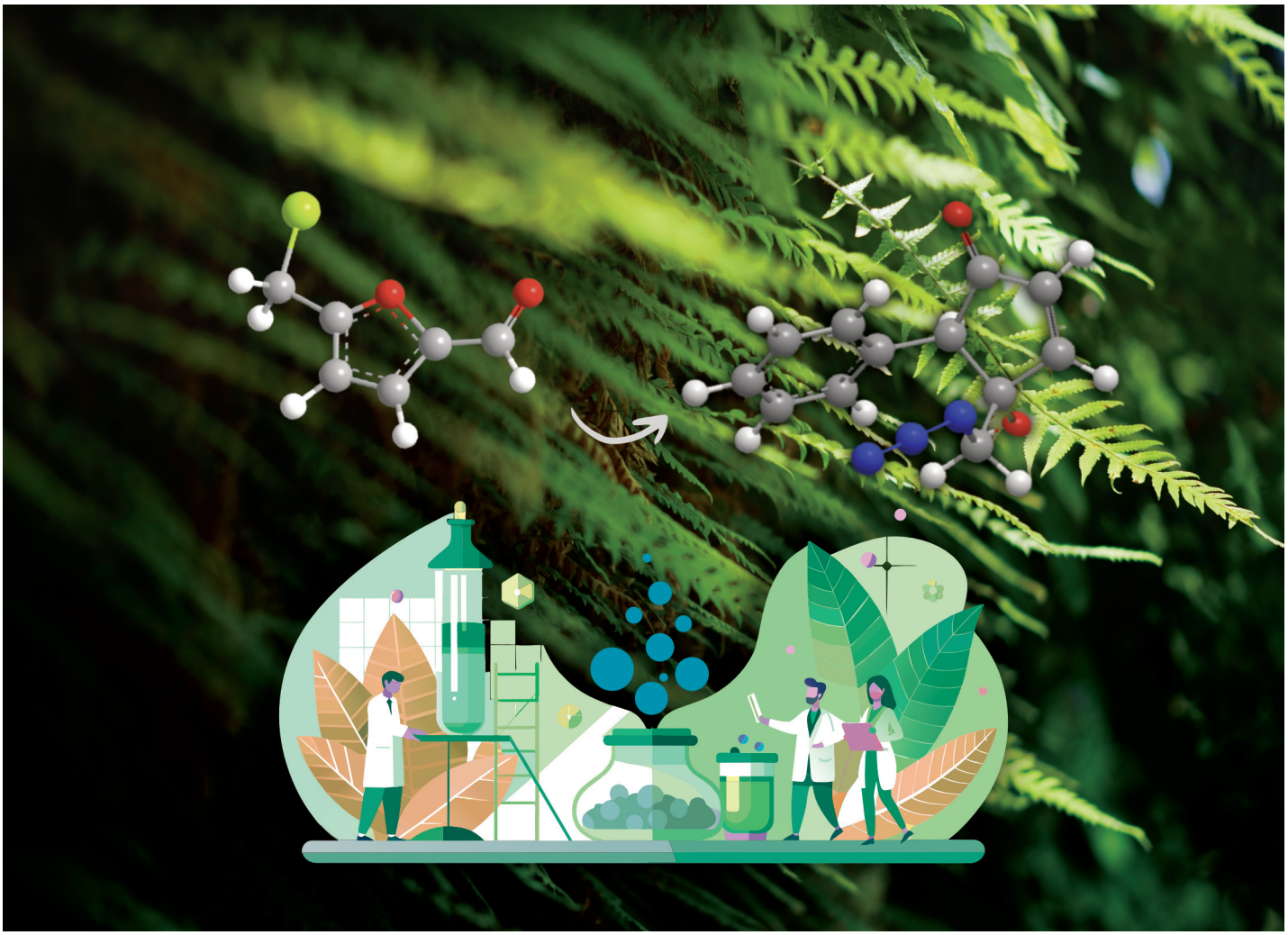

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The Piancatelli rearrangement of AMF (5-azidomethylfurfural) derivatives: a biobased opportunity for the synthesis of nitrogenous cyclopentenones

Nitrogen-containing substrates were involved in a Piancatelli rearrangement to produce nitrogenous cyclopentenones. The precursors of this rearrangement were readily prepared from CMF, a biosourced renewable material.

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The Piancatelli rearrangement of AMF (5-azidomethylfurfural) derivatives: a biobased opportunity for the synthesis of nitrogenous cyclopentenones†

Clémentine Mayet, Jérôme Bignon and Jean-François Betzer *

In the field of renewable materials to substitute petroleum-based products, one of the main areas of research is the study and transformation of small molecules derived from biomass into high value-added compounds. In this context, we report the preparation of 4-(azidomethyl)-cyclopentenones starting from AMF (5-azidomethylfurfural) derivatives, directly obtained from the well-known biosourced renewable material CMF (5-chloromethylfurfural). The Piancatelli rearrangement of these AMF derivatives, catalyzed by $Dy(OTf)_3$ and under microwave activation, affords substituted cyclopentenones with two contiguous stereogenic centres, one of which is quaternary, exhibiting high diastereoselectivity. We were able to exploit the azidomethyl side chain to produce cyclopentenones with other nitrogenous functionalities, such as amine or triazole moieties. Moreover, these 4-(azidomethyl)-cyclopentenones exhibited desired cytotoxic activity against HCT116 and HL60 cancer cell lines with nanomolar IC_{50} values.

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1. The use of bio-based materials derived from biomass (CMF = 5-chloromethylfurfural) for high value-added cyclopentenones
2. Our synthetic method provides efficient access to nitrogen-based substrates through the Piancatelli rearrangement, *via* a catalytic process under microwave activation using CHEM21 recommended solvents, *tert*-butanol and water.
3. We described the first Piancatelli rearrangement on nitrogen-based substrates. Other nitrogen functionalities might be considered to extend the scope of this major advance in the development of the Piancatelli rearrangement.

Introduction

In recent decades, increased attention from scientific and industrial communities has been focused on reducing dependence on oil-based fossil raw materials. Given their environmental impact, fossil fuels significantly contribute to carbon dioxide and other greenhouse gas emissions, and their extraction generates pollutants that degrade air and water quality. Thus, replacing fossil fuels with renewable materials is indeed a key element in developing a green and circular economy. The use of renewable biomass resources for the production of fuels, chemicals, and materials offers a valuable alternative to the fossil-based industry.[1] The two main lines of research in this field focus, firstly, on the transformation of biomass into molecular building blocks and, secondly, on the conversion of these building blocks into high value-added compounds for many applications such as precursors for pharmaceutical compounds, monomers for polymer synthesis, surfactants, lubricants, paints, plasticizers, paper additives and biocarburants.

In the field of renewable materials, lignocellulosic biomass is a cheaper and the most abundant material. This sustainable lignocellulose is composed of cellulose (50%), hemicellulose (30%), and polyphenolic lignins (20%).[2] For the transformation of this lignocellulosic biomass, the production of furfural (FFR), furfuryl alcohol (FA), and 5-hydroxymethyl-furfural (HMF) provides versatile sustainable and valuable substitutes for petrochemical building blocks.[3] HMF is regarded by the scientific community as a versatile building block platform and is considered to be one of the "Top 14" bio-based building blocks listed by the US Department of Energy.[4]

Despite significant interest and the synthetic potential of HMF to replace petroleum-based products, this compound suffers from significant drawbacks. First, HMF is a polar and hydrophilic molecule that is not easily extracted from aqueous media. Second, HMF is sensitive to the acidic conditions

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under which it is produced, leading to the formation of numerous by-products. Among these, we can mention OBMF, which results from HMF dimerization, as already observed by Ananikov[5] and Afonso.[6] Another major drawback is the formation of levulinic acid associated with the concomitant release of formic acid.[7] The major difficulty encountered when using HMF as the starting material is the formation of oligomeric and polymeric materials that are commonly called humins. These humins are formed by multiple combinations of the HMF hydrolyzed product and HMF itself to produce dark-colored solid materials.[8]

In this context, other versatile sustainable and valuable substitutes of petrochemical compounds have been prospected to identify biomass molecular building blocks for chemical applications and the conversion of these building blocks into high value-added compounds. These studies have allowed establishing a more convenient and stable derivative of HMF, namely 5-(chloromethyl)furfural (CMF) **1**.[9] Among the benefits of CMF over HMF, CMF is produced in high yield under mild conditions directly from raw biomass, and its stability and hydrophobicity markedly facilitate isolation.[10] Very recently, a comparative study of the potential between HMF and CMF was reported, clearly highlighting the advantages of CMF in terms of ease of production, stability, and reactivity.[11]

Different synthetic transformations have been described, supporting the versatility of CMF as a building block platform.[12] From them, we have highlighted the substitution reaction of the chloromethyl group into the azidomethyl function in quantitative yield by a substitution reaction, described for the first time by Mascal,[13] thus providing a nitrogenous bio-based furan derivative AMF **2**.

Considering the derivatization of AMF **2** and taking advantage of azidomethyl, aldehyde and furan functionalities, only a few selective synthetic transformations have been described. The aldehyde group can participate in the condensation reaction with ammonia for carbon–nitrogen bond formation (Fig. 1a), to produce diamine derivatives after reduction.[14]

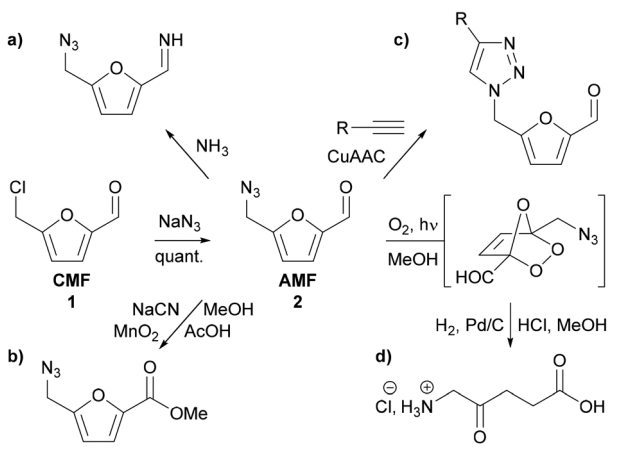


Fig. 1 Transformation of bio-sourced CMF **1** into AMF **2**, and aldehyde, azide and the furan ring reactivity of AMF **2**.

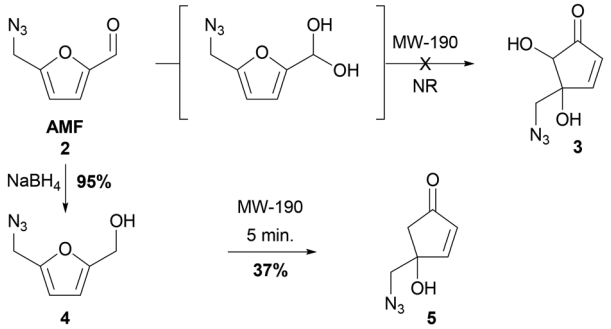
This same aldehyde group can also undergo a change in the oxidation state, to the carboxylic acid or alcohol functionalities. For instance, Ananikov has described the transformation of AMF **2** into methyl 5-(azidomethyl)furan-2-carboxylate through the Corey–Gilman–Ganem oxidative esterification process using $NaCN/MnO_2$/MeOH and AcOH (Fig. 1b).[15] Ananikov has also benefited from the azide function to perform a copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) to produce 1,4-substituted 1,2,3-triazole derivatives (Fig. 1c).[16] The use of bis-terminal alkyne allowed the formation of bis-(1,2,3-triazolyl) aldehyde derivatives (not shown).[17] The furan ring itself is able to undergo [4 + 2] cycloaddition with singlet oxygen to produce a 1,2,4-trioxolane intermediate, which is known to decompose into the corresponding butenolide derivatives. In this way, starting from AMF **2**, Mascal[13] has described the two step synthesis of δ-aminolevulinic (Fig. 1d), an effective non-toxic biodegradable herbicide and insecticide,[18] as well as a precursor for biosynthesis of tetrapyrroles, the core structure of porphyrins.[13]

Taking advantage of the great synthetic potential of AMF **2**, this compound, or its close furanic derivatives, could be converted into cyclopentenone with 4-(azidomethyl) and 4-hydroxy functionalities *via* the Piancatelli rearrangement.[19] Despite the recent number of studies on the Piancatelli rearrangement and the effectiveness of this process to produce cyclopentenones from 2-furylcarbinols,[20] C-5 substituted 2-furylcarbinol substrates have scarcely been explored. Except for the favoured intramolecular version with a tethered nucleophile at the C-5 position, the intermolecular Piancatelli rearrangement with C-5 substituted 2-furylcarbinol has only been described with substrates containing a methyl,[21] a phenyl[22] and an ethoxymethyl group.[23] The challenge in using C-5 substituted 2-furylcarbinol as the starting material for the Piancatelli rearrangement is due to this C-5 substitution, thereby significantly reducing the reactivity during the elementary step of the catalytic cycle for the C-5 addition on the furanoxonium ion intermediate.[20] In previous studies, we have shown that HMF derivatives, meaning those with a hydroxymethyl C-5 substitution, can deliver cleanly 5-substituted 4-hydroxymethyl-4-hydroxycyclopentenones.[24] We have highlighted that the combination of microwave activation and the use of a catalytic amount of $DyCl_3$ was necessary to provide high chemical yields and to ensure control of the relative configuration of the two stereogenic centers that are created in the rearrangement. In this study, we would like to extend this synthetic methodology for the preparation of 5-substituted-4-(azidomethyl)-4-hydroxycyclopentenones, starting from (5-(azidomethyl)furan-2-yl)-carbinol derivatives.

Results and discussion

Initial studies were conducted by examining the Piancatelli rearrangement directly on AMF **2** and on its simple reduced derivative **4** obtained in one step by selective reduction of the aldehyde function into carbinol using sodium borohydride in

95% yield. The implemented experimental conditions for this Piancatelli rearrangement are those optimized for the transformation of furfuryl alcohol (FA) into 4-hydroxy-2-cyclopentenone (HCP), specificallyusing microwave (MW) activation. The use of MW irradiation allows performing this rearrangement within a short time, thus leading to an efficient rearrangement while minimizing side reactions and the formation of humins.[25] An attempt to directly transform AMF **2**, or its hydrated form, which could be generated *in situ* in the reaction medium, into a cyclopentenone failed (Scheme 1). Under these conditions, no reaction was observed and the starting material was cleanly recovered unchanged. Only traces of a few new products could be observed, but none corresponded to a cyclopentenic core structure. In contrast, with the use of carbinol derivative **4** we have observed a complete conversion of the starting material and the formation of the desired 4-(azidomethyl)-4-hydroxycyclopentenone **5** in 37% yield.



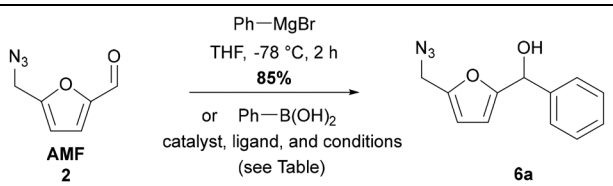
Scheme 1 Attempted Piancatelli rearrangement on AMF **1** and on its reduced derivative **4**. Piancatelli rearrangement was performed on a 1 mmol scale in a 1 : 5 *t*-BuOH/H_2O mixture at 0.1 M under microwave (MW) heating for 5 min. NR = no reaction.

Encouraged by this first result and in order to apply this methodology to the preparation of 5-substituted 4-(azidomethyl)-4-hydroxycyclopentenones, we next turned our attention to reactions involving (5-(azidomethyl)furan-2-yl)-α-substituted carbinol derivatives. The first reaction pathway to introduce a phenyl substituent on the aldehyde moiety of AMF **2** was performed with phenylmagnesium bromide. The desired carbinol adduct was obtained in a 85% yield, in the yield range of the Grignard 1,2-addition reaction on the carbonyl function for substrates also bearing an azide function.[26] Actually, it is well known in the literature that organic azides may act as nitrogen sources for electrophilic amination reactions for organometallic species such as Grignard reagents, leading to secondary amines.[27] For these reasons, we would like to take advantage of alternative milder conditions involving a transition metal-catalyzed 1,2-addition of arylboronic acids.

To identify the best reaction conditions of this 1,2-addition of benzeneboronic acid on AMF **2**, we have first used the conditions described by Miyaura, which imply the use of rhodium (I) as a catalyst combined with the bidentate phosphine 1,1′-bis(diphenylphosphino)ferrocene as the ligand. The use of $Rh(acac)(CO)_2$ led to no reaction (Table 1, entry 1),[28] while the use of more labile ligands on rhodium, specifically $Rh(acac)(coe)_2$,[29] led to a low conversion but without any formation of the desired product **6a** (entry 2).

The same reaction was then attempted with the use of rhodium(III) as the catalyst combined with *N*-heterocyclic carbene IPr (1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) as the ligand, which is easily generated in basic media from its corresponding imidazolium salts, under reaction conditions described by Fürstner,[30] but no reaction was observed (entry 3). This 1,2-addition reaction was also described by Gois with the use of dirhodium(II) complexes with axial N-heterocyclic carbene (NHC) ligands,[31] but while total conver-

Table 1 Phenylmagnesium bromide addition and screening of transition metal-catalyzed 1,2-addition of benzene boronic acid onto AMF **2**



Entry	Catalyst	Ligand	Base	*T* (°C)	Time (h)	Conv. (%)	Yield **6a**[a] (%)
1[b]	$Rh(acac)(CO)_2$ (3 mol%)	dppf (3 mol%)	—	80	18	0	NA
2[c]	$Rh(acac)(coe)_2$ (3 mol%)	dppf (3 mol%)	—	80	18	30	0
3[d]	$RhCl_3{\cdot}3H_2O$ (3 mol%)	IPrHCl (3 mol%)	NaOMe (1 eq.)	80	2	0	NA
4[e]	$[Rh_2(OAc)_4]$ (3 mol%)	IPrHCl (3 mol%)	KO*t*Bu (1 eq.)	90	0.5	100	0
5[f]	$Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%)	PPh_3 (5 mol%)	Cs_2CO_3 (1 eq.)	60	24	70	<5
6[g]	$PdCl_2$ (5 mol%)	P(1-Nap)$_3$ (5 mol%)	K_2CO_3 (3 eq.)	65	16	100	20
7[g]	$PdCl_2$ (5 mol%)	P(1-Nap)$_3$ (5 mol%)	K_2CO_3 (3 eq.)	20	16	80	60

Acac = acetylacetonate. Dppf = 1,1′-bis(diphenylphosphino)ferrocene. Coe = cyclooctene. IPrHCl = 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride. Pfb = perfluorobutyrate. P(1-Nap)$_3$ = tri-1-naphthylphosphine. [a] Isolated yield. [b] Reaction performed in a 1 : 1.6 DME/H_2O mixture at 0.2 M. [c] Reaction performed in a 3 : 2 DME/H_2O mixture at 0.2 M. [d] Reaction performed in a 4 : 1 DME/H_2O mixture at 0.2 M. [e] Reaction performed in a 5 : 1 DME/H_2O mixture at 0.3 M. [f] Reaction performed in toluene at 0.3 M. [g] Reaction performed in THF at 0.2 M.

sion was observed, no identified product could be isolated from the crude reaction mixture (entry 4). We next turned our attention to the use of palladium as a catalyst, first described by Ohta with the use of $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$[32] and investigated by Wu and Cheng with the use of $PdCl_2/P(1\text{-Naphtyl})_3$.[33] Under the optimized conditions described by these authors, the use of $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$ led to the desired compound **6a** in low yield despite a satisfactory conversion (entry 5), while the use of $PdCl_2/P(1\text{-Naphtyl})_3$ led to a complete conversion but the desired compound **6a** was isolated in only 20% yield (entry 6). Gratifyingly, by changing the conditions described in the literature, specifically by performing the reaction at a lower temperature, a cleaner reaction was observed and the compound **6a** was isolated in a satisfactory 60% yield (entry 7). Thus, this study demonstrated that it is possible to perform 1,2-addition reactions of boronic acids on AMF, opening up a wide range of possibilities considering the large number of commercially available boronic acid derivatives.

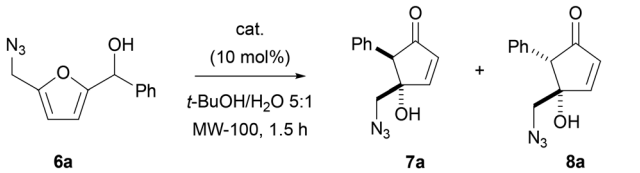
The reactivity control of substrate **6a** for the Piancatelli rearrangement is a real challenge that requires overcoming three major difficulties. First is the low reactivity of furan substrates substituted at the C-5 position. Second is the control of the diastereoselectivity of the two newly formed stereogenic centers, including one quaternary center. The final challenge is preserving the stability and integrity of the alkyl azide functional group. First, we examined the reactivity of substrate **6a**, under the same microwave conditions (MW-190) applied to the unsubstituted substrate **4**, but despite total conversion, only the decomposition of this substrate was observed (Part II in the ESI, Table S1,† entry 1). In contrast, under milder microwave conditions (MW-100), no reaction was observed and the starting material was cleanly recovered unchanged (Table 2, entry 1).

We then applied the conditions previously developed for the Piancatelli rearrangement for the C-5 substituted 2-furylcarbinol substrates, specifically the use of a catalytic amount of $DyCl_3$ under microwave activation in a mixture of *t*-BuOH/H_2O,[24] but a low conversion was observed associated with a poor NMR yield and modest diastereoisomeric ratio.

In order to improve this conversion reaction, $Dy(OTf)_3$ was used as a dysprosium catalyst[21b,23,34] under microwave activation[24], which allowed the formation of the desired cyclopent-2-enone **7a** with a satisfactory 46% yield and high diastereoselectivity, despite an incomplete conversion (entry 3). All attempts to achieve completion, which included the increase of catalyst loading, time, temperature, conventional heating (CH) and also the use of TFA as a co-catalyst (since a combination of Lewis and Brønsted acids has been well known to improve the yield of these rearrangements),[21b] and also the change of the counteranion failed (Part II in the ESI, Table S1,† entries 6–11). We considered other lanthanide catalysts used for the Piancatelli rearrangement like ytterbium[35] or cerium,[36] but no improvement was observed (entries 4 and 5), either under the described conditions or under our microwave conditions.

We next expanded our screening to include transition metals as catalysts for this Piancatelli rearrangement with the most commonly used catalyst, that is $Sc(OTf)_3$,[21b,34a] but once again an incomplete reaction was observed and unfortunately associated with poor diastereoselectivity (entry 6). This lack of stereoselectivity can be attributed to the high reactivity of scandium triflate.[37] In order to moderate this reactivity, scandium trichloride, a milder catalyst, was considered for the first time to promote the Piancatelli rearrangement. With the use of $ScCl_3$ as the catalyst, we have observed an incomplete but clean reaction, and the desired cyclopent-2-enone **7a** was obtained in 37% isolated yield with high diastereoselectivity (entry 7). An increase in temperature or the use of scandium triflimide did not improve the conversion of the reaction (Part II in the ESI, Table S1,† entries 17 and 18). The use of a transition metal from the row below, yttrium,[38] as well as other transition metals previously used with success for the Piancatelli rearrangement in the literature, namely iron,[39] cobalt,[40] or even gold,[41] did not improve the efficiency of the rearrangement of **6a** (entries 8–11).

Table 2 Screening and optimization reaction conditions for the Piancatelli rearrangement of (5-(azidomethyl)furan-2-yl)phenyl-carbinol **6a**[a]



6a **7a** **8a**

Entry	Catalyst	Conv. (%)	NMR yield[b] (%)	Isolated yield (%)	dr[c] **7a**/**8a**
1	—	0	—	—	—
2	$DyCl_3$	40	10	ND	80 : 20
3	**$Dy(OTf)_3$**	**60**	**50**	**46**	**>95 : 5**
4	$Yb(OTf)_3$	70	30	ND	85 : 15
5	$Ce(OTf)_3$	80	20	ND	ND
6	$Sc(OTf)_3$	75	35	ND	80 : 20
7	**$ScCl_3$**	**70**	**40**	**37**	**95 : 5**
8	$Y(OTf)_3$	65	35	ND	90 : 10
9	$Fe(OTf)_3$	80	20	ND	90 : 10
10	$Co(OTf)_3$	70	30	ND	85 : 15
11	$HAuCl_4{\cdot}3H_2O$	100	10	ND	ND
12	$Al(OTf)_3$	85	25	ND	85 : 15
13	$Zn(OTf)_3$	65	10	ND	ND
14	$In(OTf)_3$	80	20	ND	90 : 10
15	$Bi(OTf)_3$	75	15	ND	ND
16	$Ca(NTf)_2$	0	NA	NA	NA
17	$Ba(OTf)_3$	70	20	ND	ND
18	$B(C_6F_5)_3$	50	25	ND	90 : 10
19[d]	$(C_6HF_4)B(OH)_2$	70	0	NA	NA
20[e]	BINOL·PA	90	25	ND	ND
21[f]	TFA	100	15	ND	90 : 10
22[g]	$Dy(OTf)_3$	60	50	34[h]	>95 : 5
23[g]	$ScCl_3$	65	25	18	95 : 5

MW = microwave heating. CH = conventional heating. ND = not determined. NA = not applicable. [a] Reactions performed on the 0.2 mmol scale at 0.1 M. [b] Yield determined by ^1H NMR with trimethoxybenzene as the internal standard added at the end of the reaction. [c] The diastereoisomeric ratio (dr) was determined by ^1H NMR on the crude mixture. [d] $(C_6HF_4)B(OH)_2$ (20 mol%) at CH-90 for 24 h. [e] CH-50 for 18 h. [f] TFA (20 mol%). [g] 1 mmol scale and sodium dithionite ($Na_2S_2O_4$) in a 3 mass percentage was added. [h] 37% of the starting material **6a** was recovered.

The use of non-noble metals also known to trigger the Piancatelli rearrangement, such as aluminum,[36] zinc,[42] indium[36] and bismuth,[43] also led to disappointing results for the formation of compound **7a** (entries 12–15). The use of alkaline earth metals, such as calcium[44] or barium,[45] is also well known to promote the Piancatelli rearrangement, but is inadequate for our substrate **6a**, whether under standard conditions or under our microwave conditions (entries 16 and 17).

We have speculated that using a non-metallic Lewis acid such as $B(C_6F_5)_3$, applied recently in the literature for the Piancatelli rearrangement,[45,46] might be more compatible with the azide function, but its use also led to a low reaction conversion associated with a low yield in the formation of compound **7a** (entry 18). Brønsted acids, such as $(C_6HF_4)B(OH)_2$,[47] BINOL-derived phosphoric acid[48] and TFA,[34b,35] were also considered, but despite the high level of conversion of substrate **6a**, compound **7a** was formed in very low yields (entries 19–21).

We chose to retain the two conditions using $Dy(OTf)_3$ as the lanthanide catalyst and $ScCl_3$ as the transition metal catalyst under microwave activation. These two selected optimized conditions have been applied to a 1 mmol scale with sodium dithionite (at a 3 mass percentage). Sodium dithionite ($Na_2S_2O_4$) is a well-known additive for HMF derivative reactions, acting as a reductive agent able to avoid oxidative pathways that are involved in the oligomerization of HMF derivatives and the resulting humin formation.[6b]

For this 1 mmol scale experiment performed with $Dy(OTf)_3$ as the lanthanide catalyst, high diastereoselectivity was maintained but the yield decreased slightly to 34%. But more interestingly, we were able to recover 37% yield of the starting material **6a**, thus leading to **7a** in a 54% corrected yield, based on the conversion of **6a** (entry 22).

For this same 1 mmol scale experiment performed with $ScCl_3$ as the transition metal catalyst and $Na_2S_2O_4$ as the additive, the yield was severely reduced to 18% (entry 23).

The *trans* relative stereochemistry of cyclopentenone **7a** is the result of the relative stability of pentadienyl cation intermediates and the pericyclic conrotatory 4π-electrocyclization process, closely related to the Nazarov reaction (Part III in the ESI, Scheme S1†).[49] This *trans* relative stereochemistry was assigned based on NMR NOESY 2D experiments (Part IX in the ESI†).

Thus, for the continuation of our study, we examined the scope of (5-(azidomethyl)furan-2-yl)-α-substituted carbinol derivatives **6**. These substrates were prepared starting from AMF **2**, using the two identified conditions in Table 1, namely the use of Grignard reagents or the palladium-catalyzed 1,2-addition of boronic acids. The details of these preparations are provided in the ESI (Part VI in the ESI).†

Under the optimized reaction conditions for the Piancatelli rearrangement (Table 2, entry 3), namely $Dy(OTf)_3$ 10 mol%, *t*-BuOH/H_2O 5 : 1, microwave heating, 100 °C, and 1.5 h, the variety of (5-(azidomethyl)furan-2-yl)-α-substituted carbinols **6a–n** delivered the expected C5-substituted 4-(azidomethyl)-4-hydroxycyclopentenone **7a–n** in moderate to good isolated yields (Scheme 2). The rearrangement of carbinols **6a–f** into cyclopentenones **7a–f** does not appear to depend on the steric hindrance of the substituent R, as the same range of yields was observed, along with good diastereoselectivities. The best yield was obtained with substrate **6d** containing a 9-phenanthrenyl substituent that provides cyclopentenone **7d** in 62% yield.

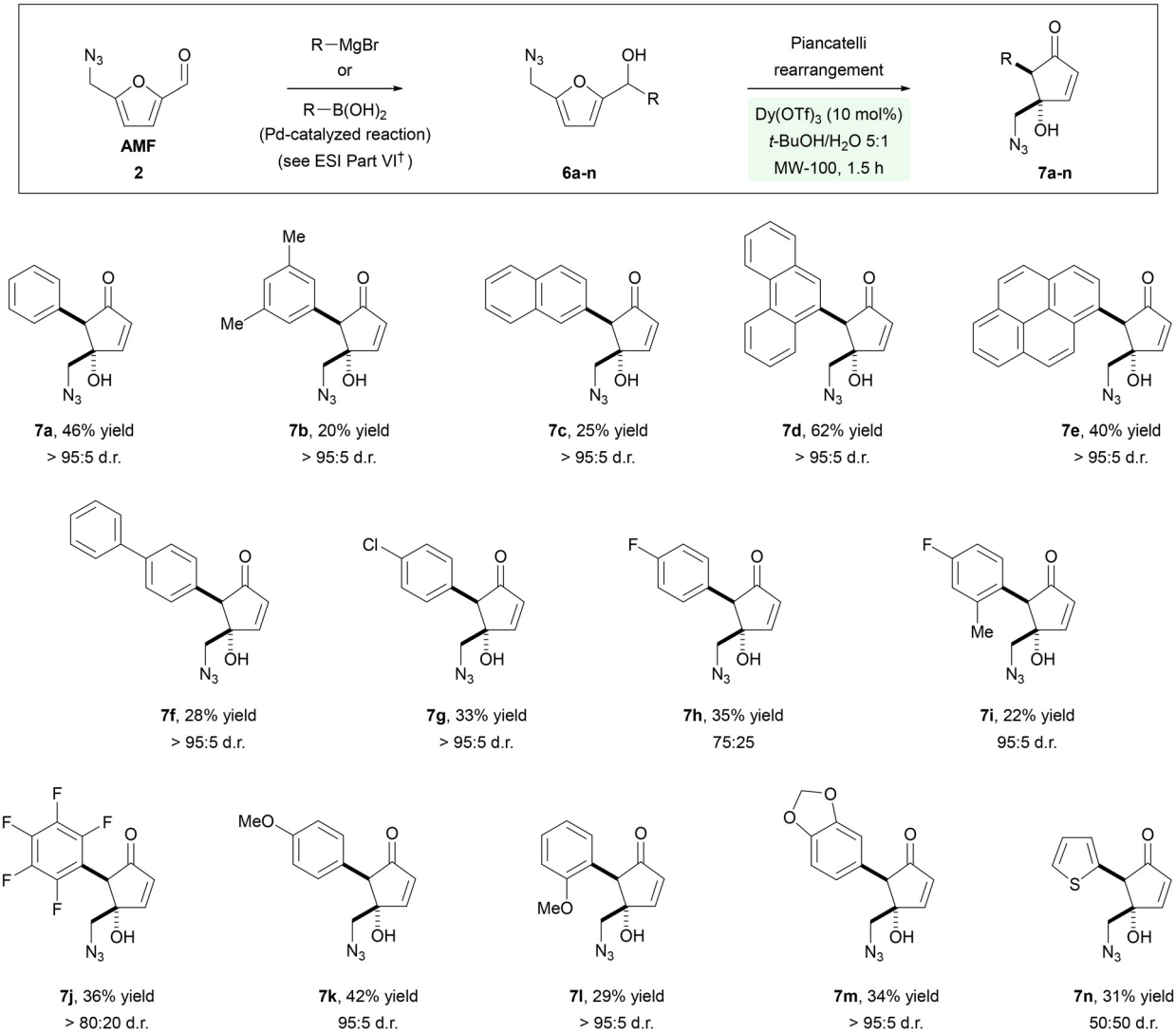
The reaction proved to be quite general, since both electron-withdrawing and electron-donating groups were tolerated on the aromatic substituent of **6**, affording products **7** in the same range of yields. However, with an electron-withdrawing group, a slight decrease of diastereoselectivity was observed, which could be attributed to the higher acidity of the proton in the benzylic position, specifically for compound **7j** with the perfluorophenyl substitution. The high level of diastereoselectivity was maintained with electron-donating groups for compounds **7k–m**.

The use of 2-thienyl as the heteroaryl group resulted in a loss of diastereoselectivity for compound **7n**. We would also like to mention that when the aryl group was replaced with an alkyl substituent, such as *n*-butyl, *t*-butyl or cyclopropyl, no reaction was observed and the starting material was cleanly recovered unchanged. The same Piancatelli rearrangements were also performed on carbinols **6** under optimized reaction conditions for $ScCl_3$ as the catalyst (Table 2, entry 7). However, as observed for compound **6a**, slightly lower yields were observed for the formation of cyclopentenones **7** compared to that with the use of $Dy(OTf)_3$ as the catalyst (Part VII in the ESI†).

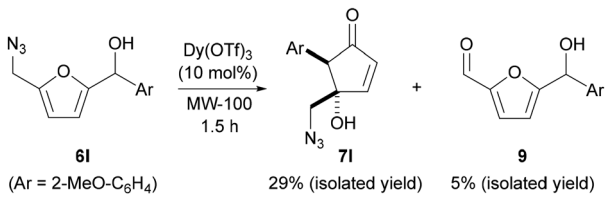
In the case of substrate **6l**, in addition to the formation of cyclopentenone **7l**, we also observed the formation of aldehyde compound **9** in 5% yield, which is the outcome of the decomposition of the primary alkyl azide followed by alpha hydrogen deprotonation to generate an aldimine, which, upon hydrolysis, releases the aldehyde function (Scheme 3). This oxidative conversion of primary azides to aldehydes, useful for the installation of aldehydes from a non-oxygenated precursory functional group, was previously described using molybdenum xanthate[50] or iron(III) chloride[51] under harsh reaction conditions, and more recently under milder conditions involving the use of metalloproteins such as cytochrome P450s and myoglobin.[52]

To confirm the relative stability of this alkyl azide function under our reaction conditions, the azide function was introduced at an sp^2-hybridized carbon center, both on the aromatic and vinylic parts of the cyclopentenone, leading to better yields in the Piancatelli rearrangement (Part IV in the ESI†). To overcome this issue of azide function stability, other nitrogen functions such as aliphatic or aromatic amines and protected the amine function in phthalimide derivatives have been considered, but all attempts for the Piancatelli rearrangement on these substrates failed (Part V in the ESI†).

To showcase the synthetic versatility of the obtained cyclopentenones **7** with the azidomethyl side chain, further functional group elaborations were performed (Scheme 4). First, the carbonyl function was selectively reduced towards the double bond and azide function under Luche[53] conditions to

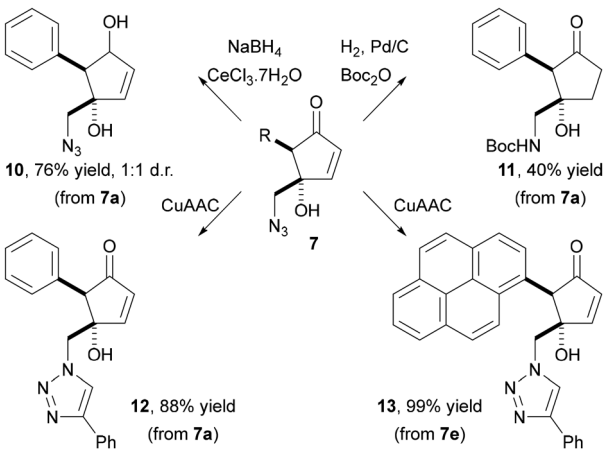


Scheme 2 Substrate scope in the $Dy(OTf)_3$-catalyzed MW-100 °C Piancatelli rearrangement of (5-(azidomethyl)furan-2-yl)-α-substituted carbinols **6a–n**.



Scheme 3 Denitrogenative reaction of **6l** leading to the formation of aldehyde compound **9**.

provide the secondary alcohol **10** in 76% yield, without stereoselectivity as previously observed in the literature for similar substrates.[54] Azide and double reduction were performed *via* the mild catalytic hydrogenation in the presence of Boc_2O,[55] which gave the cyclopentanone **11** with the *N*-Boc-protected-methyl side chain in 40% yield.



Scheme 4 Synthetic transformation of 4-(azidomethyl)-cyclopentenones **7**.

Moreover, subjecting **7a** and **7e** to the conditions of copper-catalyzed azide–alkyne cycloaddition (CuAAC)[56] with phenylacetylene resulted in the formation of cyclopentenones with a triazole-methyl side chain **12** and **13** in 88% and 99% yields, respectively.

As some natural products with a hydroxylated cyclopentenone scaffold, such as the marine natural products trichodenone A,[57] didemnenone D[58] and Terrein[59] from the fungi *Aspergillus terreus*, have exhibited significant cytotoxicity against cancer cell lines, we evaluated the cytotoxicity activity of the newly synthesized compounds **7a–n**. Moreover, we also intend to take advantage of the azidomethyl side chain, as many well-known chemotherapeutic drugs contain these metabolically active azide groups.[60]

Biological preliminary results are highly promising as compounds **7a–n** exert antiproliferative effects at nanomolar concentrations for two different tumor cell lines. Concentrations inducing 50% cell growth inhibition (IC_{50}) are given in Tables 3 and 4. The first observation is that substitution with an aromatic moiety on the C5 position of the cyclopentenone is necessary, as the unsubstituted compound **5** does not exhibit cytotoxic activity.

For all the C5 substituted compounds, the antiproliferative effects are more pronounced on the HL60 non-adherent leukemia cell line. Moreover, some compounds such as **7c**, **7d** and **7h** behave differently towards these two tumor cell lines, which may indicate some tissue specific antiproliferative activity of these molecules.

Table 3 *In vitro* anti-proliferative activity (IC_{50}) of compounds **5** and **7a–n** against the HCT116 cancer cell line (human colon cancer cell line)

Compound	IC_{50}[a] (nM)	Compound	IC_{50}[a] (nM)
5	>10 000	**7h**	**2462 ± 316**
7a	2607 ± 243	**7i**	742 ± 16
7b	1570 ± 241	**7j**	811 ± 43
7c	**2700 ± 222**	**7k**	294 ± 129
7d	**1080 ± 144**	**7l**	3163 ± 243
7e	491 ± 16	**7m**	1320 ± 16
7f	3295 ± 880	**7n**	568 ± 29
7g	3724 ± 465		

[a] Data are the mean ± standard error (SEM) of three independent experiments.

Table 4 *In vitro* anti-proliferative activity (IC_{50}) of compounds **5** and **7a–n** against the HL60 cancer cell line (human leukemia cell line)

Compound	IC_{50}[a] (nM)	Compound	IC_{50}[a] (nM)
5	10 200 ± 180	**7h**	**126 ± 3.7**
7a	145 ± 4.3	**7i**	144 ± 64
7b	220 ± 33	**7j**	194 ± 19
7c	**136 ± 10.6**	**7k**	535 ± 43
7d	**131 ± 8.4**	**7l**	149 ± 7.5
7e	104 ± 1.5	**7m**	190 ± 16
7f	264 ± 64	**7n**	330 ± 10
7g	160 ± 2.8		

[a] Data are the mean ± standard error (SEM) of three independent experiments.

Conclusions

In conclusion, we have shown for the first time that AMF (5-azidomethylfurfural) derivatives, biosourced renewable materials directly obtained from CMF (5-chloromethylfurfural), could lead to nitrogenous cyclopentenones with an azidomethyl side chain. These cyclopentenones with two contiguous stereogenic centres, one of which is quaternary, were obtained in moderate to good yields with high diastereoselectivity *via* the Piancatelli rearrangement. $ScCl_3$ as a transition metal catalyst was used for the first time to catalyse this rearrangement, and even better results were obtained using lanthanide $Dy(OTf)_3$ as the catalyst.

The introduction of this azido group is particularly innovative in these Piancatelli rearrangements. On the one hand, it allows taking advantage of the high synthetic potential of this functional group, which can be derivatized into a wide variety of other functionalities and for the synthesis of a range of nitrogen-based scaffolds of biologically active compounds and functional materials. Moreover, these 4-(azidomethyl)-cyclopentenones **7** exhibited relevant cytotoxic activity against HCT116 and HL60 cancer cell lines with nanomolar IC_{50} values.

This work has led to the first proof of concept that a nitrogen-containing substrate can participate in the Piancatelli rearrangement. We have no doubt that this methodology, based on the Piancatelli rearrangement on a substrate with the azido function, will subsequently be used to construct other nitrogen derivatives with multiple applications.

Author contributions

J-FB designed the experiments and supervised the project. CM performed all chemical syntheses and characterization of data of compounds. JB carried out the bioassays for cytotoxicity activities. J-FB wrote the manuscript and CM revised the manuscript. All the authors have given approval to the final version of the manuscript.

Data availability

The authors confirm that the data supporting this article and the findings of this study have been included as part of the ESI.† The software used for drawing chemical structures is ChemDraw 23.0. The dose–response curves were plotted using GraphPad Prism software and the IC_{50} values were calculated from these polynomial curves using the same software.

Conflicts of interest

There are no conflicts to declare.

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