

Iteroselectivity, the missing sibling of chemo-, regio- and stereoselectivities

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Abstract: Iteroselectivity is the selectivity that governs the number of repeating chemical transformations that occur on a substrate bearing multiple identical reactive functions or when the reactive function is regenerated like in the case of polymerization. This new concept of selectivity is defined and compared with the classical chemo-, regio- and stereoselectivities encountered in chemical synthesis. Examples of iteroselective reactions are given ranging from very common reactions such as electrophilic aromatic substitutions to advanced methods involving large supramolecular complexes.

Introduction

Selectivity plays a crucial role in organic synthesis. Selective reactions are most commonly categorized as chemoselective,^{1,2} regioselective,^{1,3} and stereoselective.^{1,4} There is, however, one type of selectivity commonly encountered in various reactions (*e.g.* substitutions, polymerizations, etc.) that does not fit in these three categories. The purpose of this work is to present the selectivity observed when a given reaction can occur at least twice on a substrate (*e.g.* the alkylation of ethylene glycol, see Figure 1A) but stops selectively after a given number of iterations i . This is distinct from selectivity imposed through sequential reactions,⁵ and applies only to one-pot reactions. In 2014, we proposed to name this selectivity “iteroselectivity”⁶ (Figure 1B) and, since then, this term was used in various articles.^{7–15} To the best of our knowledge, the concepts arising from this type of selectivity have not been yet properly named and defined in the literature.

Herein, we propose to define properly this type of selectivity and related concepts, to compare it to the three main types of selectivity in organic synthesis (see Figure 2 for an overview of the comparison), and to list some concrete examples from the literature.

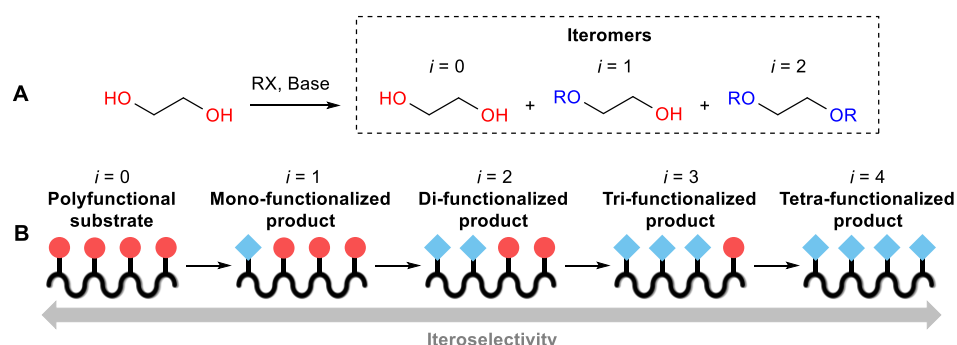


Figure 1. Iterative reactions that may show iteroselectivity. (A) The alkylation of ethylene glycol is a simple example of iterative reaction. (B) Substrates bearing several identical functions can react iteratively in a single pot. Iteroselectivity arises when one or several products are predominantly formed against the expected outcome if reaction kinetics were equal for each iteration.

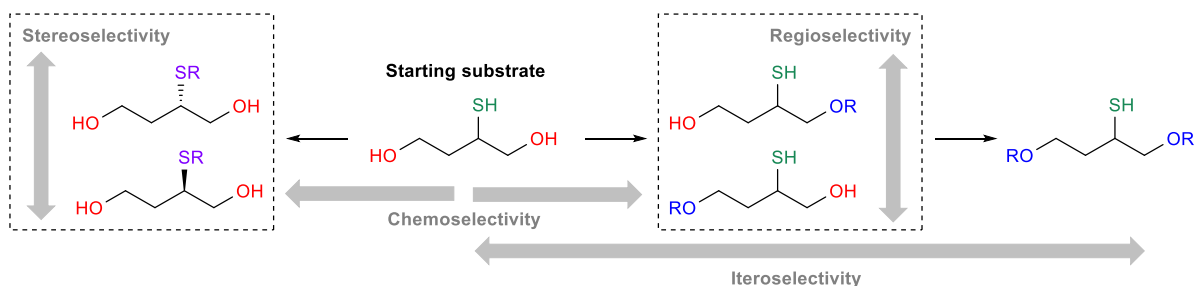


Figure 2. Overview of the differences between stereo-, chemo-, regio-, and iteroselectivities exemplified with the functionalization (e.g. alkylation) of a diol-monothiol.

Discussion

Definition of iteroselectivity and related concepts

a) Iteroselectivity and iteromers

Iteroselectivity is defined as the preferential formation of products (*i.e.* iteromers) differing by the number of repeating chemical transformations the starting substrate underwent, where preferential means different from a normal product distribution (see below).⁶ The products of an iterative reaction are not isomers and thus must be named iteromers instead of iteroisomers. Repeating chemical transformations designate reactions occurring on equivalent starting functional groups yielding equivalent final functional groups (e.g. alkylation of primary alcohols under the same conditions affording ethers). We originally proposed the name “iteroselectivity” as this type of selectivity concerns iterative processes such as the modification of a given number of functional groups iteratively. The iteroselectivity discussed herein applies only to one-pot reactions involving iterative chemical steps and should not be confused with sequential multi-step processes such as peptide syntheses relying on protection/deprotection steps.⁵

Iteroselectivity may originate from a wide diversity of phenomena such as electronic, steric, supramolecular effects, or even difference in solubilities. Iteroselectivity under kinetic control involves a modification of the reactivity after a given number of iterations, *i.e.* activating or deactivating one iteromer in regard to other iterations of the chemical reaction, thus accumulating an iteromer regardless of its relative stability compared to other iteromers. Thermodynamic control is only seen at equilibrium in reversible reactions in which the most stable iteromer(s) will form preferentially.

b) Calculating the degree of iteroselectivity

In the case of stereoselectivity, the absence of selectivity is trivially defined as a 1:1 ratio between two stereoisomers. This is sound in the case of enantiomers that both have the same thermodynamic stability, but this is an arbitrary decision in the case of diastereomers as these isomers display different relative stabilities, and a diastereomeric excess (*de*) of 0% is thus unexpected under any condition.

Similarly, defining a normal distribution of iteromers in absence of iteroselectivity implies arbitrary decisions. We propose to define the normal distribution of iteromers as the distribution obtained after complete consumption of the limiting reactant(s) for iterative irreversible reactions with identical kinetic constants (see details in the Supporting Information). The evolution of the concentration of iteromers under this definition is illustrated in Figure 3 for a tetra-functional substrate. These arbitrary choices ensure that the normal distributions are relatively simple to calculate, invariant to changes in concentration, and that complete per-functionalization results from an excess of reagent to the

number of functional groups on the substrate. Yet, we are conscious that these choices lead to a poor description of a normal distribution of iteromers in reversible reactions at equilibrium. Further considerations are discussed in the Supporting Information including formulas to calculate the normal distributions and precalculated tables for convenience. Rebek Jr and co-workers previously described the normal distribution in a similar fashion to evaluate the iteroselectivity of a reaction over time despite not using the terminology and definitions introduced herein.¹⁶

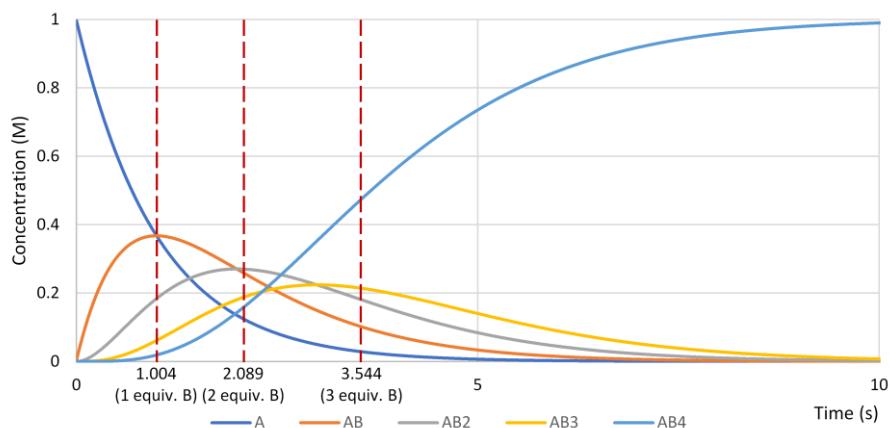


Figure 3. Evolution of the concentration of iteromers for an iterative reaction in absence of iteroselectivity (*i.e.* same kinetics for each iteration) on a tetra-functional substrate A reacting with B. The graph corresponds to an iterative reaction with first order kinetics in each iteromer. The starting concentration of A and the kinetic constant are arbitrarily set to 1 M and 1 s^{-1} , respectively. The initial stoichiometry of A and B is the only parameter that determines the normal distribution of iteromers after complete consumption of the limiting reactant. Red dashed lines show the normal distribution of iteromers upon complete consumption of B as limiting reactant (1, 2, or 3 equivalents). Formulas to calculate the concentration evolution and normal distributions are detailed in the Supporting Information, followed by precalculated tables of normal distributions for convenience.

To determine the degree of iteroselectivity, we introduce the concept of iteromeric excess *ite* by analogy to enantiomeric and diastereomeric excesses. Since the ratio of each iteromer can be different under a normal distribution, we define the *ite* based on the difference between the ratio of the iteromer *i* obtained experimentally r_{exp} (that can be assimilated to the yield) and the normal ratio r_{normal} that both range from 0 to 1 (equation 1). The *ite* ranges from 0 to 100% for positive iteroselectivity, and from $-\infty$ to 0 for negative iteroselectivity. Conveniently, in presence of an excess of reagent, r_{normal} equals 0 for any product other than the per-functionalized product and, therefore, the *ite* equals the yield (r_{exp}).

$$ite = \frac{r_{exp} - r_{normal}}{1 - r_{normal}} \times 100\% \quad (1)$$

It is noteworthy that for any intermediate iteromer (*i.e.* neither the starting substrate nor the per-functionalized product) r_{normal} is always smaller than 0.37 as per the definition of normal distribution (*e.g.* the ratios of AB, AB₂, and AB₃ in Figure 3). Consequently, any synthesis of intermediate iteromer in yield greater than 37% shows positive iteroselectivity. This condition is sufficient to describe a reaction as iteroselective and reporting the *ite* is informative but optional. Cases of perfect normal distribution are extremely rare or possibly inexistent. As such, most reported reactions are at least mildly iteroselective. Therefore, we recommend to refrain emphasizing the iteroselective character of a reaction unless “high” iteroselectivity is observed. The term iterospecificity should be avoided to describe complete iteroselectivity as recommended by IUPAC for other selectivities.¹

c) Iteroselectivity in polymerization

Interestingly, iteroselectivity is not limited to reactions only modifying existing functions on a substrate but also applies to oligo- and polymerizations (Figure 4). Indeed, a polymerization is an iterative reaction involving a repeating chemical transformation in which the reacting function is regenerated after each iteration. Therefore, a reaction leading to a major oligomer comprising a definite number of repeating units is iteroselective. Iteroselectivity is better suited to describe the selective formation of short oligomers while, for large polymers, the established concept of degree of polymerization is more appropriate. Indeed, large polymers are generally synthesized in batches of various lengths that are better described by their average length or weight rather than a precise number of iterations.

Some of the most striking examples of iteroselective oligomerization are (i) the peptide synthesis controlled by the complex ribosome activity in biological organisms¹⁷ (Figure 4A) and (ii) the syntheses of oligomeric macrocycles such as cucurbiturils,¹⁸ calixarenes,¹⁹ or pillararenes²⁰ which are, in some cases, templated by metal cations or solvent molecules to form iteroselectively a macrocycle of definite size (Figure 4B for calixarenes). Note that, for n repeating units, the number of iterations $i = (n - 1)$ for linear oligomers but $i = n$ for oligomeric macrocycles due to the additional iteration closing the macrocycle. For homo-polymerizations, the normal distribution would consist of a single polymer of maximum length (see Supporting Information), thus the normal ratio for any given length of polymer is essentially 0 and the *ite* is conveniently equal to the yield. For hetero-polymerizations, the normal distribution is more complex to calculate but some cases are covered in the Supporting Information.

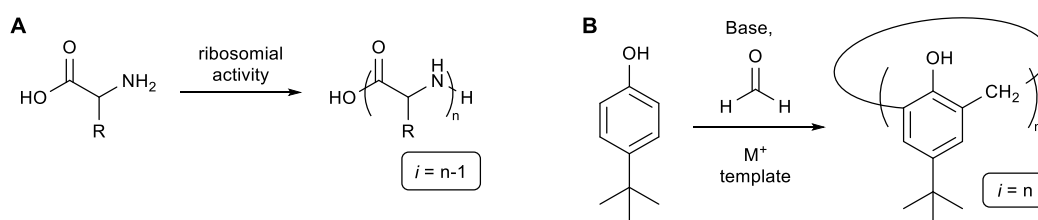


Figure 4. Examples of iteroselective oligomerization. (A) Peptides as linear oligomers. (B) Calix[n]arenes as oligomeric macrocycles. i : number of iterations.

Comparison between iteroselectivity and other main selectivities

a) Iteroselectivity vs regioselectivity

Iteroselectivity and regioselectivity are fundamentally different but complementary. Indeed, while the former leads to iteromers and the latter leads to regioisomers, several regioisomers may arise at each iteration of an iterative reaction. One simple example is the electrophilic aromatic substitution ($\text{S}_{\text{E}}\text{Ar}$) of functionalized benzene rings (Figure 5). If one considers the Friedel–Crafts alkylation of anisole, it is usually fair to assume that it will generate *ortho/para*-alkylated anisoles with relatively good regioselectivity (*ortho* and *para* positions) and iteroselectivity (from mono to trialkylated anisoles). In contrast, the nitration of anisole expresses a similar regioselectivity (*ortho* and *para* positions favored) but the iteroselectivity is greatly enhanced due to the strong deactivation imparted by nitro groups leading mainly to mononitro anisole in mild reaction conditions. In this last case, the iteroselectivity is driven by electronic effects with a deactivating kinetic control.

To describe the products and selectivity of such reactions that involve both iteroselectivity and regioselectivity, it is necessary to express both the iteromeric excess *ite* and the ratio of regioisomers. Following with the example of the $\text{S}_{\text{E}}\text{Ar}$ in Figure 5, let us consider the reaction of anisole with one

equivalent of alkylating agent leading to the monoalkylated products in *ortho* and *para* positions (20% and 60% yield, respectively). Both regioisomers correspond to the first iteration, thus the r_{exp} for $i = 1$ is the combined yields of both products (20% + 60% = 0.8). r_{normal} is 0.368 (see precalculated Table S4 in the Supporting Information). The result of the reaction for $i = 1$ can be described completely with $ite_1 = 100\% \times (0.8 - 0.368) / (1 - 0.368) = 68\%$ (iteroselectivity) and the ratio between all three possible regioisomers functionalized in *ortho/meta/para* positions is 1:0:3 (regioselectivity).

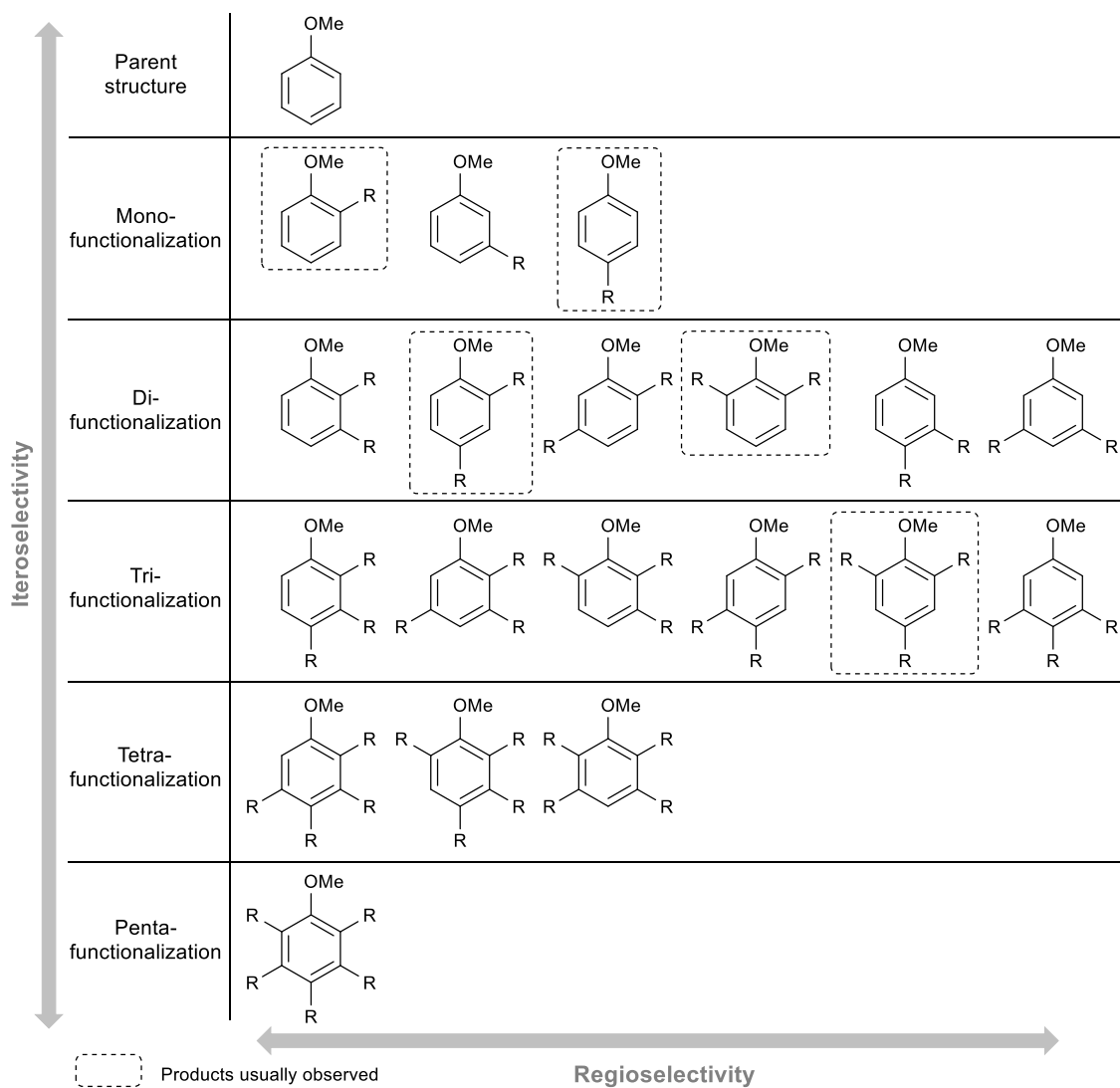


Figure 5. Comparison between iteroselectivity and regioselectivity for the SEAr of anisole. The electron-donating methoxy group activates the *ortho* and *para* positions which favors the formation of the five framed products iteroselectively and regioselectively.

Another example of reactions involving both types of selectivity is the functionalization of oligomeric macrocycles such as cyclodextrins²¹ or calixarenes^{8,22} which was studied for decades to seek efficient itero- and regioselective reactions (Figure 6). While most reactions to functionalize oligomeric macrocycles are not highly itero- or regioselective, some examples stand out and are described in the last section (see below).

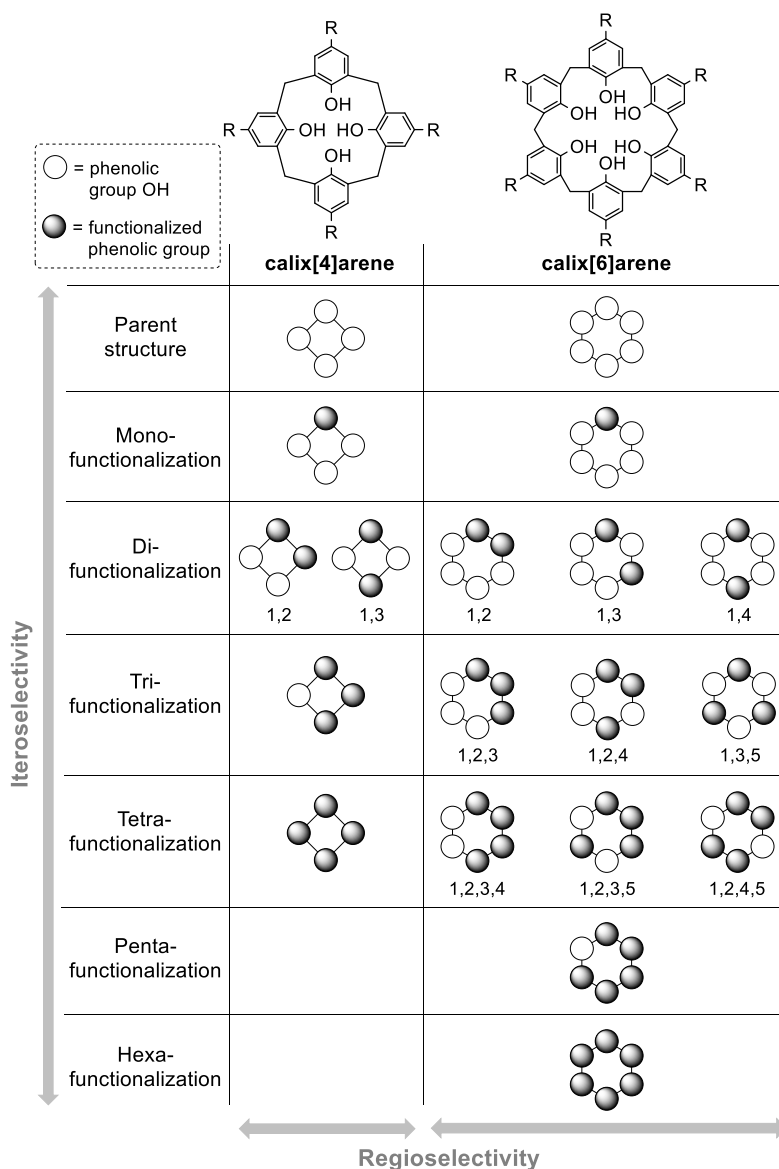


Figure 6. Comparison between iteroselectivity and regioselectivity for the functionalization of phenolic positions of calix[4 and 6]arenes.

b) Iteroselectivity vs stereoselectivity

Similarly to the comparison with regioselectivity, itero- and stereoselectivities are orthogonal but complementary since several stereoisomers may arise after each iteration of a reaction. A simple case such as a first-order nucleophilic substitution (S_N1) performed on an enantiopure dibromoalkane can illustrate this complementarity between the two selectivities (Figure 7). To describe completely the outcome of such reaction presenting both itero- and stereoselectivities, it is necessary to express both the iteromeric excess *ite* and the ratio of stereoisomers *dr* (or *ee/de* when applicable) for a given iteration *i*.

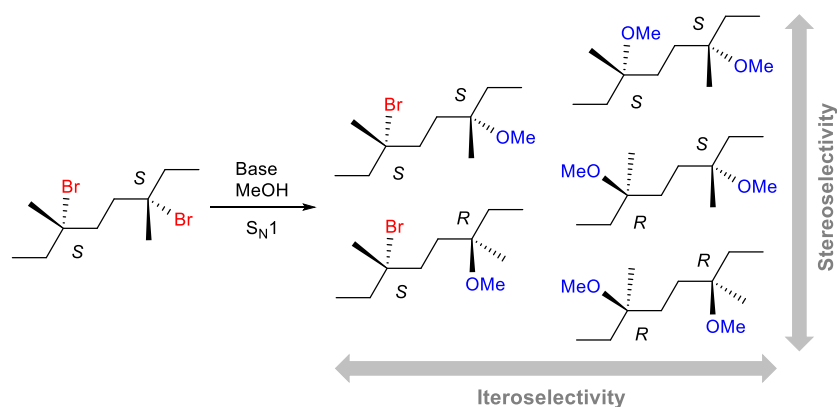


Figure 7. Comparison between iteroselectivity and stereoselectivity in the case of an S_N1 reaction involving a chiral dibromoalkane.

c) Iteroselectivity vs chemoselectivity

Considering the definition of iteroselectivity proposed herein that concerns repeating chemical transformation on the same chemical function, iteroselectivity is fundamentally different from chemoselectivity that concerns the selectivity between different chemical functions.¹ A lack of chemoselectivity in a potential iterative reaction would lead to side products which are out of the iterative process studied (Figure 8). Thus, iteroselectivity and chemoselectivity differ to such an extent that they cannot be used in a concerted manner to describe the products of a reaction as opposed to the complementarity between iteroselectivity and regio- or stereoselectivity discussed above.

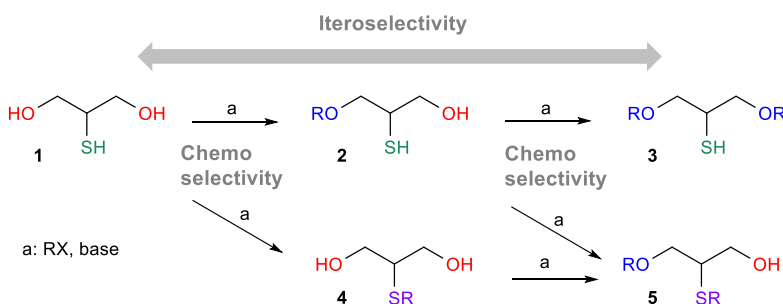


Figure 8. Comparison between iteroselectivity and chemoselectivity. Side products 4 and 5 resulting from the functionalization of the thiol group break the iterative path (1→2→3) and cannot lead to the iteromers 2 and 3.

Examples of iteroselective reactions from the literature

A tremendous amount of iteroselective synthesis examples are described in the scientific literature. However, it is difficult to search efficiently for these examples as they are not tagged as “iteroselective” and we have seen that iteroselectivity may apply to very simple reactions on small substrates as well as to more complicated cases. Therefore, the following list will not be exhaustive or representative of the diversity of substrates and reactions showing iteroselectivity but rather show recent and inspiring examples of highly iteroselective reactions. When possible, iteromeric excesses based on the reported yields and conditions were calculated. Details of iteromeric excess calculations are provided in the Supporting Information.

a) Tosylation of polyethyleneglycols

Polyethyleneglycols (PEGs) have two terminal hydroxy groups separated by a long distance. It is thus difficult to selectively modify one of these two groups as the transformation of one group has no influence on the reactivity of the second one. The iteroselective mono-tosylation of PEGs was however successfully achieved in presence of silver(I) oxide particles and potassium iodide (Figure 9).²³ The iteroselectivity was rationalized by an activation of one of the two terminal OH groups through its chemisorption on the surface of the silver particles, the other group remaining inactivated due to the entropically unfavorable backfolding of the PEG chain. For 1.0 equiv. of tosyl chloride, the authors obtained a ratio of starting, mono-tosyl, and di-tosyl PEGs ($i = 0, 1, 2$) of 179:733:88 (PEG-1500) and 158:762:79 (PEG-2000). The normal distribution for these iteromers under these conditions is 318:364:318 (see Table S1 in the Supporting Information). Accordingly, the iteromeric excess *ite* for the mono-tosylated products are 58% (PEG-1500) and 63% (PEG-2000).

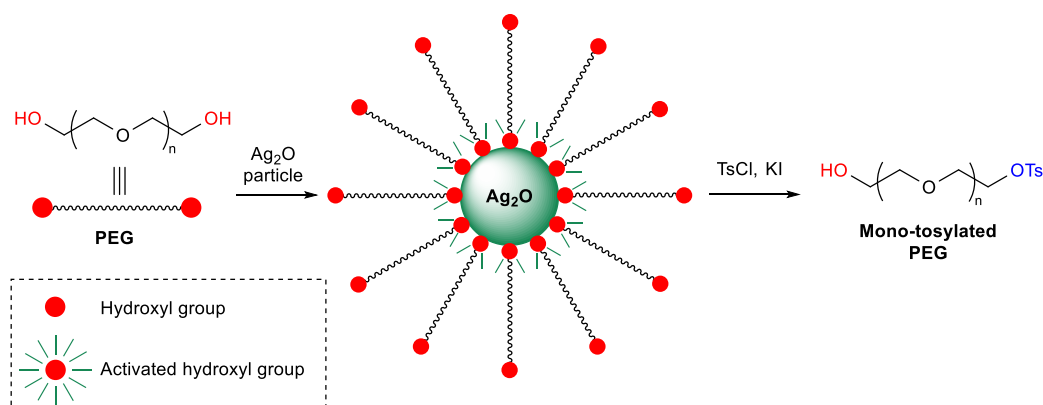


Figure 9. Selective-mono-tosylation of PEGs mediated by silver(I) oxide particles.

b) *O*-debenzylation of cyclodextrins

In the field of cyclodextrins, Sinaý and co-workers reported an iteroselective *O*-debenzylation of per-benzylated cyclodextrins with DIBAL-H (diisobutylaluminium hydride).²¹ Large excess of DIBAL-H (30–120 equiv.) under mild or harsher conditions led to the mono- and di-*O*-debenzylation of per-benzylated α -cyclodextrin bearing 18 benzyl ethers in 64% and 82% yield, respectively (Figure 10). In both cases the *ite* corresponds to the yield (64% and 82%) because the large excess of reagent should lead to the exclusive per-*O*-debenzylation under a normal distribution. The selectivity was rationalized by the limited number of bulky DIBAL groups allowed on the cyclodextrin narrow rim, thus leading to a maximum of two debenzylation at distant positions, thus achieving both itero- and regioselectivity. Sollogoub and co-workers later employed the mono-*O*-debenzylation to achieve an impressive multistep hetero-hexa-functionalization of α -cyclodextrin that required high itero- and regioselectivities over each step (Figure 10).²⁴

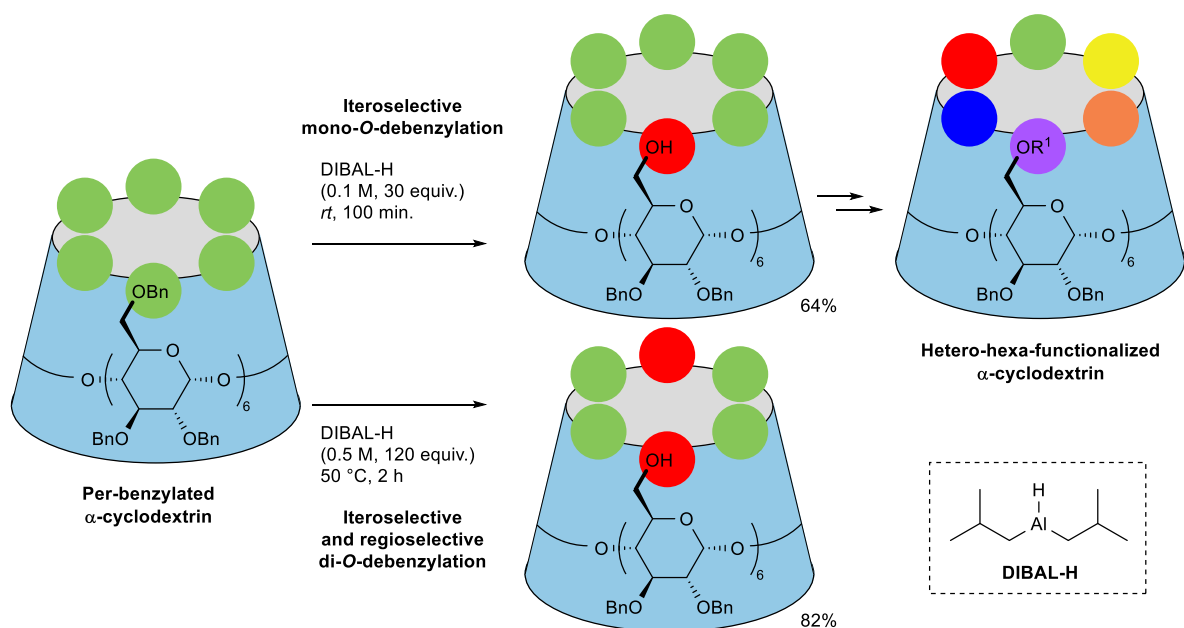


Figure 10. Multistep hetero-hexa-functionalization of α -cyclodextrin using an iteroselective mono-*O*-debenzylation reaction. Iteroselective and regioselective di-*O*-debenzylation can also be achieved under harsher conditions.

c) Carbamation of calixarenes

Over the last decade, we developed several strategies for the regio- and iteroselective modifications of calixarenes.⁸ As a representative example, we reported an iteroselective carbamation of calixarenes in aprotic solvents through the addition of an excess of *tert*-butyl isocyanate under basic conditions (Figure 11A).^{6,7,10} The “all-but-one” iteroselectivity was rationalized by an internal proton assisted mechanism. This mechanism involves a phenolate attacking the isocyanate and a nearby phenol to provide a proton. When only one unreacted phenolic unit remains, the absence of nearby proton donor prevents the last addition. Interestingly, unlike other examples described herein this all-but-one selective method does not lead to a specific number of iterations but depends on the number of starting reactive functions: $i = m - 1$ for m reactive functions. The reaction was shown to work efficiently on a wide scope of substrates including parent or partially functionalized calixarenes and homooxalixarenes (typical yields >90%). The first example of this all-but-one carbamation on *p*-*t*Bu-calix[6]arene with 18 equiv. of *tert*-butyl isocyanate showed a *ite* of 91% equal to the yield (Figure 11B).⁶ It is noteworthy that the all-but-one carbamation can also lead to regioselectivity when multiple regioisomers are possible. The all-but-one carbamation of dihomooxalix[4]arene leads to a single regioisomer among two possibilities, thus achieving high iteroselectivity (*ite* of 98%, equal to the yield) and regioselectivity (Figure 11C).⁷

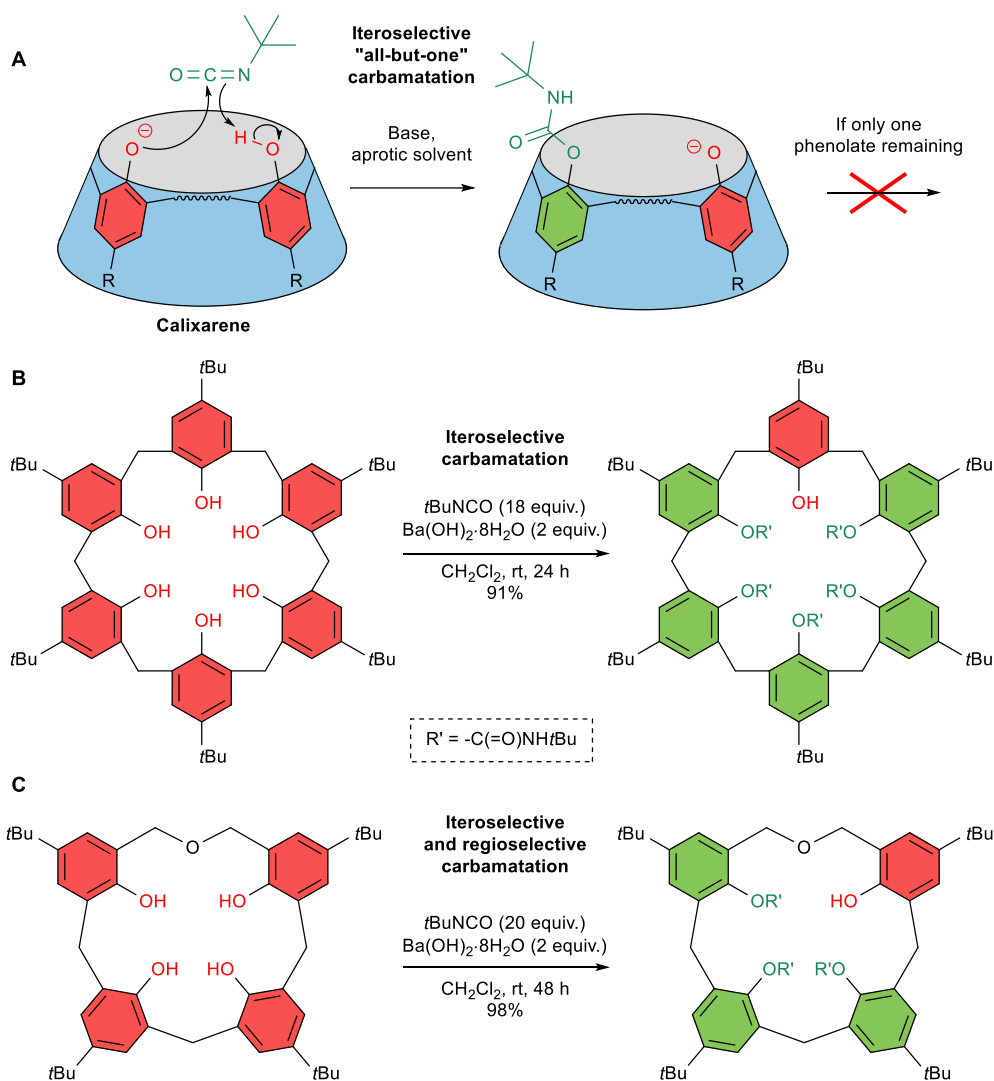


Figure 11. All-but-one carbamation of calixarenes. The reaction stops when only one phenolate is left unreacted. (A) Internal proton transfer assisting the carbamation of calixarenes and source of the iteroselectivity. (B) Example of iteroselective all-but-one carbamation of *p*-*t*Bu-calix[6]arene. (C) Example of iteroselective and regioselective all-but-one carbamation of *p*-*t*Bu-dihomooxalix[4]arene.

d) Supramolecular protection

Rebek Jr and co-workers reported several cases of iteroselective reactions on di-functional molecules via a supramolecular protection of one reactive site within a deep cavitand.^{16,25–28} Unlike conventional covalent protecting groups modifying chemical functions, supramolecular protecting groups modify the environment and, consequently, the reactivity of the functional groups, which is the origin of the iteroselectivity. One remarkable example is the Staudinger mono-reduction of diazido alkanes in water (Figure 12).²⁶ The diazido alkane guest is included in a resorcinarene-based deep cavitand with one of the two azides nesting in the cavity. The other azide protrudes from the cavity and can readily react with an excess of trimethylphosphine, affording the mono-amine product in 99% yield (the *ite* is equal to the yield). The further reaction of the unreacted azide is inhibited as this group is less polar than the amine and is thus preferentially hidden from the water. Such a strategy based on host–guest chemistry can be used to achieve regio- and iteroselective reactions on either the guest^{29,30} or the host,³¹ but also reactions of the host with the guest.^{32–34}

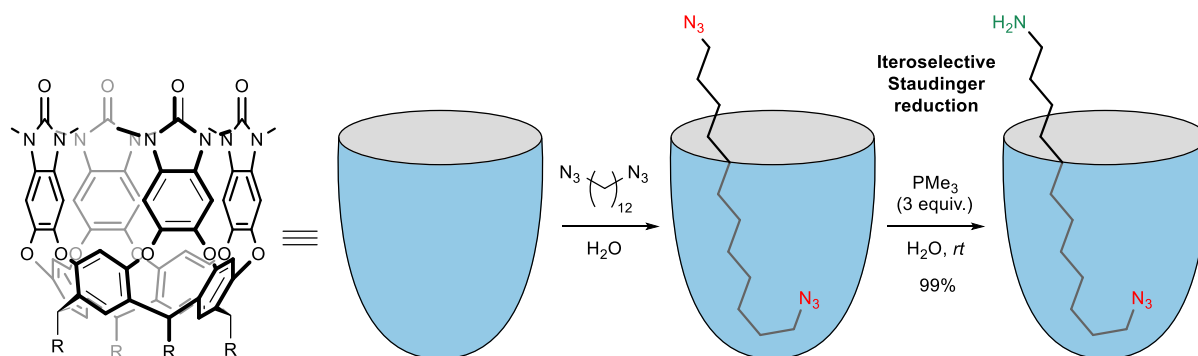


Figure 12. Itroselective Staudinger reduction on a diazido alkane with one azide protected inside a deep cavitand.

In a similar fashion, recent advances in the functionalization of fullerenes showed the successful use of shadow masks to protect a given number of reactive positions of C_{60} and C_{70} and achieve mono- to tetra-functionalization (Figure 13).^{35–39} In these reported complexes, the unfunctionalized fullerene guest is initially in free rotation with all identical reactive sites showing equal reactivity (30 for C_{60}). Upon the first and subsequent functionalizations, the rotation of the fullerene in the complex is impeded, thus effectively deactivating reactive sites masked by the host. For the synthesis of the tetrakis-diethylmalonate- C_{60} adduct with 4 equiv. of diethyl bromomalonate, the *ite* calculated is 99% from r_{normal} and r_{exp} of 20% and 99%, respectively.³⁶ It is noteworthy that this shadow mask strategy not only allows itroselective control but also regioselective control of the products. In the case exemplified in Figure 13, the shadow mask permits only the formation of the tetrakis-*e,e,e,e*-adduct as ultimate product but other shadow masks were used to access different regio- and itroselectivities.^{35–39}

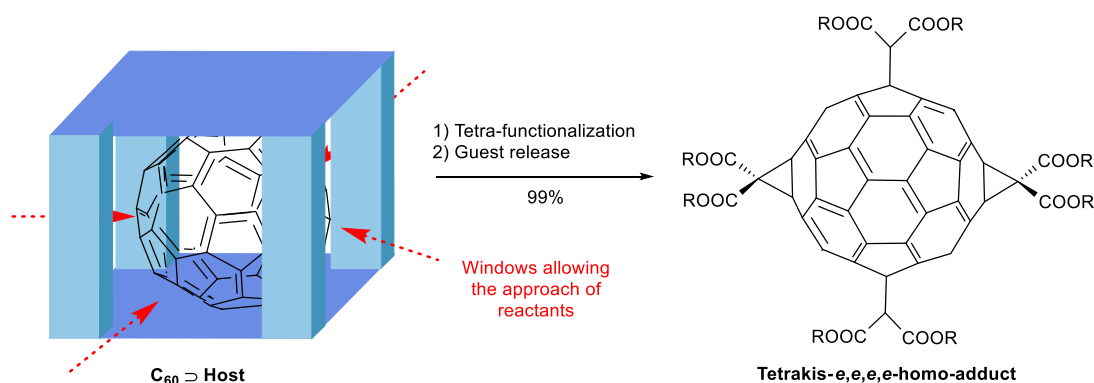


Figure 13. Regio- and itroselective tetra-functionalization of fullerene C_{60} via a shadow-mask strategy. There are 30 equally reactive sites on the starting C_{60} .

e) Itroselectivity in subcomponent self-assembly

Nitschke and co-workers reported the itroselective functionalization of tris-anilines via a dynamic subcomponent self-assembly process (Figure 14).⁴⁰ Several supramolecular structures can arise from the reported self-assembly including one kinetically metastable intermediate formed by the condensation of two of the three amine functions with an aldehyde to form imines stabilized by coordination to iron(II). The remaining unreacted amine of the kinetically trapped itroselectively di-protected tris-anilines is then functionalized prior to disassembling the supramolecular structures. This process is a clear example of kinetically controlled itroselective reaction. It is important to note that the functionalization of the last free amine does not constitute the itroselective reaction but rather the initial condensation of two amines with aldehydes. Indeed, in protection / functionalization /

deprotection sequences, the substrate that bears several identical functions that can undergo an iterative transformation is the initial substrate before protection. The following functionalization reaction is merely a per-functionalization of the remaining reactive sites, thus not showing any iteroselectivity. This difference is crucial to not confuse a seemingly apparent overall iteroselective reaction and the true iteroselective protection step. For the bis-condensation of tris(4-aminophenyl)amine with two equivalents of 2-formylpyridine, the *ite* calculated is 93% from r_{normal} and r_{exp} of 26% and 95%, respectively.

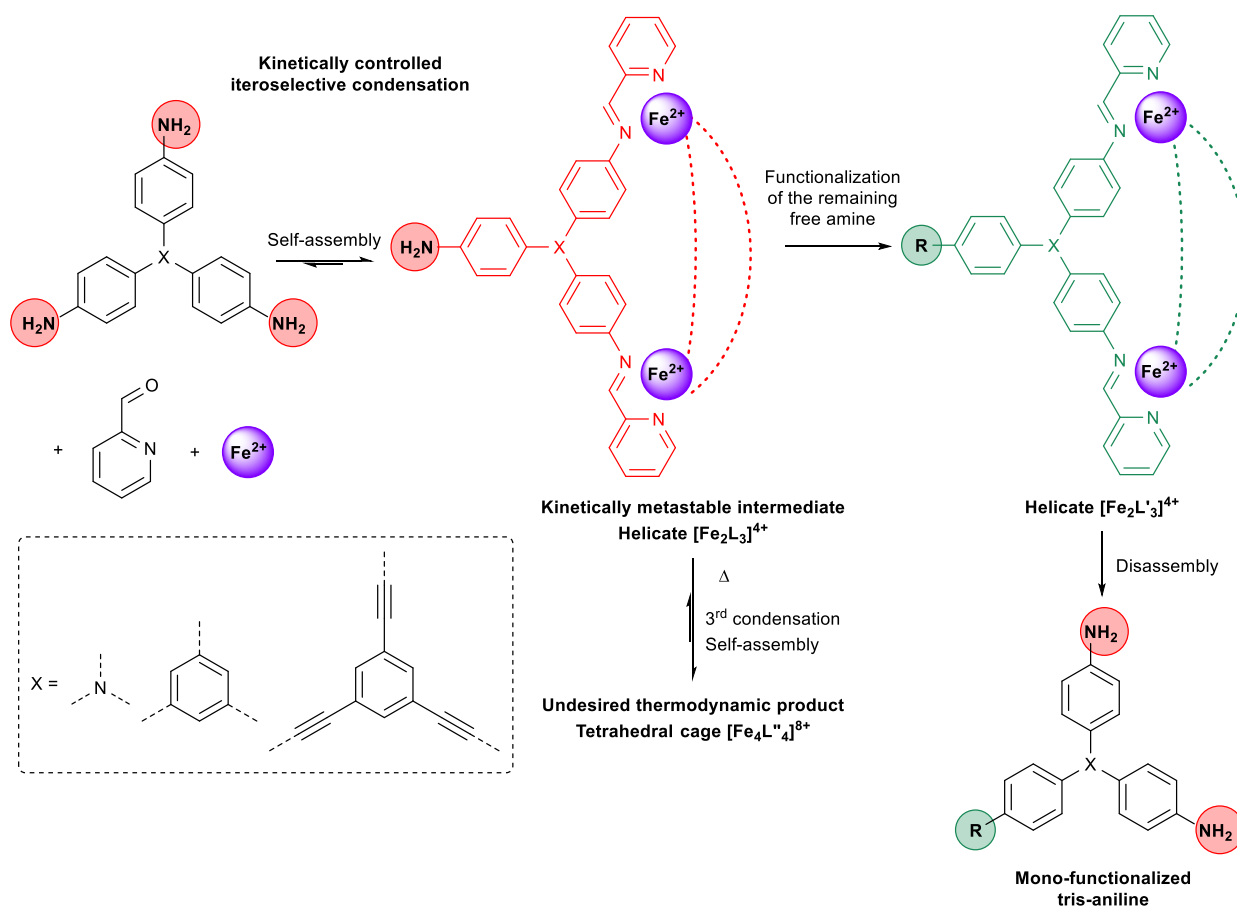


Figure 14. Iteroselective condensation of amines and aldehydes via self-assembly into supramolecular architectures.

f) Templated cyclooligomerization

The synthesis of oligomeric macrocycles is generally challenging as their size has to be controlled and the formation of linear polymers avoided. One of the most popular strategies is the use of a template that will drive the closure of the macrocycle with a defined number of monomers. A representative example is the synthesis of pillar[n]arenes using the solvent as a template (Figure 15). Ogoshi *et al.* showed that a small solvent such as 1,2-dichloroethane could serve as a suitable template for the small pillar[5]arene macrocycle ($i = 5$, yield = *ite* = 71%)⁴¹ while the larger solvent chlorocyclohexane templates the formation of the large pillar[6]arene macrocycle ($i = 6$, yield = *ite* = 87%).⁴² The oligomerization was shown to be reversible in presence of Lewis or Brønsted acids. Therefore, the iteroselectivity is under thermodynamic control. This templating strategy was successfully used to prepare larger macrocycles with reversible reactions (*e.g.* imine-based macrocycles)⁴³ or irreversible reactions (*e.g.* porphyrin nanorings).⁴⁴ Irreversible reactions, however, tend to lead to lower

iteroselectivity due to the occasional formation of any smaller macrocycle or larger oligomer than the templated product.

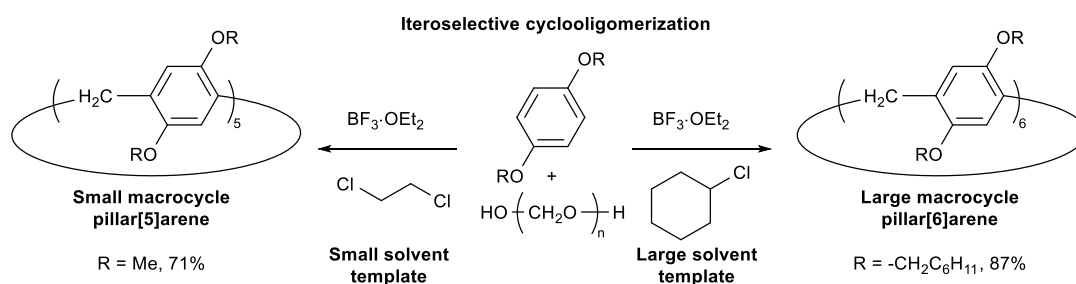


Figure 15. Iteroselective synthesis of pillar[n]arene macrocycles via solvent templation.

Conclusion

Iteroselectivity is observed when a limited number of repeating chemical transformations occurs in regard to the maximum number of reactive sites on a substrate. It is surprising that this concept was not properly named and defined earlier considering its common occurrence in simple reactions such as the alkylation of diols or aromatic substitutions. Moreover, the numerous recent studies successfully achieving iteroselective reactions through advanced methods clearly show a great interest of the chemistry community for this type of selectivity. We have now lifted the lack of definition and naming convention. Additionally, we provided means for measuring the degree of iteroselectivity through the calculation of iteromeric excess. The concepts described herein should lead to a better description of iteroselective processes in the literature and we hope that they will be helpful in other fields than organic and supramolecular chemistries including biochemistry and inorganic chemistry.

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Notes

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