OLEFIN BOND CHEMODIFFERENTIATION THROUGH CROSS-METATHESIS REACTION; STEREOCONTROLLED SYNTHESIS OF FUNCTIONALIZED β-AMINO ACID DERIVATIVES

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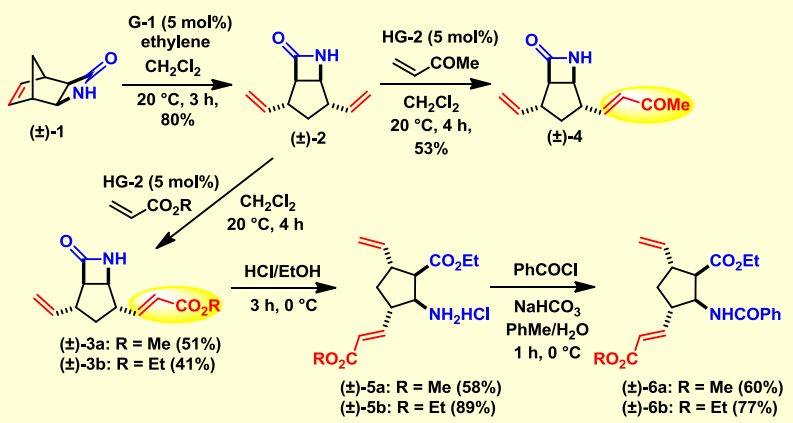
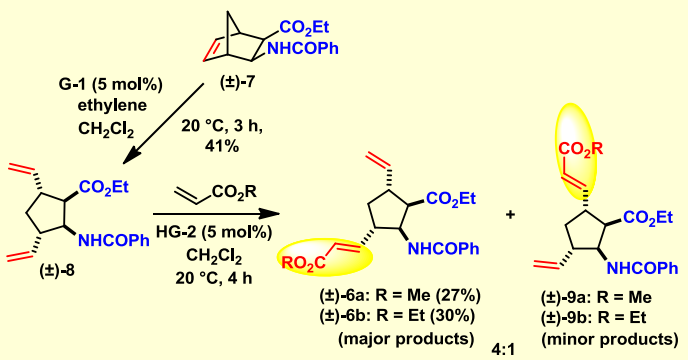
Because of their high biological potential β-lactams and β-amino acids and their highly functionalized derivatives are considered to be relevant scaffolds in medicinal chemistry. Some small molecular entities from this class of compounds such as icofungipen, cispentacin, oxetin or tilidin exhibit various biological properties [1-3].
In the recent work some diolefinated cyclopentanes have been investigated by cross-metathesis reactions to explore chemodiscrimination of the carbon-carbon double bonds in some divinylated azetidinones. The transformations consisted of ring opening of unsaturated β-lactams or bicyclic β-amino acid derivatives followed by cross-metathesis of the divinyl-substituted azetidinones or β-amino ester.

Divinyl-substitued azetidinone (±)-2 was subjected to CM reaction with methyl vinyl ketone or acrylic esters in the presence of commercially available Grubbs catalysts. Cross-metathesis products were detected only in the presence of Hoveyda-Grubbs 2nd generation catalyst (HG-2).
By variation of the amount of catalyst monometathesised products (±)-3 or (±)-4 were isolated in moderate yields. In the products, the α,β-unsaturated carbonyl or ester parts are located near to the amide N-atom (Scheme 1). We suppose that stereochemical factors (chelate ring stability), H-bonding interaction ability and the distance of the NH function relative to the C=C bond might be responsible for the observed selectivity. Mono-coupled cispentacin hydrochlorides (±)-5a,b were prepared from the corresponding β-lactams (±)-3a,b by ethanolysis Next, the products were submitted to benzoylation when novel mono-coupled β-amino acid derivatives ((±)-6a,b could be isolated (Scheme 1).

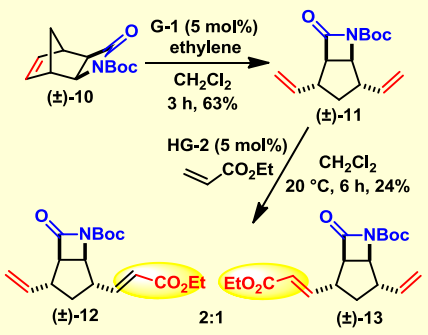


Scheme 1.

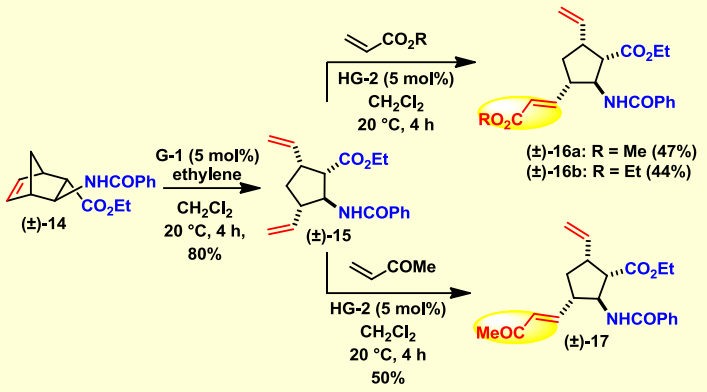


Scheme 2.

Expanding our investigation of olefin bond chemodifferentiation across cross-metathesis, β-amino acids with five-membered ring were next used as starting model compounds. Divinyl-substitued cispentacin (±)-8, was submitted to CM reaction. Contrary to lactam (±)-2, cross-metathesis reaction of compound (±)-8 with the α,β-unsaturated carbonyl compound and esters in view of the monocoupled products was not 100% selective, two regioisomers (±)-6 and (±)-9 was formed in a 4:1 ratio through partial hydrogen bonding directing effect (Scheme 2). The major product (±)-6 was isolated by crystallization from hexane/EtOAc, Unfortunately, the minor product (±)-9 could not be isolated in pure form Further manipulations with catalyst quantity did not give any better results: either the dicoupled derivative or (and) a polymeric material was detected.
N-Boc protected β-lactam (±)-10, without H-bond donor ability, was submitted to CM with ethyl acrylate in the presence of HG-2 catalyst. In this case when the directing effect was excluded, the coupling reaction led to a mixture of the two monometathesized isomers (±)-12 and (±)-13 in nearly 2:1 ratio (Scheme 3). Our efforts to separate and isolated these two isomers failed.

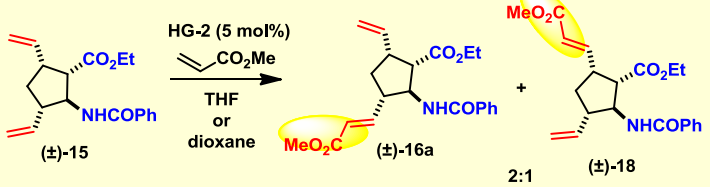


Scheme 3.

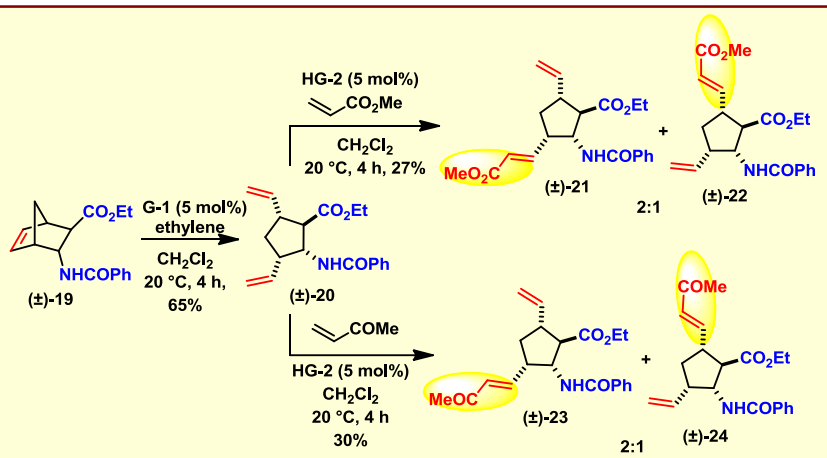


Scheme 4.

The synthetic procedure developed to synthetize mono-coupled β-amino acid derivatives could be extended towards the synthesis of divinylated transpentacins. Diolefinated amino ester (±)-15 where the protected amino group and the ester function are in a trans relationship, was subjected to cross-metathesis with methyl vinyl ketone and acrylic esters in the presence of HG-2 catalyst. In contrast with divinyl-cispentacin (±)-8, the single monocoupled isomers (±)-16a,b and (±)-17 were formed (Scheme 4).
Since H-bond acceptor solvents can disrupt the H-bonding interaction between the catalyst and the substrate, we planned to investigate the effect of solvents. The transformation of compound (±)-15 with methyl acrylate (which in dichloromethane afforded selectively a single regioisomer) was accomplished in three additional solvents. The results showed that solvents able of participating in H bonding with the substrate (dioxane, THF), compete with the catalyst providing a mixture of product (±)-16a and (±)-18 (approximately 2:1 ratio, In contrast, solvents which cannot form a hydrogen bond (dichloromethane, toluene), gave only a single regioisomer (Scheme 5).



Scheme 5.



Scheme 6.

When transpentacin stereoisomer (±)-20 was subjected to CM reaction either with methyl vinyl ketone or acrylic esters, an inseparable mixture of regioisomers (±)-21/(±)-22, and (±)-23/(±)-24 was formed each in nearly 2:1 ratio (Scheme 6). The ring-opening/cross-metathesis protocol was efficiently further extended towards the access of isomers O-heterocylic β-amino acid derivatives (Figure 1).

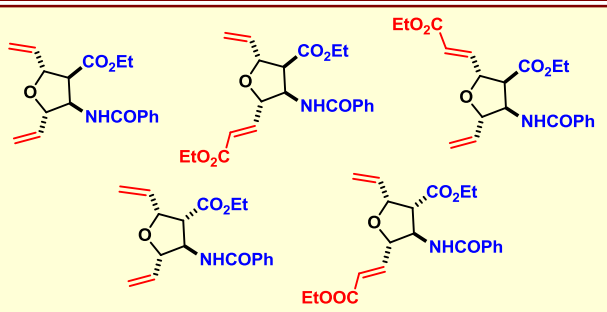


Figure 1

Summary: In summary, transformations by chemodifferentiation of some divinylated functionalized cyclopentanes and bicyclic azetidinones were investigated under cross-metathesis reaction conditions. Depending on their structure, CM reaction of diolefinated β-amino acids or β-lactams furnished selectively functionalized olefinated derivatives. The H-bonding directing effect and the stereochemical factors across chelate ring formation proved to be responsible for the chemodiscrimination.

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