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Water-mediated Desymmetrization Reactions

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The development of environmentally friendly organic reactions has been of central importance in synthetic organic chemistry. As water is among the most environmentally friendly solvents, water-mediated organic reactions thus represent a typical "green chemistry." Among various synthetic conversions, desymmetrization of symmetric compounds is one of the most cost-effective reactions, because the starting symmetric compounds are typically obtained on a large scale from inexpensive sources, or are commercially available inexpensively. Therefore, water-mediated desymmetrization of symmetric organic compounds is of remarkable synthetic values.

However, distinguishing the identical functional groups in symmetric compounds is considered challenging. Organic compounds are also generally considered not to significantly dissolve in water due to their hydrophobic nature. Therefore, the studies on water-mediated desymmetrization reactions have been rather limited. This editorial highlights some of the recent progress in the research of water-mediated desymmetrization reactions.

Enzyme reactions are a relatively common approach to accomplishing desymmetrization in aqueous media [1-8]. Conditions for enzyme reactions are typically mild and environmentally friendly, and therefore this approach is considered green chemistry. However, the mechanisms of enzyme reactions are mostly unknown, in particular, in the area of desymmetrization, and therefore one must screen various enzymes and substrates in order to reach desirable outcomes.

Among the most well-known non-enzymatic desymmetrization reactions are ring opening reactions of strained cyclic compounds such as epoxides and aziridines [9-14]. The driving force of these reactions is the relief of bond angle strain. Some asymmetric versions are also reported in this area.

Without such a driving force, desymmetrization is more difficult. Perhaps among the most pioneering non-enzymatic water-mediated desymmetrization are selective monohydrolysis of symmetric diesters reported by Niwayama [15-23]. This reaction distinguishes the two identical ester groups with high selectivity (>99%) and with high yields (>99%) in water, a selectivity which was previously impossible in the organic media. The reaction mechanism remains unknown, but potential conformational bias due to attractive interactions between two closely located carboalkoxy groups in these diesters may have contributed for this selectivity, because especially high selectivities were observed in the symmetric diesters with "*cis*" stereochemistry, facilitating the hydrolysis of a carboalkoxy group from one particular direction. The existence of the n->π^* interaction is suggested by theoretical studies for such an interaction [16]. An additional proposed mechanistic insight includes formation of micelle-like aggregates in which the hydrophobic carboalkoxy groups are pointed inside and hydrophilic COO^- groups are pointed outside, prohibiting further hydrolysis by the aqueous NaOH solution [23].

Chong et al. also reported selective monobromination of symmetric diols in the aqueous HBr/toluene two-phase media with high selectivities, producing high (>90%) yields of monobromides, despite the fact that the expected yields are a maximum of 50% as in the above monohydrolysis [24]. They propose that the reversed micelle-like structure by the bromo alcohol in which the polar hydroxy groups are pointed inside, which is expected to keep away from the exposure from the aqueous HBr.

More recently, other non-enzymatic desymmetrization reactions in aqueous media such as selective monobenzylation of 1,2- and 1,3-diols [25], selective monocycloisomerization of bispropargylic carboxylic acids [26], desymmetrization of 1-ferrocenedicarboxaldehyde [27], and aldol reactions toward cyclohexanone [28] have been reported. The key intermediate for the mechanism of the first reaction is proposed to involve a cyclic stannyl structure [25]. The transition state involving the enamines formed by the proline-based chiral amines is proposed for the last reaction [28]. Yields vary for all these reactions, but these reactions were performed in aqueous media with the use of water as a main solvent or a co-solvent. However, considering the obscure nature of the desymmetrization and the difficulty of the elucidation of the mechanisms, the reported studies and cited references in this editorial are expected to stimulate organic chemists and help pave the way for further development of additional green reactions.

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