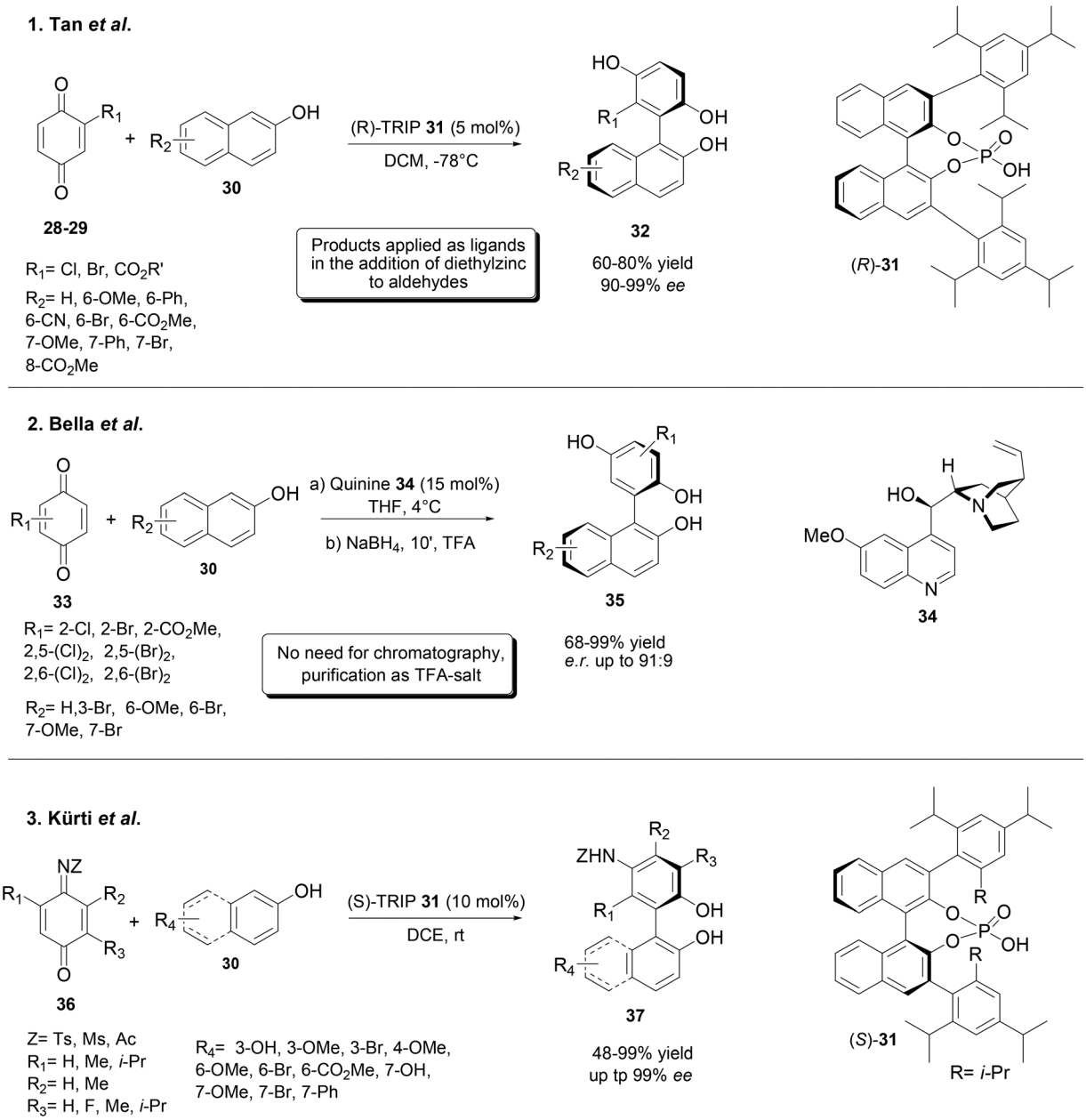


Fig. 5 Summary of transition states proposed. Kürti and co-workers did not show the catalyst in the transition state suggested.

structure **38** was redesigned and modified to *N*-sulfonyl-protected iminoquinones **36**.[21]

All authors reported a mechanism proposal (Fig. 5). For both the quinine and the phosphoric acid catalysed reactions, developed respectively by the groups of Bella[19] and Tan,[18] a bifunctional mode of activation by the catalyst was proposed. Bella and Tan suggested that the naphthol can be activated by deprotonation either by the quinuclidinic unit of quinine **34** or by hydrogen bond formation with the phosphate group of TRIP **31**. On the other hand, the quinone reagent is activated by hydrogen bonding with the 9-hydroxy functionality of the *Cinchona* alkaloid base or the phosphoric group of the acid (Fig. 5, transition states F and G). Based on theoretical calcu-



Scheme 5 Organocatalytic synthesis of axially chiral BINOL-like biaryls: summary of strategies.

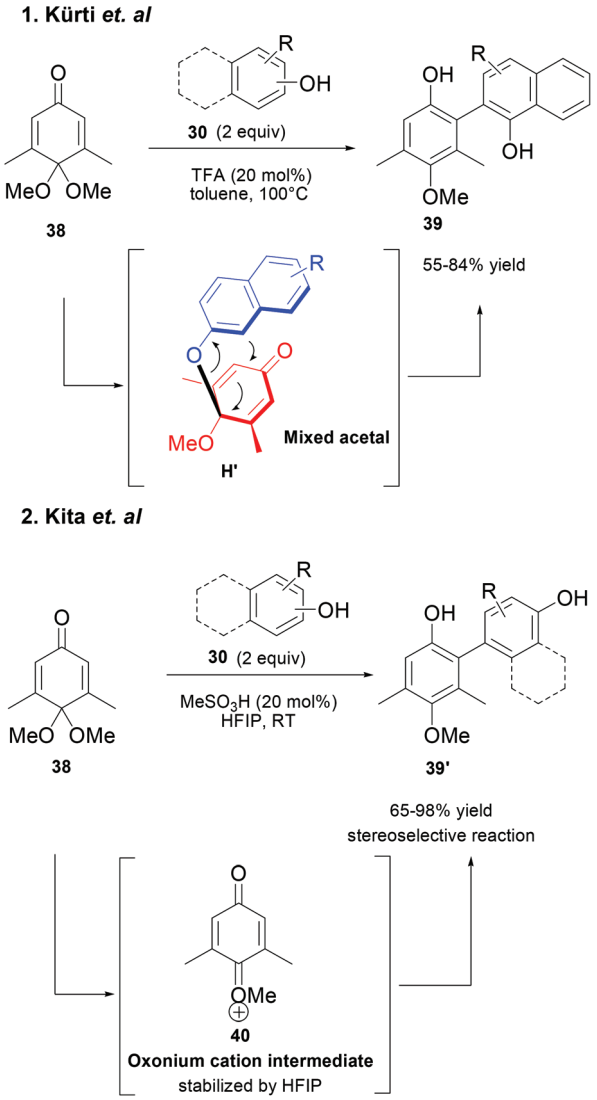
lations and experimental evidence, Kürti *et al.* proposed an acid-catalysed *in situ* aminal formation followed by a [3,3]-sigmatropic rearrangement/aromatization sequence (Fig. 5, transition state H).[20,21]

Despite the fact that different reaction conditions were employed, higher dilutions appear to be beneficial to the enantioselectivity in all protocols. High yield and enantioselectivity were obtained under mild conditions and all transformations were demonstrated on a gram scale. A high functional group tolerance was observed for both 2-naphthols and quinones (Scheme 5). Most importantly, privileged frameworks structurally correlated to BINOL are accessed in a straightforward way. The results obtained by their application as ligands in the enantioselective addition of diethylzinc to aldehydes by Tan hint at this hypothesis (89% ee with (*S*)-BINOL *vs.* 96–99% ee obtained with the new biaryldiols).

In late 2016, the Kita group published a new achiral version of the reaction previously reported by Kürti[20] but describing a completely different regioselectivity (Scheme 6).[24] The trifluoroacetic acid in toluene employed by Kürti was substituted with methanesulfonic acid ($MeSO_3H$) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). According to the high regioselectivity observed for product **39′**, Kita *et al.* proposed a different reaction mechanism from the one described by Kürti (Scheme 6, transition state H′). According to this proposal no mixed-acetal H′ is formed, instead in HFIP the oxonium cation intermediate **40** is stabilized and it can react with phenol **30** to give product **39′** instead of its regioisomer **39** (Scheme 6). Moreover, HFIP is also proposed to have a key role in solvating and/or protonating the phenol hydroxyl group preventing the *O*-nucleophilic attack of phenols.

Chiral biaryl backbones are generally restricted to binaphthyl, biphenyl and phenyl–naphthyl frameworks. Only recently Li and Shi made a step forward developing the synthesis of chiral heterobiaryl backbones by introducing an indole ring into the biaryl scaffold.[25] This new strategy opens up the possibility to access structures with a new catalytic activity since the NH group will give the potential for the formation of a hydrogen-bond, a feature which is not present in the BINOL-derived catalysts. Instead of quinones **28**, **29**, and **33**, 2-indolmethanols **41** were chosen as coupling partners with 2-naphthols **30** in the presence of the chiral phosphoric acid **42** (Scheme 7). The C3-position of 2-indolmethanols displays in fact the electrophilic character while the 2-naphthol is a large nucleophile with a high reactivity.

According to this model, the steric congestion at the *ortho–ortho* positions of the product is necessary to avoid free rotation around the C–C axis formed thus obtaining a stable atropisomer **43**. This was made possible by the 2-naphthol size and by the presence of two large phenyl groups on the 2-indolmethanols **41**, which also allowed the stabilization of the cation intermediate (Scheme 7). Also in this case, the dilution helped in facilitating the chiral induction and increasing the enantioselectivity. This transformation has a broad scope (91 : 1–99 : 5 er, 87–99% yield) and no significant decrease in the enantioselectivity was obtained with monocyclic phenols

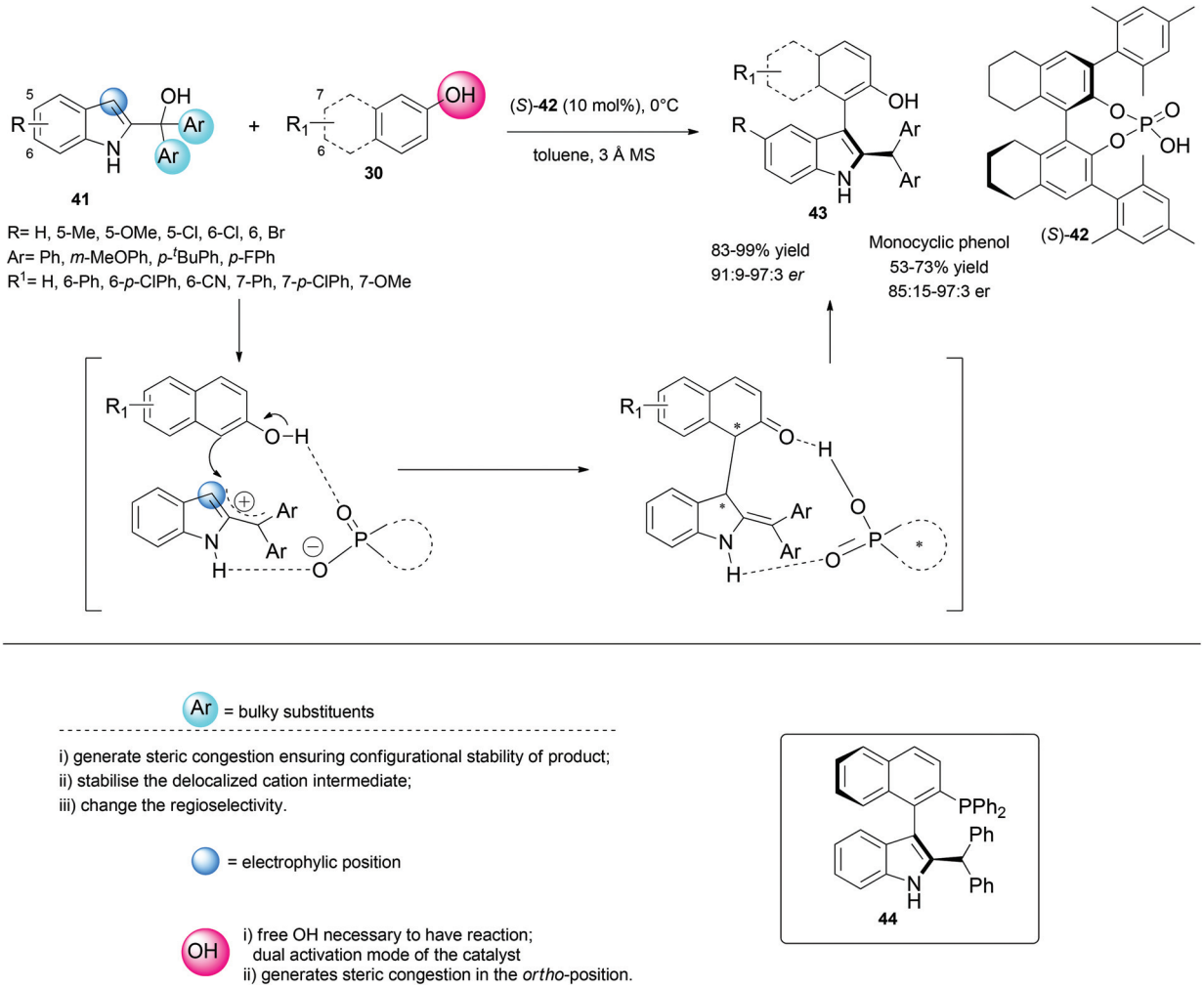


Scheme 6 A different regioselectivity for the same reaction with a different acid as the catalyst.

(85 : 15–93 : 7 er, 53–75% yield) presenting a lower steric congestion than the naphthol moieties. The reaction was shown to proceed well at a larger scale and the products show high stability to racemisation; racemisation, in fact, was observed only by heating the product **43** for 36 hours at a temperature >150 °C. The utility was also shown on product conversion to phosphine **44** which was employed as a catalyst in a [3 + 2]-annulation.

4. Conclusion and outlook

Despite the fact that the dynamic kinetic resolutions described in the second section can be considered elegant strategies, the preparation of the racemic starting materials still requires, in most cases, metal catalysed cross-coupling reactions. Additionally, few direct applications to the synthesis of ligands or catalysts of the products obtained have been reported so far.



Scheme 7 Organocatalytic synthesis of chiral heterobiaryl backbones.

A step forward was made by Tan, Bella and Kürti who described for the first time a direct access to BINOL-like structures from simple starting materials. The biaryldiol moiety obtained offers the possibility for a direct conversion to the corresponding chiral phosphoric acid. Moreover, the halogen groups, present at different positions of the BINOL-backbone, could be exploited for further functionalization opening up the way to the synthesis of new densely functionalised catalysts or ligands for enantioselective transformations. Quite quickly, a new step forward was made by Li and Shi developing the synthesis of chiral heterobiaryl backbones. A significant growth of strategies leading to new atropisomeric structures enabled by organocatalysis is expected in the near future.

Acknowledgements

The research of Polyssena Renzi is supported by the European Research Council (ERC-CoG 614182-IonPairsAtCatalysis). The author thanks Dr Armando Carlone for proof-reading of the manuscript.

Notes and references

1 G. H. Christie and J. Kenner, *J. Chem. Soc., Dalton Trans.*, 1922, **121**, 614.
2 For recent reviews on the synthesis of chiral biaryls by means of transition metal catalysis, see: (*a*) P. Loxq, E. Manoury, R. Poli, E. Deydier and A. Labande, *Coord. Chem. Rev.*, 2016, **308**(Part 2), 131; (*b*) J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev.*, 2015, **44**, 3418.
3 For recent reviews on the synthesis of atropisomers, see: (*a*) S. Shirakawa, S. Liu and S. Kaneko, *Chem. – Asian J.*, 2016, **11**, 330; (*b*) G. Ma and M. P. Sibi, *Chem. – Eur. J.*, 2015, **21**, 11644.
4 (*a*) H. U. Blaser and H.-J. Federsel, *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, Wiley-VHC, Weinheim, 2nd edn, 2010; (*b*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VHC, Weinheim, 2005, ch. 14.

5 (*a*) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (*b*) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem.*, 2005, **117**, 5518, (*Angew. Chem. Int. Ed.*, 2005, **44**, 5384).
6 G. Bencivenni, *Synlett*, 2015, 1915.
7 J. L. Gustafson, D. Lim and S. J. Miller, *Science*, 2010, **328**, 1251.
8 P. G. Cozzi, E. Emer and A. Gualandi, *Angew. Chem.*, 2011, **123**, 3931, (*Angew. Chem. Int. Ed.*, 2011, **50**, 3847).
9 M. E. Diener, A. J. Metrano, S. Kusano and S. J. Miller, *J. Am. Chem. Soc.*, 2015, **137**, 12369.
10 R. Miyaji, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2015, **137**, 6766.
11 K. T. Barrett and S. J. Miller, *J. Am. Chem. Soc.*, 2013, **135**, 2963.
12 S. Shirakawa, X. Wu and K. Maruoka, *Angew. Chem.*, 2013, **125**, 14450, (*Angew. Chem. Int. Ed.*, 2013, **52**, 14200).
13 S. Shirakawa, X. Wu and K. Maruoka, *Tetrahedron*, 2016, **72**, 5163.
14 J. D. Jolliffe, R. J. Armstrong and M. D. Smith, *Nat. Chem.*, 2017, DOI: 10.1038/nchem.2710.
15 (*a*) M. J. O'Donnell, W. D. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353; (*b*) M. J. O'Donnell, J. M. Boniece and S. E. Earp, *Tetrahedron Lett.*, 1978, **19**, 2641.
16 K. Mori, T. Itakura and T. Akiyama, *Angew. Chem.*, 2016, **128**, 11814, (*Angew. Chem. Int. Ed.*, 2016, **55**, 11642).
17 C. Yu, H. Huang, X. Li, Y. Zhang and W. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 6956.
18 Y.-H. Chen, D.-J. Cheng, J. Zhang, Y. Wang, X.-Y. Liu and B. Tan, *J. Am. Chem. Soc.*, 2015, **137**, 15062.
19 M. Moliterno, R. Cari, A. Puglisi, A. Antenucci, C. Sperandio, E. Moretti, A. Di Sabato, R. Salvio and M. Bella, *Angew. Chem.*, 2016, **128**, 6635, (*Angew. Chem. Int. Ed.*, 2016, **55**, 6525).
20 H. Gao, Q.-L. Xu, C. Keene, M. Yousufuddin, D. H. Ess and L. Kürti, *Angew. Chem.*, 2016, **128**, 576, (*Angew. Chem. Int. Ed.*, 2016, **55**, 566).
21 J.-Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti and Q.-L. Xu, *J. Am. Chem. Soc.*, 2016, **138**, 5202.
22 C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principals and Applications*, Royal Society of Chemistry, Cambridge, U.K., 2007, ch. 3.
23 A. M. Stalcup, Chiral Separations, *Annu. Rev. Anal. Chem.*, 2010, **3**, 341.
24 T. Kamitanaka, K. Morimoto, K. Tsuboshima, D. Koseki, H. Takamuro, T. Dohi and T. Kita, *Angew. Chem.*, 2016, **128**, 15764, (*Angew. Chem. Int. Ed.*, 2016, **55**, 15535).
25 H.-H. Zhang, C.-S. Wang, C. Li, G.-J. Mei, Y. Li and F. Shi, *Angew. Chem.*, 2017, **129**, 122, (*Angew. Chem. Int. Ed.*, 2017, **56**, 116).

