Organocatalysis

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Atroposelective Organocatalysis**

Pier Giorgio Cozzi, Enrico Emer, and Andrea Gualandi*

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The stereochemical phenomenon that arises from hindered rotation around bonds in nonplanar molecules is termed atropoisomerism.[1] The presence of a stereogenic axis is the distinct feature in these molecules. One type of atropoisomeric molecule is generated when bulky substituents are placed at the *ortho* positions of an aryl ring such that there is restricted rotation around the biaryl bonds. Many naturally occurring compounds contain biaryl rings that cannot freely rotate and their stable atropoisomeric conformation controls their biological and functional properties.[2] Several biologically active compounds that contain a single atropoisomer in their structure have been characterized, including (+)-gossypol (**1**), (−)-steganone (**2**), and vancomycin (**3**; Figure 1) to name just a few. Atropoisomers are also a key element for the design of effective chiral catalysts wherein the atropoisomer is the structural element essential for transmission of chiral information by the catalytic metal complex. The metal complex can alter and adapt its conformation during the course of a reaction. Binap (**4**; Figure 1)[3] is a well-known atropoisomeric ligand that contains a stereogenic axis. In principle, different strategies can be explored for the synthesis of biaryl atropoisomers (Scheme 1). The direct intramolecular coupling of biaryls can be induced by chiral auxiliaries when chiral derivatives of binol are used.[4a] In other strategies diols,[4b] amino alcohols,[4c] or sugars[4d] have been used as chiral auxiliaries. The stereoselective coupling of two biaryl rings inserted into a chiral backbone, such as a peptidic chain, is conducted under oxidative conditions.[5a] Alternatively, chiral substituents capable of hindering rotation present in the aryl ring can control the intermolecular coupling during Grignard addition,[5b] Ullmann coupling,[5c] or Suzuki-type reactions.[5d] Atropoisomeric biaryl compounds can also be formed in an effective way by oxidative coupling[6a] in the presence of chiral additives, for example using an electron-rich naphthol.[6b]

Metal-catalyzed cross-coupling reactions run in the presence of chiral ligands were effective in performing the atroposelective reaction through established organometallic methodologies.[7] By using these methodologies, atroposelective transformations can be realized with prostereogenic biaryls when the two biaryl rings are rotationally hindered but achiral, or when the biaryls are chiral but have unstable configurations. The selective reactions of a single atropoisom-

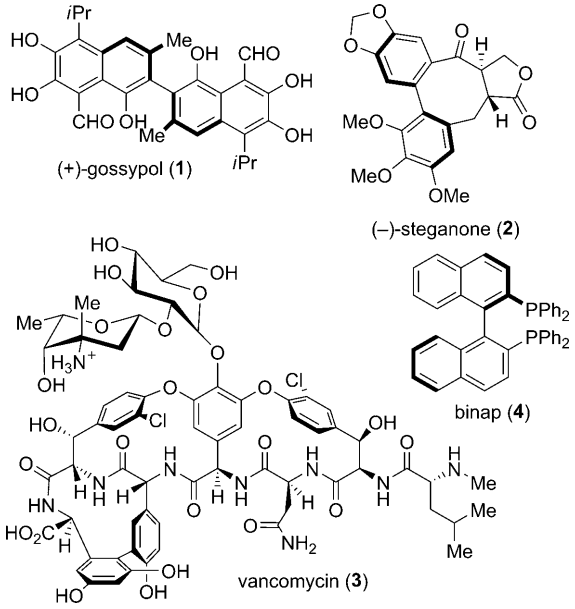
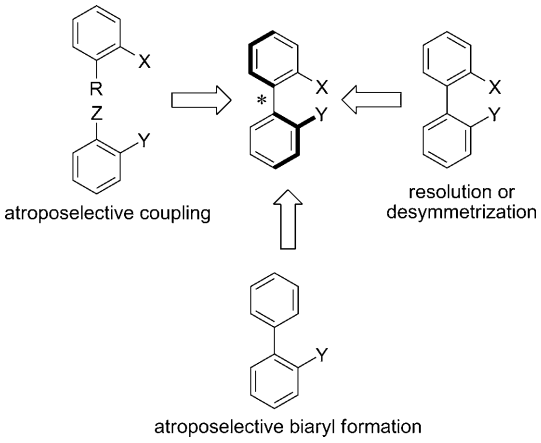


Figure 1. Natural (**1**–**3**) and unnatural (**4**) molecules, containing stereogenic axes, that are able to form atropoisomers.



Scheme 1. Possible strategies for atroposelective reactions.

[*] Prof. P. G. Cozzi, Dr. E. Emer, Dr. A. Gualandi
Dipartimento di Chimica "G. Ciamician"
ALMA MATER STUDIORUM Università di Bologna
Via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 052-209-9456
piergiorgio.cozzi@unibo,it

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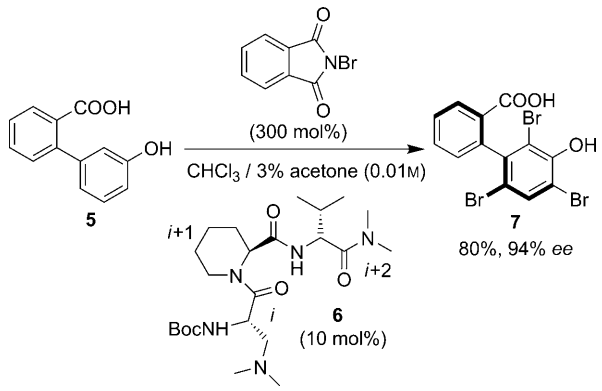
er in a dynamic mixture of freely rotating and rapidly racemizing biaryl rings, which make use of catalytic metal mediated transformations, have been described.[8a,b]

In recent years those in the field of organocatalysis have explored new approaches for the control of issues related to absolute or relative stereochemical configurations; however, addressing the problem of selectivity in a dynamic mixture of freely rotating atropoisomers still constitutes a formidable challenge. Recently, this challenge was undertaken by Miller and co-workers[9] who have described a dynamic kinetic resolution of biaryl atropoisomers by peptide catalysis (Scheme 2). Peptides were effective catalysts[12] for the derivatization of aromatic compounds, and Miller and co-



Scheme 2. Atroposelective bromination of biaryl substrates promoted by catalyst **6**. Boc = *tert*-butoxycarbonyl.

workers have reported a peptide catalyst that is capable of mediating an electrophilic aromatic substitution that takes place at the *ortho* position of a biaryl molecule, thus forming stereoisomers with high atroposelectivity. To control the formation of the favored atropoisomers, they considered the folding properties of the peptide chain of the catalyst,[10] along with formation of hydrogen bonds.[11]

Of all possible biaryl molecules for study, they envisaged the biaryl **5**, which contains atoms that are able to form a hydrogen-bond network, and a group that is activates the aryl bond towards aromatic electrophilic substitution (Scheme 2). Electrophilic bromination is catalyzed by Lewis bases,[12,13] therefore the selective bromination of **5** was investigated in the presence of peptidic catalysts bearing Lewis basic centers. To prepare chiral peptide catalysts for the atropoisomers, the chiral environment of the peptide was designed to induce specific folding properties[14] such as a β-turn motif. Since the D-Pro-L-amino acid sequence had been a well-documented biasing element in the catalyst design,[15] a series of different tripeptides, containing this sequence, were prepared and tested in the model reaction. β-(*N*,*N*-Dimethylamino)alanine (Dmaa) was introduced as the N-terminal residue, with the aim of introducing an interaction with the acid group of the biaryl compound. An important discovery for the development of the catalyst was the introduction of a L-pipecolinic acid as central residue of the peptide. The catalyst **6**, obtained after substitution of a range of amino acids in the $i+2$ position, was identified as the lead catalyst and was used for further study (Scheme 2). It appears that this catalytic methodology could be quite useful for asymmetric synthesis of bioactive natural product substructures containing heteroarene moieties. The background reaction was not of concern in this process, as the bromination was proven to be sluggish in the absence of catalysts. Control experiments were performed on the model substrates with *N*,*N*-dimethylamino valine as the catalyst and they confirmed the possibility that the amides introduced into the peptide catalyst are playing an important role; the terminal *N*,*N*-dimethylamide is probably involved in the formation and activation of the [O-Br]– cationic species. The folding properties of the peptide catalyst, and the preference of N-acyl piperidines to adopt conformations with axial substituents at the 2-position to avoid allylic strain, dictate the conformation of the catalyst **6**. The substrate is interacting, just as in an enzymatic reaction, with the catalyst. Simultaneously, hydrogen bonds between the phenolic proton and the amide are blocking possible rotation and interconversion of the atropoisomers.

The formation of the diastereoisomeric complex favors an atropoisomer, such that the O-bromonium ion complex formed by the reaction of the brominating species with the catalyst is now inclined toward formation of this stereoisomer (Figure 2). When the dibromo derivates are formed, a barrier

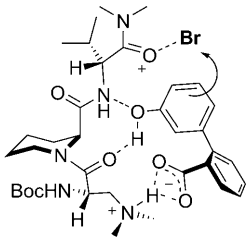


Figure 2. Possible docking model that explains the selectivity.

to rotation is high enough to prevent product racemization. Although other alternative mechanisms have yet to be examined, this powerful model suggests that foldamers could be used in the control of other reactions via diastereoselective formation of a complex between the atropoisomer and the catalyst. Although a great deal of work will be necessary to establish whether this model is correct, the implications for organocatalytic reactions are quite noteworthy. Chiral thioureas[16] and hydrogen-bond networks[16] can be used in new reaction methodologies, that is, combining foldamers with established principles in organocatalysis can be applied to atroposelective reactions.[17]

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