Organic LETTERS

Letter

pubs.acs.org/OrgLett

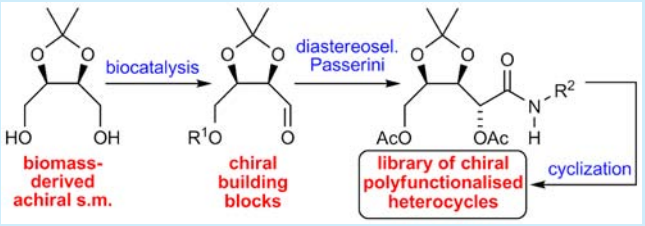
Diastereoselective Passerini Reaction of Biobased Chiral Aldehydes: Divergent Synthesis of Various Polyfunctionalized Heterocycles

Lisa Moni, Luca Banfi, Andrea Basso, Elisa Martino, and Renata Riva*

Department of Chemistry and Industrial Chemistry, University of Genova, via Dodecaneso, 31, 16146 Genova, Italy

Supporting Information

ABSTRACT: Lewis acid catalyzed Passerini reactions on chiral aldehydes derived from desymmetrized erythritol take place with unprecedented diastereoselectivity. The resulting adducts have been selectively and efficiently converted into a variety of densely functionalized, polyoxygenated heterocycles.



Isocyanide-based multicomponent reactions (IMCRs) have been demonstrated to be very useful in the diversity-oriented synthesis of peptide-like acyclic structures. Moreover, post-condensation cyclizations allow the obtainment of a nearly limitless variety of heterocycles.[1] However, one of the major issues of these reactions is represented by the poor stereocontrol typically achieved, which is mainly due to the low steric requirements of isocyanides.

The three-component Passerini reaction,[2] which involves interaction of an aldehyde (or ketone) with a carboxylic acid and an isocyanide, is the oldest IMCR and is endowed with high atom economy (all the atoms of reagents are incorporated in the product). It is probably the best method to convert carbonyl compounds to α-acyloxyamides in one of the first examples of "unpolung" of reactivity.[3] When aldehydes different from formaldehyde or unsymmetric ketones are used, this reaction generates a new stereogenic center. While some success has been achieved in enantioselective Passerini reaction with chiral catalysts,[4] surprisingly, nearly all of the examples reported to date of Passerini reactions with chiral components have led to poor diastereoselectivity. The only exceptions are (a) the use of a rigid bicyclic isocyanide by Ugi and Bock (only one example reported),[5] (b) the use of some chiral carboxylic acids, like galacturonic acid or mandelic acid (with dr's not exceeding 90:10),[6] (c) the use of four-membered cyclic ketones,[7] and (d) the use of oxoacids in intramolecular Passerini reactions.[8] Recently, a Passerini–Smiles reaction (a variant of the Passerini reaction employing phenols) on chiral aldehydes has afforded dr's up to 85:15,[9] but until now good diastereoselectivities (>4:1) have never been obtained in classical intermolecular Passerini reactions of chiral aldehydes.

Our research group is currently pursuing an overall strategy, depicted in the graphical abstract, where renewable starting materials derived from biomass are first chemoenzymatically converted into polyfunctionalized chiral building blocks that are subjected to multicomponent reactions followed by post-condensation cyclization steps. The result is a fast and sustainable[10] access to a variety of druglike, biobased heterocycles with control of absolute and relative stereochemistry over several stereogenic centers.

Erythritol, a *meso* compound, is a natural polyalcohol that can be found in fruit and fermented food and is used as an artificial sweetener. It is biotechnologically produced from common sugars using various microorganisms[11] and, thus, is a renewable feedstock. As previously reported by us and others,[12] desymmetrization of its 2,3-acetonide using lipases can afford both monoester **1** and its pseudoenantiomer **2** in high ee. We reasoned that oxidation of **1** or **2** to the corresponding aldehydes (e.g., **3**), followed by Passerini reaction, would afford interesting polyfunctionalized intermediates that could be manipulated to give a variety of heterocycles.

The main problem was expected to be the anticipated low diastereoselectivity in the multicomponent reaction. We have recently reported that structurally similar aldehyde **4** gives a nearly 1:1 diastereomeric ratio in Passerini or "truncated" Passerini reactions.[13]

In this process, we chose to use a one-pot, tandem procedure involving oxidation with the catalytic TEMPO/stoichiometric BAIB (bis-acetoxyiodosobenzene) system[14] followed by addition of the isocyanide. This procedure is operationally very simple and has distinct advantages over the use of IBX, which was previously introduced as the reagent of choice for one-pot oxidation–Passerini reactions.[15] BAIB is indeed commercially available, affordable, and safer than IBX. Moreover, in this protocol, the carboxylic component involved in the Passerini reaction is the acetic acid formed as the side product by reduction of BAIB. This represents a good example of waste recycling in a tandem reaction.[16]

We used *tert*-butyl isocyanide for the optimization study. When the sequence was carried out in CH_2Cl_2 with no additive, the diastereomeric ratio was 79:21. Reasoning that a Lewis acid could be chelated by the aldehyde oxygen and one of the ring oxygens, creating a more rigid transition state, we investigated a

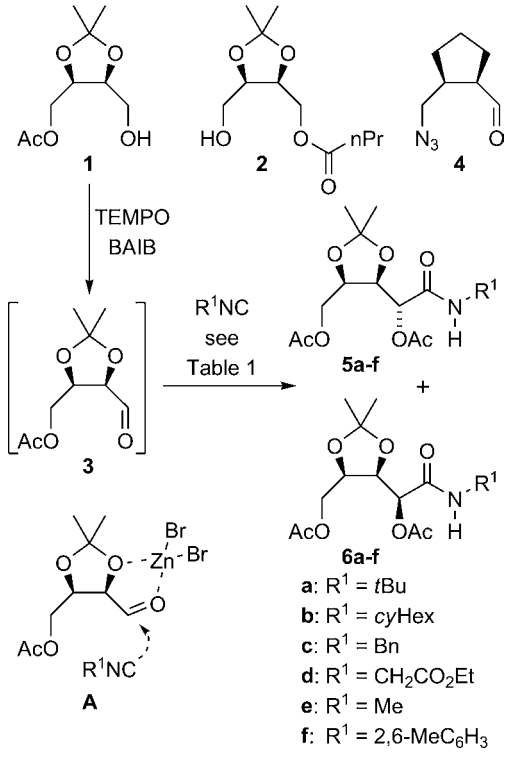
Received: February 23, 2016
Published: March 17, 2016

DOI: 10.1021/acs.orglett.6b00487
Org. Lett. 2016, 18, 1638–1641

series of Lewis acid additives. While the improvement of diastereoselectivity in Ugi reactions by using Lewis acids as catalysts is well established,[17] the use of achiral Lewis acids as a tool for increasing diastereoselection in the related Passerini reaction is unprecedented. Details on this thorough optimization can be found in the Supporting Information. The best dr's were observed with $ZnBr_2$ and $CuBr_2$, but with the latter the reaction was very sluggish. On optimizing reaction conditions with $ZnBr_2$, we discovered that the best results were obtained by working in the presence of THF, at low reaction times (40 min), and at room temperature. At long reaction times, the isolated yield was low because of the partial reaction of the acetal. Finally, the amount of catalyst was reduced to 0.4 equiv. Under the best conditions, we obtained an 80% yield and an 86:14 diastereomeric ratio. Although not exceptional, this diastereomeric ratio is unprecedented for classical Passerini reaction with chiral aldehydes. We never noticed epimerization of aldehyde **3** during its preparation or under the Passerini conditions. On the contrary, partial epimerization was observed by carrying out, starting from **3**, the related Ugi reaction (unpublished preliminary results).

We think that the improvement of diastereoselection in the presence of $ZnBr_2$ catalysis may be due to chelation of the metal by the carbonyl oxygen and one of the dioxolane oxygens (see formula **A** in Scheme 1). This chelation would fix the

Scheme 1. Diastereoselective Passerini reaction of in Situ Generated Aldehyde 3



position of the carbonyl as depicted. In this arrangement, the upper face would be more encumbered by the dioxolane methyls, and thus, attack would take place from the bottom. The observed relative configuration of **5a** is in agreement with this hypothesis. In the absence of Lewis acid, free rotation along the C−C═O bond would allow a different positon of the carbonyl oxygen (i.e., pointing toward the CH_2OAc group) leading to opposite diastereoselection.

We then examined the scope of the reaction by varying the isocyanide (Table 1, entries 1−6). We also submitted alcohols

Table 1. Scope of Diastereoselective Passerini Reaction[a]

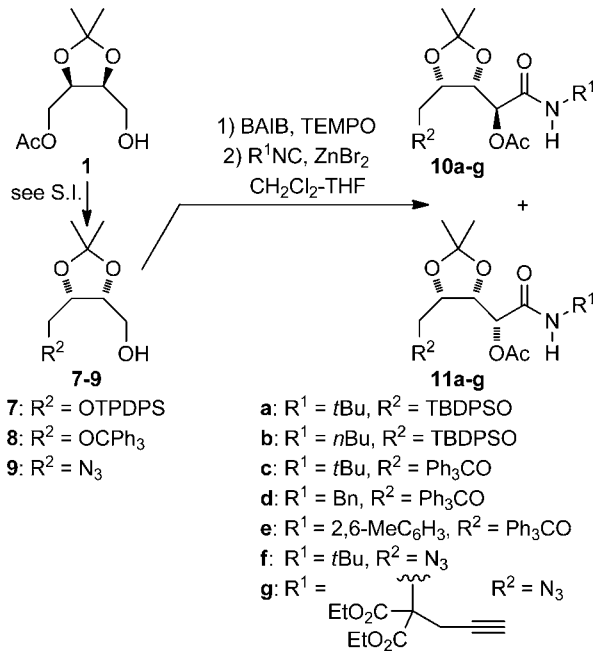
entry	products	time (min)	yield[b] (%)	**5:6** or **10:11** ratio[c]
1	**5a**, **6a**[d]	40	69 (80)	86:14
2	**5b**, **6b**	40	65 (72)	90:10
3	**5c**, **6c**	40	69 (78)[e]	88:12
4	**5d**, **6d**	50	80 (87)[e]	92:8
5	**5e**, **6e**	40	71 (82)	87:13
6	**5f**, **6f**	40	73 (78)	94:6
7	**10a**, **11a**	40	81 (92)	88:12
8	**10b**, **11b**	40	69 (75)	92:8
9	**10c**, **11c**	40	70 (79)	88:12
10	**10d**, **11d**	100	66 (72)	90:10
11	**10e**, **11e**	300	72 (78)	92:8
12	**10f**, **11f**	40	75 (86)	87:13
13	**10g**, **11g**	180	50 (56)[e]	92:8

[a]All reactions were carried out at rt: BAIB and TEMPO were added to a 1 M solution of alcohol in CH_2Cl_2. After 2 h, equal amounts of THF, $ZnBr_2$ (0.4 equiv), and the isocyanide were added. [b]Isolated yield of diastereomerically pure **5** or **10** from alcohols **1** or **7**−**9**; the overall yield of the diastereoisomeric mixtures is shown in parentheses. [c]Determined by NMR on the crude. [d]The relative configuration of major adduct **5a** was established as described below by conversion into lactone **13a**. [e]In order to remove traces of truncated Passerini products, an acetylation of the crude was performed with Ac_2O, Et_3N, and DMAP.

7−**9** to the oxidation−Passerini process (Scheme 2), which were obtained in high yield and few steps from **1**, as described in the Supporting Information.

The results shown in Table 1 indicate that the diastereoselectivity was in all cases good, and even higher than for the first model compound, ranging from 87:13 to 94:6. Often, small amounts of the "truncated" Passerini adducts (not

Scheme 2. One-Pot Oxidation−Diastereoselective Passerini Starting from Alcohols 7−9

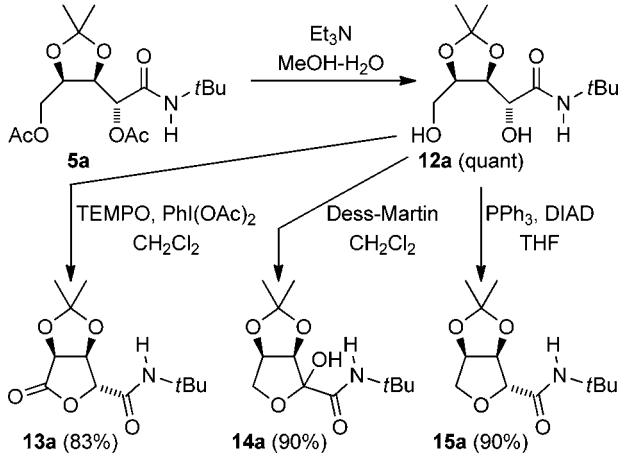


DOI: 10.1021/acs.orglett.6b00487
Org. Lett. 2016, 18, 1638−1641

incorporating acetic acid) were found. From a synthetic point of view, this is not a big problem since, as shown below, both acetates have to be removed later. However, for a correct assessment of diastereoselection, we preferred to acetylate the crude product. The major diastereomers **5** or **10** were in all cases obtained in pure form by chromatography.

Having established the general scope of diastereoselective Passerini on chiral erythritol-derived alcohols **1** and **7**–**9**, we studied the conversion of major adducts **5** or **10** (as pure diastereomers) into a variety of heterocycles (Schemes 3 and 4).

Scheme 3. Transformation of Pluripotent Passerini Adducts into Tetrahydrofurans

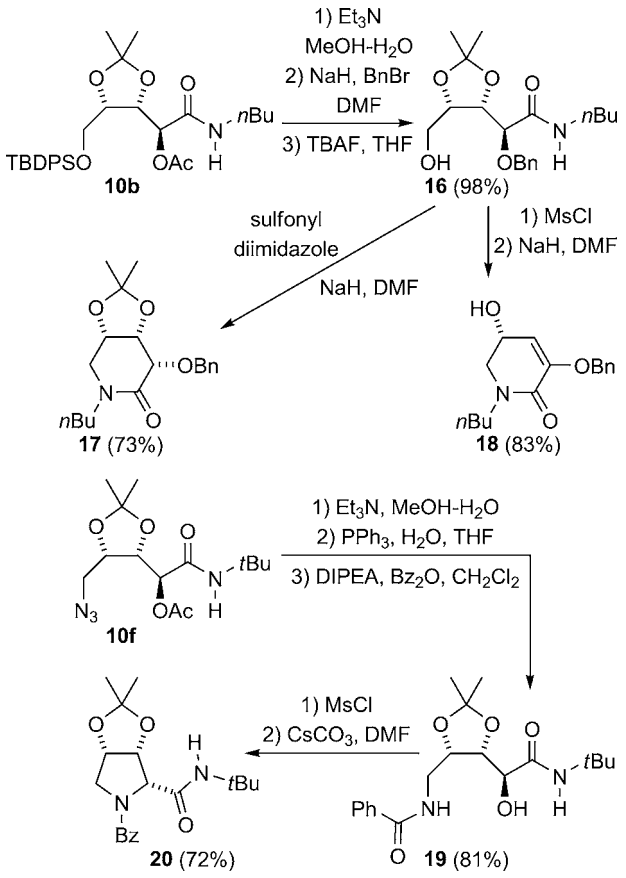


Compound **5a** was deacetylated to diol **12a**. Oxidation gives rise to two different products, depending on the reagent used. With the TEMPO–BAIB system, oxidation takes place exclusively at the primary alcohol, forming lactone **13a** in high yields. Examination of ^{1}H NMR (in particular of relevant vicinal *J*) unambiguously demonstrated the relative configuration and, hence, the relative configuration of **12a** and **5a**. On the contrary, the Dess–Martin reagent exclusively attacks the secondary alcohol, leading to **14a** as a single diastereomer (the relative configuration at the hemiacetal carbon was not established).

Treatment of **12a** under Mitsunobu conditions was expected to afford a pyridone by substitution of the primary alcohol by the secondary amide nitrogen. On the contrary, tetrahydrofuran **15a** was unexpectedly obtained in excellent yields. The Mitsunobu reaction[18] is generally not used for the intermolecular Williamson synthesis of alkyl ethers, apart from special acidic alcohols, such as fluorinated ones. However, some sporadic examples of intramolecular ether formation can be found in the literature, also regarding tetrahydrofurans.[19] Since in principle both OH groups could be substituted, a mixture of diastereomers was expected, but in our case, only a single diastereomer was isolated. The relative configuration was again demonstrated by ^{1}H NMR, revealing a complete retention of configuration. We think that the electron-withdrawing effect of the adjacent aminocarbonyl group makes the secondary alcohol more acidic than the amide or the primary alcohol, making it the preferred nucleophilic group.

In order to access pyridones, we therefore needed to selectively deprotect the primary alcohol in **5a**. This turned out to be impossible because, even if chemical or enzymatic

Scheme 4. Transformation of Pluripotent Passerini Adducts into Nitrogen Heterocycles



hydrolysis of the primary acetate was kinetically faster, it was suddenly followed by very rapid migration of the acetyl group from the secondary to the primary OH (see the Supporting Information for details). In order to obtain **17**, we therefore started from **10b** and followed a longer, albeit very efficient (in terms of yields), route. Cyclization of benzyl-protected intermediate **16** with sulfonyl diimidazole[20] gave in good yield the desired pyridone **17**. Interestingly, by activating the primary alcohol as the mesylate, followed by treatment with NaH, a completely different product **18** was formed, arising from opening of the dioxolane ring. Although in **18** the chiral information derived from diastereoselective Passerini is lost, this polyfunctionalized synthon can also be interesting in view of synthetic applications.

Finally, another "privileged structure" that can be accessed, this time from azide **10f**, is pyrrolidine **20**. Such systems have been recently prepared by us, starting from desymmetrized erythritol derivatives **1** or **2**, through an Ugi–Joullié reaction on a chiral cyclic imine.[12a] However, the synthesis reported here is fully complementary, since it leads to the *all-cis* stereoisomer **20** that can not be obtained by the Ugi–Joullié reaction, which is instead completely stereoselective in favor of the other epimer.

In conclusion, we have reported the first example of a good diastereoselection in a Passerini reaction of chiral aldehydes. The employed aldehydes are derived from desymmetrization of a renewable feedstock, erythritol, and the resulting, densely functionalized products may be transformed into a variety of heterocyclic systems. Thus, adducts **5** and **10** may be viewed as "pluripotent" intermediates.

DOI: 10.1021/acs.orglett.6b00487
Org. Lett. 2016, 18, 1638–1641

Opening of the dioxolane ring can lead to polyalcohols, which can act as glycomimetics. Application of these methodologies to the total synthesis of biologically relevant molecules is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00487.

Experimental procedures, optimization data, characterization of all new compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: riva@chimica.unige.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Sergio Mulone, Francesco Ferraro, Mattia Bondanza, and Maryna Cherednichenko (students at University of Genova) and Franziska Merkt (Erasmus student on leave from Düsseldorf University) for practical collaboration to this work.

■ DEDICATION

This paper is dedicated to Prof. Giuseppe Guanti (retired professor from University of Genova) on his 75th birthday.

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DOI: 10.1021/acs.orglett.6b00487
Org. Lett. 2016, 18, 1638−1641