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INTRODUCTION TO ASYMMETRIC DOMINO REACTIONS

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1.1 INTRODUCTION

A domino reaction has been defined by Tietze as a reaction that involves two or more bond-forming transformations, taking place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step [1]. It must be recognized that a relatively narrow distinction exists between domino and consecutive cascade or tandem reactions. From the point of view of an operator, the only difference between the two lies in the point along the sequence at which one or more catalysts or reagents had to be added to effect either the initiation of a sequence (i.e., domino reaction) or propagation to the next step (i.e., consecutive reaction). It should be noted that the descriptors domino, cascade, and tandem are often used indistinguishably from one another in the literature [2], and various opinions exist on how such reactions should be classified. According to Tietze, a domino reaction is strictly defined as a process in which two or more bond-forming transformations occur on the basis of functionalities formed in the previous step and, moreover, no additional reagents, catalysts, or additives can be added to the reaction vessel, nor can reaction conditions be changed [1]. Denmark further posited, however, that most domino reactions, as defined by Tietze, fell under the broader category of tandem processes [3]. Other tandem reactions that are not cascades involve the isolation of intermediates, a change in reaction conditions, or

Domino and Intramolecular Rearrangement Reactions as Advanced Synthetic Methods in Glycoscience, First Edition. Edited by Zbigniew J. Witczak and Roman Bielski.

the addition of reagents or coupling partners. Furthermore, other authors classified domino reactions with even stricter conditions [4, 5]. The quality and importance of a domino reaction can be correlated to the number of bonds generated in such a process and the increase in molecular complexity. Its goal resembles nature in its highly selective sequential transformations. The domino reactions can be performed as one-, two-, and multicomponent transformations. Multicomponent reactions are defined as domino reactions involving at least three substrates and, consequently, constitute a subgroup of domino reactions [4, 6]. It is worth noting that there are some confusing ideas among chemists about the definition of a multicomponent reaction. According to Yus [6c], this type of reactions should be clearly differentiated from other one-pot processes, such as tandem or cascade reactions, and in general from all processes that involve the reaction between two reagents to yield an intermediate that is captured by the successive addition of a new reagent (sequential component reactions). Multicomponent reactions are convergent chemical processes that involve the well-defined condensation or coupling of more than two reactants to form a product that contains significant portions of all reactants, ideally all atoms [6b]. Moreover, no additional reagents, catalysts, or additives can be added to the reaction vessel, nor can reaction conditions be changed as in domino processes, according to Tietze. The use of one-, two-, and multicomponent domino reactions in organic synthesis has been increasing constantly, since they allow to economically synthesize a wide range of complex molecules, including natural products and biologically active compounds by employing a methodology that requires neither costly and time-consuming protection-deprotection processes nor the purification of intermediates [7]. Indeed, decreasing the number of laboratory operations and the quantities of chemicals and solvents has made domino and multicomponent reactions unavoidable processes [8]. The proliferation of these reactions is evidenced by the number of recent reviews covering the literature through 1992 [1, 4, 6c, 9]. Although asymmetric synthesis is sometimes viewed as a subdiscipline of organic chemistry, actually this topical field transcends any narrow classification and pervades essentially all chemistry [10]. Indeed, the preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry, mainly due to the fact that most natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. The use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity, and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. The growing economic importance of chiral compounds has spurred major research efforts toward the selective preparation of chiral compounds. The synthesis of optically active chiral compounds, which play an important role in medicine and materials, is one of the most fascinating aspects of modern organic synthesis. Over the last three decades, an explosive growth of research in the field of asymmetric synthesis has occurred. Asymmetric synthesis constitutes one of the main strategies to gain access to enantioenriched compounds, involving the use of either chiral substrates and auxiliaries or catalysts derived preferentially from cheap chiral pool sources. In particular, asymmetric catalysis of organic reactions to

provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry. In this context, the possibility of preparing chiral compounds by joining two or more reactions into one asymmetric domino process has rapidly become a challenging goal for chemists, due to economical advantages, such as the avoidance of costly protecting groups and time-consuming purification procedures after each step. In particular, the combination of these fascinating one-pot reactions with asymmetric catalysis has quickly become one of the most rapidly growing areas of the current organic chemistry.

1.2 ASYMMETRIC DOMINO REACTIONS USING CHIRAL CARBOHYDRATE DERIVATIVES

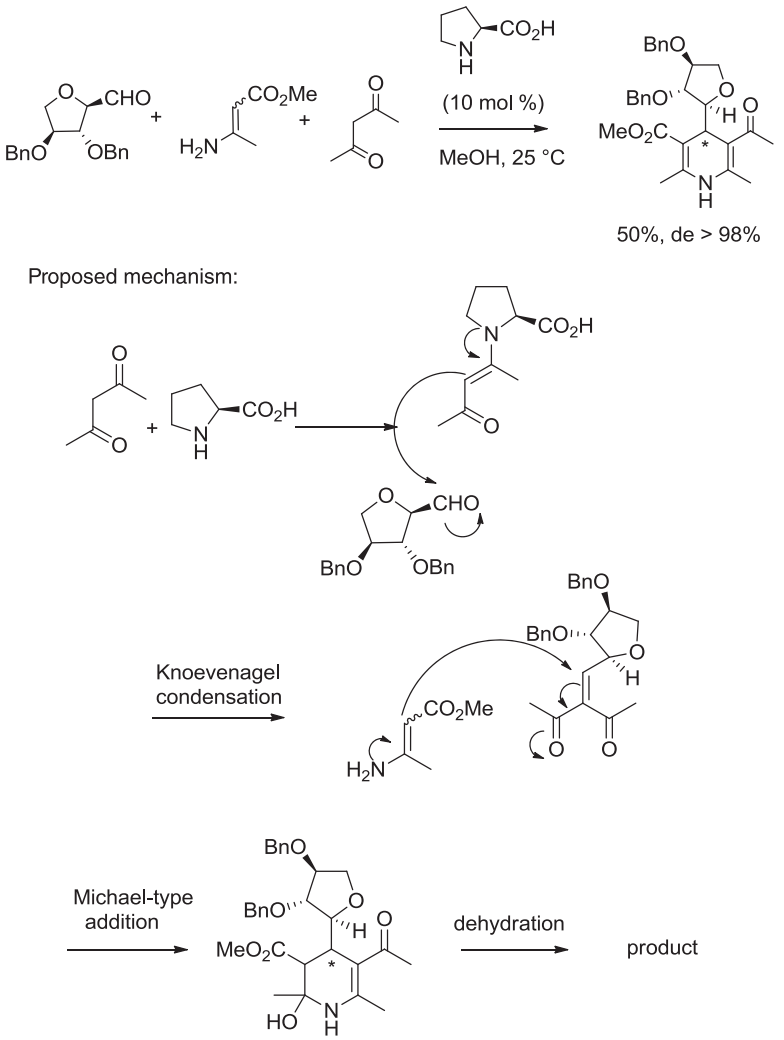
In spite of the explosive development of asymmetric domino processes including multicomponent reactions, domino reactions involving chiral carbohydrate derivatives still remain rare in the literature. It is particularly true with regard to carbohydrate-derived organocatalysts. This section highlights several important works dealing with stereocontrolled domino reactions of chiral carbohydrate derivatives in a first part, and a rare enantioselective domino reaction catalyzed by a chiral carbohydrate derivative in a second part. It must be noted that all the discussed domino reactions are multicomponent ones.

1.2.1 Stereocontrolled Domino Reactions of Chiral Carbohydrate Derivatives

One of the challenges in organic synthesis is to implement various reaction strategies in a multicomponent reaction, which is a domino reaction involving at least three substrates [1, 4–6] to achieve multibond formation. Moreover, the process is to take place in a single-reaction vessel and the newly formed product must contain portions of all the employed reactants. Multicomponent reactions convert more than two educts directly into their product by one-pot reactions. The starting materials for this kind of chemical transformation may be rich in functional groups. Typically, multicomponent reactions lead to very complex products by reacting relatively simple starting materials. The multicomponent reaction proceeds according to the domino principle, since subsequent transformations are a consequence of the functionalities produced in the previous transformation. These processes are highly flexible, (chemo)-selective, convergent, atom efficient, and of high exploratory power. Inspired by the mode of action of nature, they have brought the concept of ideal synthesis closer to reality [11]. Indeed, the discussed strategy is atom economical and avoids the necessity of protecting groups and isolation of intermediates. Its goal resembles nature in its highly selective sequential transformations. Even though the history of multicomponent reactions dates back to the second half of nineteenth century with the reactions of Strecker, Hantzsch, and Biginelli, it was only in the last decades with the work of Ugi that the concept of the multicomponent reaction has

emerged as a powerful tool in synthetic chemistry [12]. In particular, one should mention a venerable and old multicomponent reaction, the so-called Hantzsch reaction, which was first reported in 1882 [13]. It allows the synthesis of 1,4-dihydropyridines through the reaction of enamines, aldehydes, and 1,3-dicarbonyl compounds. Dihydropyridines are well known for their activity against calcium channels, multidrug inflammatory targets in addition to their usefulness as tools for reducing imines to amines. The harsh reaction conditions usually applied to carry out the Hantzsch reaction have significantly decelerated the development of asymmetric versions of this reaction. In comparison with other asymmetric multicomponent reactions, the asymmetric Hantzsch process has probably observed the greatest progress during the last 6 years. In 2006, Dondoni et al. reported the synthesis of chiral 1,4-dihydropyridines through the three-component Hantzsch reaction between chiral aldehydes bearing a *N*-Boc benzyl glycinate group, β-keto esters, and enamino esters, which led to the corresponding chiral 1,4-dihydropyridines [14]. The scope of this methodology was later extended by the same authors to the synthesis of various enantiopure *C*-glycosylmethyl pyridylalanines starting from the corresponding chiral aldehydes [15]. A collection of eight novel *C*-glycosylmethyl pyridine amino acids was achieved in 55–68% yields with total preservation of the stereocenter and protective group's integrity. Furthermore, in 2009, the same authors developed the first organocatalyzed three-component Hantzsch reaction occurring between a chiral *C*-glycosyl aldehyde, a β-diketone, and an enamine, to provide the corresponding enantiopure substituted 1,4-dihydropyridine *C*-glycoconjugate in a 50% yield and excellent diastereoselectivity of >98% de, as shown in Scheme 1.1 [16]. This method, based on a double asymmetric induction, arising from the use of a chiral auxiliary associated to a chiral organocatalyst, allowed the synthesis of biologically relevant *C*-nucleosides, which were not accessible through uncatalyzed procedures.

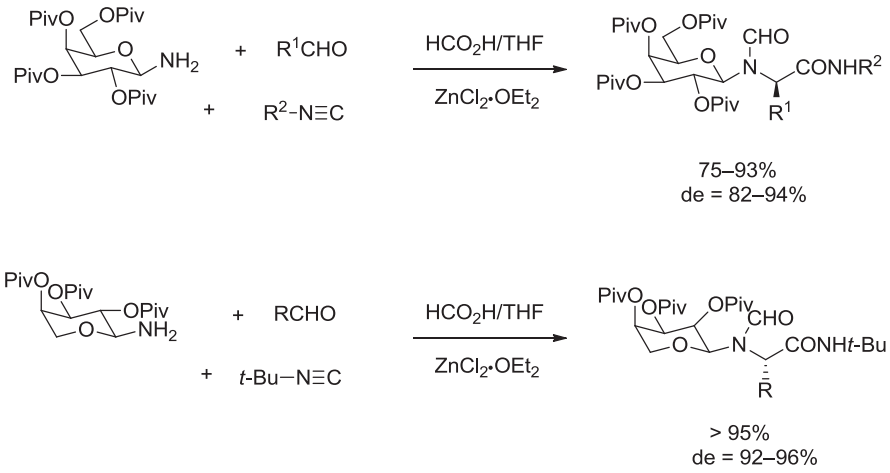
The modern concept of multicomponent reaction is intimately related to the reactions developed with isocyanide reagents [17]. The Ugi four-component reaction is the reaction of a carbonyl compound (usually an aldehyde), an amine, an isocyanide, and a carboxylic acid (or an alcohol) to yield α-amino acid derivatives. In general, the mechanism involves *in situ* formation of an imine from the aldehyde or ketone and the primary amine, followed by α-addition of the isocyanide component to the imine and carboxylic acid and subsequent rearrangement to furnish diversely substituted α-amino acid derivatives. This reaction, first described in 1959, has been more widely studied and used than any other multicomponent reaction [12]. In their early work, Ugi et al. determined that the use of a chiral acid or isonitrile in the reaction did not provide any degree of stereoselectivity [18]. In contrast, chiral ferrocenylamine inputs resulted in the synthesis of nonracemic amino acid derivatives with low to modest levels of diastereoselectivity [19]. Later, Kunz et al. developed more versatile chiral auxiliaries for the Ugi reaction, using carbohydrate derivatives [20]. High diastereoselectivities of up to 94% de of (*R*)-amino acids were obtained in reactions employing a galactosylamine derivative (Scheme 1.2, first equation) [20a]. A drawback of this asymmetric Ugi reaction was that high levels of stereoselectivity were observed only for reactions using *tert*-butyl isonitrile. In addition, the asymmetric synthesis of (*S*)-amino acids with excellent diastereoselectivities of up to 96% de



SCHEME 1.1 Three-component Hantzsch reaction of a chiral *C*-glycosyl aldehyde.

via the Ugi reaction was achieved using an arabinosylamine derivative (Scheme 1.2, second equation) [20b]. A single variant of the chemistry developed by Kunz was reported by Goebel et al. in 1991 [21]. These authors showed that 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines used as chiral amine components were even more efficient than the *O*-acyl-aldopyranosylamides used by Kunz et al. since diastereoselectivities of up to >99% de were reached with these chiral substrates.

The Passerini three-component reaction, discovered in 1921, involves the condensation of carbonyl compounds, carboxylic acids, and isocyanides to afford the corresponding α-acyloxy carboxamides [22]. Among several advantages are the

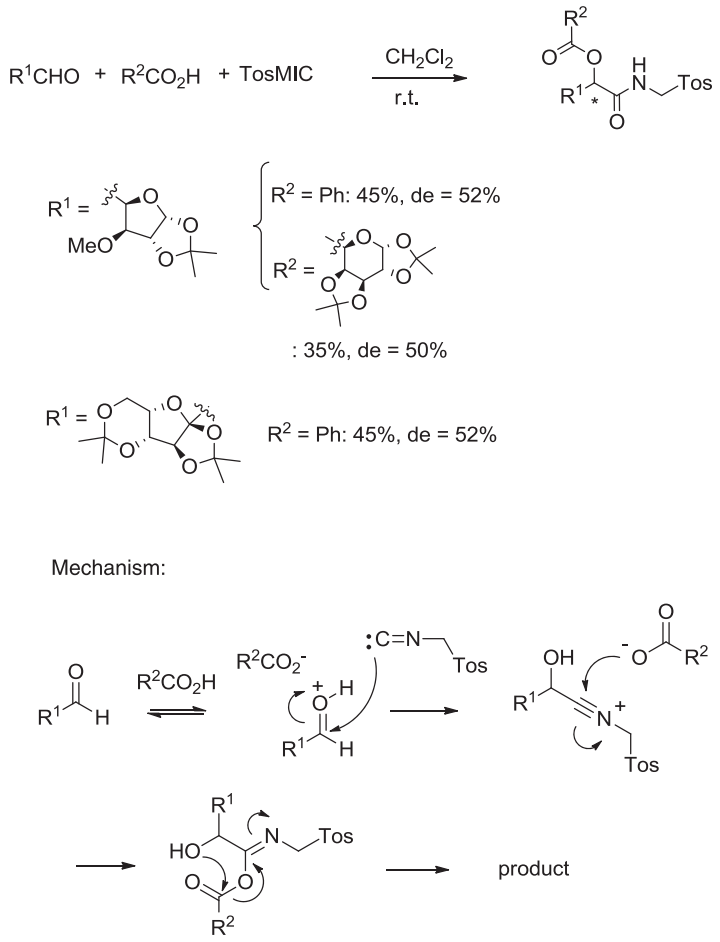


SCHEME 1.2 Three-component Ugi reactions of chiral carbohydrate-derived amines.

mildness of the reaction conditions, the broad scope, and high variability of the inputs [23]. Several chiral auxiliaries and substrates have been applied to control the stereochemical outcome of the diastereoselective Passerini reaction [24]. A particularly interesting Passerini reaction was reported by Krishna et al. in 2006 [25], who used (*p*-toluenesulfonyl)methylisocyanide (TosMIC) for the first time in this reaction as the isonitrile component. As shown in Scheme 1.3, the process employed carbohydrate-derived aldehydes as the chiral auxiliaries to react with TosMIC and carboxylic acids, providing the corresponding products as mandelamides in moderate yields (35–45%) and diastereoselectivities (50–52% de). The use of a chiral carboxylic acid in this reaction did not enhance the stereoselectivity.

The classic direct Mannich reaction, discovered in 1912 [26], is an aminoalkylation of carbonyl compounds involving ammonia (or a primary or secondary amine derivative), a nonenolizable aldehyde (usually formaldehyde) or a ketone, and an enolizable carbonyl compound, leading to β-aminocarbonyl derivatives [27]. In addition to enantioselective catalytic Mannich reactions [28], all of the possibilities of using chiral starting materials for this asymmetric multicomponent reaction have been reported. In their aim of discovering novel glycopeptide-based drugs for the treatment of bacterial and viral infections, cancer, and inflammatory processes [29], Dondoni et al. have employed a range of chiral *C*-glycosyl aldehydes as chiral auxiliaries in the Mannich reaction with *p*-methoxybenzylamine, and commercially available ketene silyl acetal, 1-methoxy-2-methyl-1-trimethylsilyloxypropene [14]. This process was promoted by $InCl_3$ and provided the corresponding chiral *C*-glycosyl α,α-dimethyl β-amino esters in high yields (60–90%) and complete diastereoselectivity in all cases of substrates studied, as shown in Scheme 1.4.

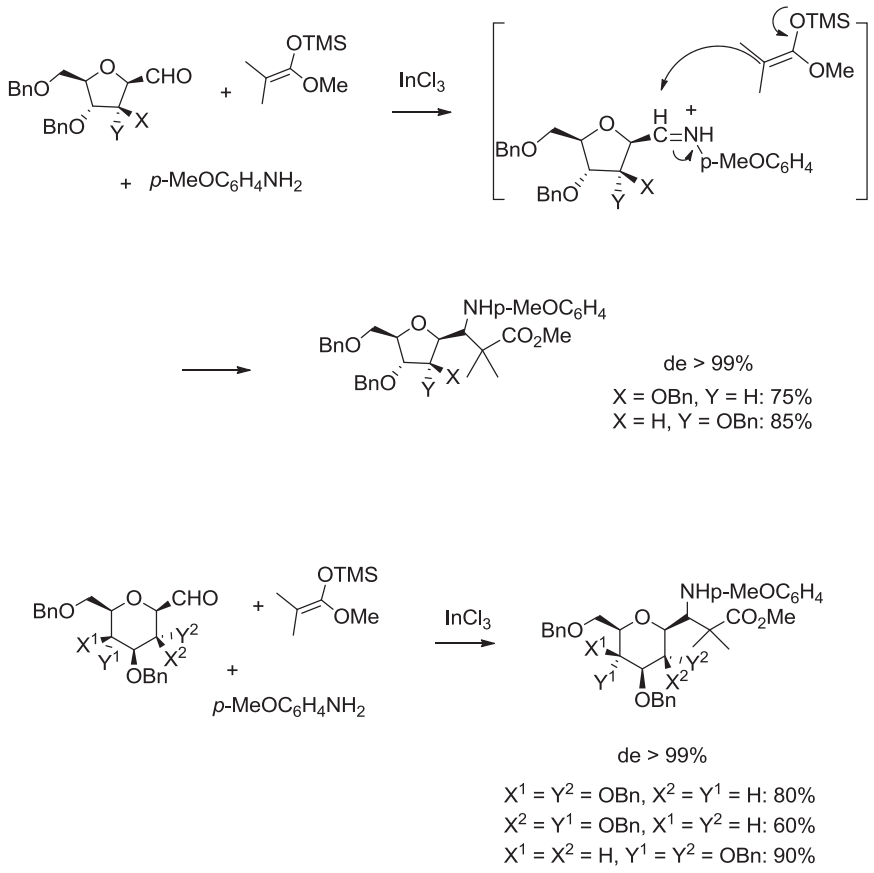
Diastereoselective nickel-catalyzed asymmetric four-component domino Reformatsky-type reactions have been developed by Dondoni et al. with the aim of achieving chiral *C*-glycosyl β-amino esters [14]. As shown in Scheme 1.5, an



SCHEME 1.3 Three-component Passerini reaction of chiral carbohydrate-derived aldehydes.

in situ initial coupling of chiral *C*-glycosyl aldehydes with *p*-methoxybenzylamine led to the corresponding imines, which reacted with bromozinc enolate (*in situ* generated from dimethylzinc and ethyl bromoacetate). The resulting chiral Reformatsky products were obtained in moderate to good yields and as single diastereomers in all cases of substrates studied.

More recently, Beau and Norsikian reported remarkable diastereoselective domino Petasis/Diels–Alder reactions of unprotected carbohydrates with allylamines and boronic acids [30]. As shown in Scheme 1.6, free sugars, such as D-ribose and D-fucose, reacted through a three-component reaction to give the corresponding complex heterocyclic chiral domino products in good yields and often complete diastereoselectivity. The domino process started with a Petasis reaction occurring

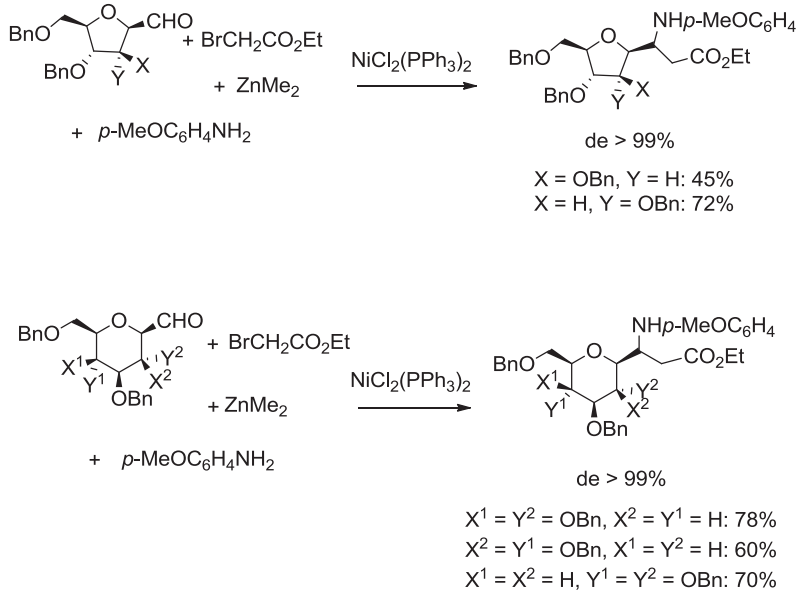


SCHEME 1.4 Three-component Mannich reactions of chiral *C*-glycosyl aldehydes.

between the free sugar and allylamine to give the corresponding acyclic Petasis product, which subsequently underwent an intramolecular Diels–Alder reaction to provide the final bicyclic chiral domino product. The process was performed in 9:1 dichloromethane/hexafluoroisopropanol as a solvent by heating the mixture at 120°C under microwave irradiation. In almost all cases studied, the reaction afforded a single diastereomer, except for the reaction of D-ribose with diallylamine and 2-furanylboronic acid, which led to a 7:3 mixture of two diastereomers, as shown in Scheme 1.6.

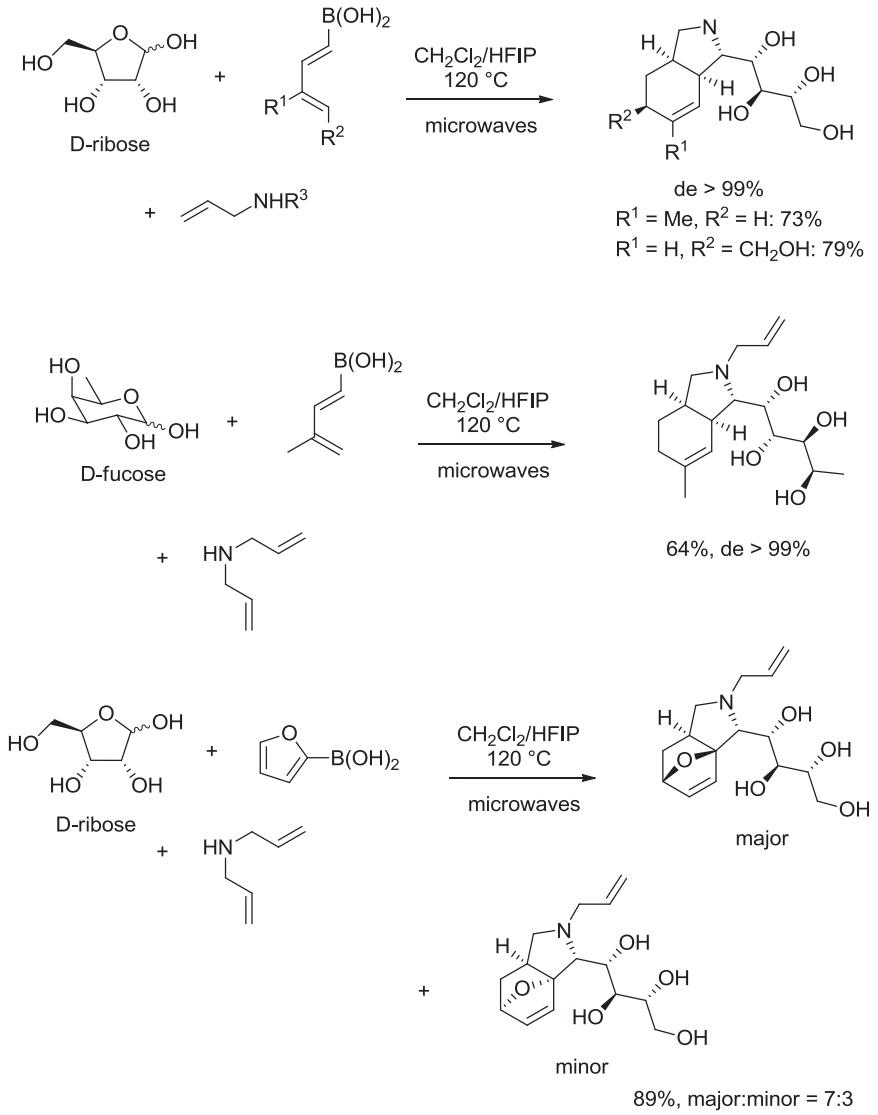
1.2.2 Enantioselective Domino Reactions Catalyzed by Chiral Carbohydrate Derivatives

The economical interest in combining asymmetric catalytic processes with domino reactions is obvious. The use of metal [10, 31] and biocatalysis [32] dominated the



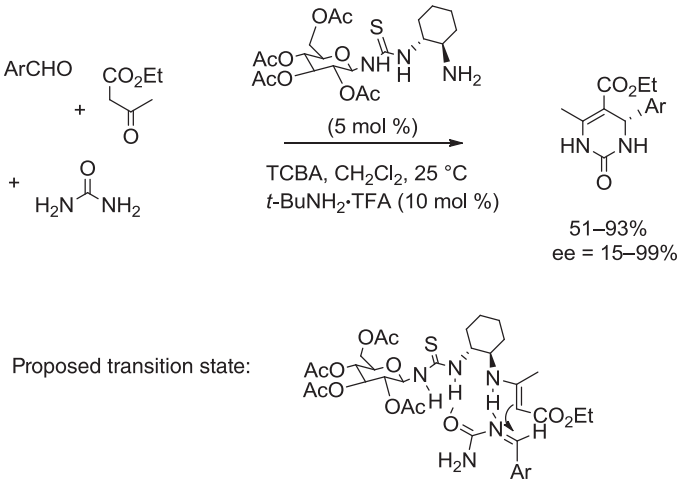
SCHEME 1.5 Four-component domino Reformatsky-type reactions of chiral *C*-glycosyl aldehydes.

catalytic processes at the end of the last century. However, a change in perception occurred during the last decade when several reports confirmed that relatively simple organic molecules, such as proline, could be highly effective and remarkably enantioselective catalysts of various fundamentally important transformations [33]. This rediscovery has initiated an explosive growth of research activities in organocatalysis, both in industry and in academia. Organocatalysts have several important advantages, since they are usually robust, inexpensive, readily available, and nontoxic. Enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications describing applications of this type of reactions, which paint a comprehensive picture for their real possibilities in organic synthesis [9l-m,9o,9q] [34]. The application of chiral organocatalysts has permitted the preparation of a number of highly valuable chiral products containing no traces of hazardous metals. The methodology offers several advantages from an economical and environmental point of view [35]. The ability of organocatalysts to promote a wide range of reactions by different activation modes makes organocatalysis ideal for applications in domino reactions, processes taking place in one pot and building complex frameworks from simple starting compounds. These organocatalyzed domino reactions are often highly efficient and follow, in some way, different biomimetic pathways, and principles that are found in biosynthetic processes in nature. In this context, the chemists have devoted more and more effort into the development of new and powerful strategies in domino reactions that avoid the use of costly and time-consuming protection–deprotection processes, as well as purification procedures of intermediates. Among enantioselective



SCHEME 1.6 Three-component domino Petasis/Diels–Alder reactions of unprotected carbohydrates.

organocatalyzed reactions, the Biginelli reaction [36], which is a three-component reaction between urea or thiourea, a 1,3-dicarbonyl derivative, and an aldehyde providing medicinally relevant 3,4-dihydropyrimidin-2-(1*H*)-ones or -thiones, is known to give high enantioselectivities when induced by organocatalysts [37]. In 2009, chiral bifunctional primary amine-thiourea catalysts derived from D-glucose were demonstrated by Chen et al. to be very efficient to promote highly enantioselective



SCHEME 1.7 Carbohydrate-derived primary amine-thiourea-catalyzed Biginelli reaction.

Biginelli reaction of a range of benzaldehydes, (thio)urea, and ethyl acetoacetate [38]. The best results were obtained when using gluco-2-aminocyclohexylthiourea depicted in Scheme 1.7 in combination with 2,4,6-trichlorobenzoic acid (TCBA) and *tert*-butylammonium trifluoroacetate as additives in dichloromethane as a solvent. Under these conditions, the corresponding dihydropyrimidines were formed in moderate to high yields (51–93%) with enantioselectivities of up to 99% ee, as shown in Scheme 1.7. In order to explain the stereoselectivity of the reaction, the authors proposed that both hydrogen-bonding interactions and enamine activation of the β-ketoester occurred in the transition states (Scheme 1.7). It must be noted that a low catalyst loading of only 5 mol % was sufficient to reach the discussed results. However, poor enantioselectivities were obtained for aliphatic aldehydes, such as *n*-butanal, which provided the corresponding product in only 15% ee. The asymmetric synthesis of dihydropyrimidines can also be catalyzed by chiral bifunctional primary amine-thiourea catalysts, as reported by the same authors [39]. The activation of the intermediate imine and carbonyl component toward nucleophilic attack was effectively catalyzed by the primary amine and thiourea moieties of the catalyst. The incorporation of a carbohydrate fragment in the catalyst was particularly attractive for the well-defined stereogenic centers and ubiquity. The combination of the primary amine-thiourea catalyst depicted in Scheme 1.7, TCBA, and *t*-BuNH_2-TFA as an additive proved superior in terms of reactivity and selectivity for the catalytic enantioselective Biginelli reaction depicted in this scheme. The scope of the reaction was investigated with various aromatic aldehydes producing the corresponding dihydropyrimidines with good to high enantioselectivities, while the reaction of aliphatic aldehyde was less efficient (51% yield) and offered lower stereoselectivity (15% ee). The authors proposed a transition state, in which the *Si*-face of the intermediate imine was predominately attacked by the enamine intermediate to afford the (*S*)-configured

dihydropyrimidine, because the *Re*-face was shielded by the cyclohexane ring of the catalyst. More recently, the same authors investigated the same reaction under phase transfer conditions [40]. Indeed, by using the same catalyst at 15 mol % of catalyst loading combined with 15 mol % of TfOH and 10 mol % of *t*-$BuNH_2$·TFA as an additive, the reaction could be performed in aqueous media, providing the Biginelli products in good to high yields (62–93%) and high to excellent enantioselectivities (87–99% ee).

1.3 CONCLUSIONS

This chapter illustrates the power of asymmetric domino reactions, which have quickly become a powerful, fascinating, and highly efficient tool in organic chemistry. Indeed, these beautiful one-pot reactions can be considered as one of the most influential reaction classes of the last century. It demonstrates that this type of reactions can be successfully applied to the field of carbohydrate chemistry. Indeed, various stereocontrolled multicomponent domino reactions involving chiral carbohydrate derivatives as substrates have been developed in the last decade. For example, remarkable diastereoselectivities of up to >99% de were reported by Dondoni in various types of asymmetric multicomponent reactions, such as three-component Hantzsch reactions, three-component Mannich reactions, and four-component Reformatsky reactions. The same level of diastereoselectivity (>99% de) was also recently achieved by Beau and Norsikian in novel asymmetric three-component domino Petasis/Diels−Alder reactions. Moreover, other types of asymmetric multicomponent reactions of carbohydrate derivatives have provided excellent diastereoselectivities. For example, three-component Ugi reactions reported by Kunz offered up to 96% de. Other diastereoselectivities such as those described by Krishna for three-component Passerini reactions were moderate (52% de). When discussing the use of chiral substrates and auxiliaries in asymmetric synthesis, it should be noted that catalytic, particularly organocatalytic, asymmetric synthesis has attracted most attention. Its combination with the concept of domino sequences has allowed reaching high-molecular complexity with very often excellent levels of stereocontrol under environmentally friendly conditions, with simple operational procedures, and advantages of savings in solvents, time, energy, and costs. Major progress has been achieved in the last years through the creation of highly enantioselective versions of existing and novel organocatalytic domino and multicomponent reactions. For example, in the area of carbohydrate-derived organocatalysts, Chen et al. [40] reported remarkable enantioselective Biginelli reactions that allowed accomplishing enantioselectivities of up to 99% ee when catalyzed by chiral bifunctional primary amine-thiourea catalysts derived from D-glucose. These significant improvements are expected to influence the development of novel asymmetric domino reactions to a great extent and will make them even more useful tools for the total synthesis of natural and biologically active products. Undoubtedly, the future direction in this emerging field is to continue expanding the scope of asymmetric domino reactions especially to inexpensive carbohydrate derivatives through the identification of novel modes of reactivity and apply these

powerful, simple, and easy-to-perform strategies to the synthesis of important, biologically interesting molecules including natural products.

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