Au(I)-Catalyzed Pictet-Spengler Reactions: a Journey Around the Indole Ring

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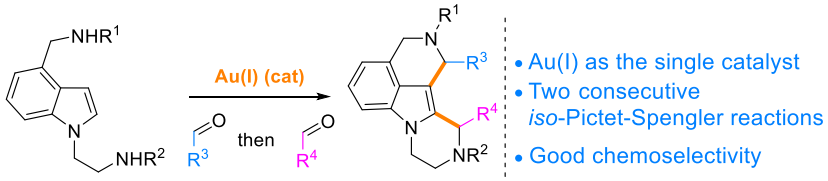


Au(I) complexes catalyze iso-Pictet-Spengler reactions. Ethylamine or methylamine chains were introduced at C2, C4 or at the nitrogen atom of the indole ring, and the corresponding substrates were reacted in the presence of aldehydes and catalytic amounts of Au(I) complexes, leading to a variety of polycyclic scaffolds. Selectivity could be achieved in the course of a double iso-Pictet-Spengler reaction involving two successive aldehydes, leading to highly complex molecules.

Indole alkaloids are major heterocycles because of their prevalence natural and bioactive compounds.[1] Among the privileged scaffolds, tetrahydro-β-carbolines **1** are important molecules and their structural unit is embedded in numerous natural products, among which a huge number are bioactive.[2] The Pictet-Spengler reaction[3,4] combining tryptamines and aldehydes is unarguably the easiest and fastest way to prepare such scaffolds.[2b] Rich of more than a century of research, this reaction and its mechanism has been intensively studied[5] and applied to numerous total syntheses.[2b] Interestingly, because of the nucleophilicity of indole at C2 and C3,[6] numerous variants of this reaction lead to structurally related compounds, such as 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **2**,[7] tetrahydro-γ-carbolines **3**, [8] and 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4** [7b, 9] (Figure 1). These so-called *iso*-Pictet-Spengler reactions are far less studied than the venerable historic reaction, despite allowing access to interesting heterocycles.

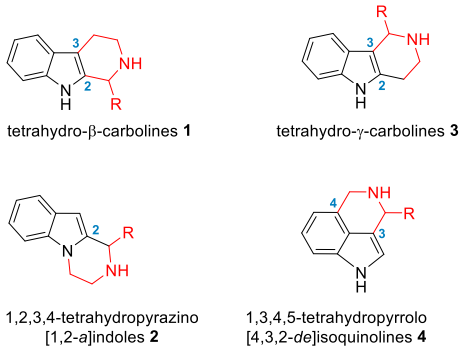
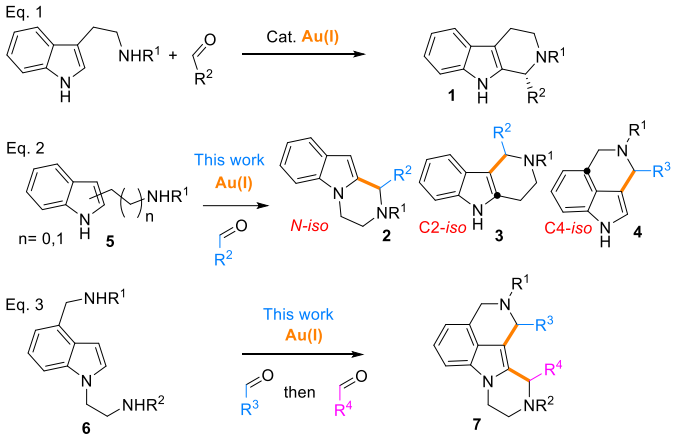


Figure 1. Tetrahydro-β-carbolines and regioisomeric congeners

Our group has long been interested in gold-catalyzed reactions[10] involving indolic compounds, in particular the functionalization of indoles with alkynes.[11,12] Recently, we discovered that Pictet-Spengler reactions could be catalyzed by Au(I) complexes[13,14] (Scheme 1, eq. 1). These reactions occur *via* a mechanism involving the auration of the indole ring that we established through both experimental and computational studies. We hypothesized that similar reactions catalyzed by Au(I) complexes should occur from the use of other regioisomeric alkylamines **5**. Herein, we show that it is possible to obtain regioisomeric compounds **2**, **3** and **4** from gold-catalyzed *iso*-Pictet-Spengler reactions (Scheme 1, eq. 2).

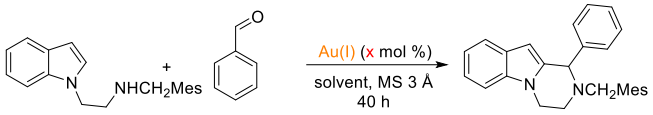


Scheme 1. Context of this work

For clarity purpose, we defined those reactions as *N-iso*-, C2-*iso*- and C4-*iso*-Pictet-Spengler reactions, depending on the connecting atom of the indole ring to the alkylamine chain. With a good knowledge of each of these different versions of the reaction, we could achieve a one-pot, selective process including successively a C4-*iso* and a *N-iso*-Pictet-Spengler reaction for the synthesis of complex compounds **7** via the C3 then C2 ring-closures, with two different aldehdyes (Scheme 1, eq. 3).

Our journey started with the study of the *N-iso*-Pictet-Spengler reactions from *N-iso*-tryptamine **5a** and benzaldehyde **8a**, reacted in toluene in the presence of molecular sieves over a 40 h period (Table 1). In the absence of catalyst, no background reaction occurred (entry 1). Though counterintuitive, the reaction did not proceed either in the presence of an acidic catalyst, as previously reported[7e] for C3-unsubstituted *N-iso*-tryptamines (entry 2).[15] We next screened a series of three Au(I) catalysts (entries 3-5), for which only the Gagosz catalyst[16] led to a moderate conversion (20%, entry 4). The solvent was replaced by DCM, allowing to reach a 69% conversion, further optimized to 74% after slight increase of the reaction temperature (entries 6-7).

Table 1. Optimisation of the *N-iso* Pictet-Spengler reaction



5a 8a 2a

entry	Catalyst (mol%)	Solvent	T (°C)	Conv (%)[a]
1	-	PhMe or DCM	rt	0
2	$(PhO)_2POOH$ (5)	PhMe	rt	0
3	Cat a (5)	PhMe	rt	0
4	Cat b (5)	PhMe	rt	20
5	Cat c (5)	PhMe	rt	Traces
6	Cat b (5)	DCM	rt	69
7	Cat b (5)	DCM	30	74

cat a cat b cat c

[a] Conversion were measured by ^{1}H NMR.

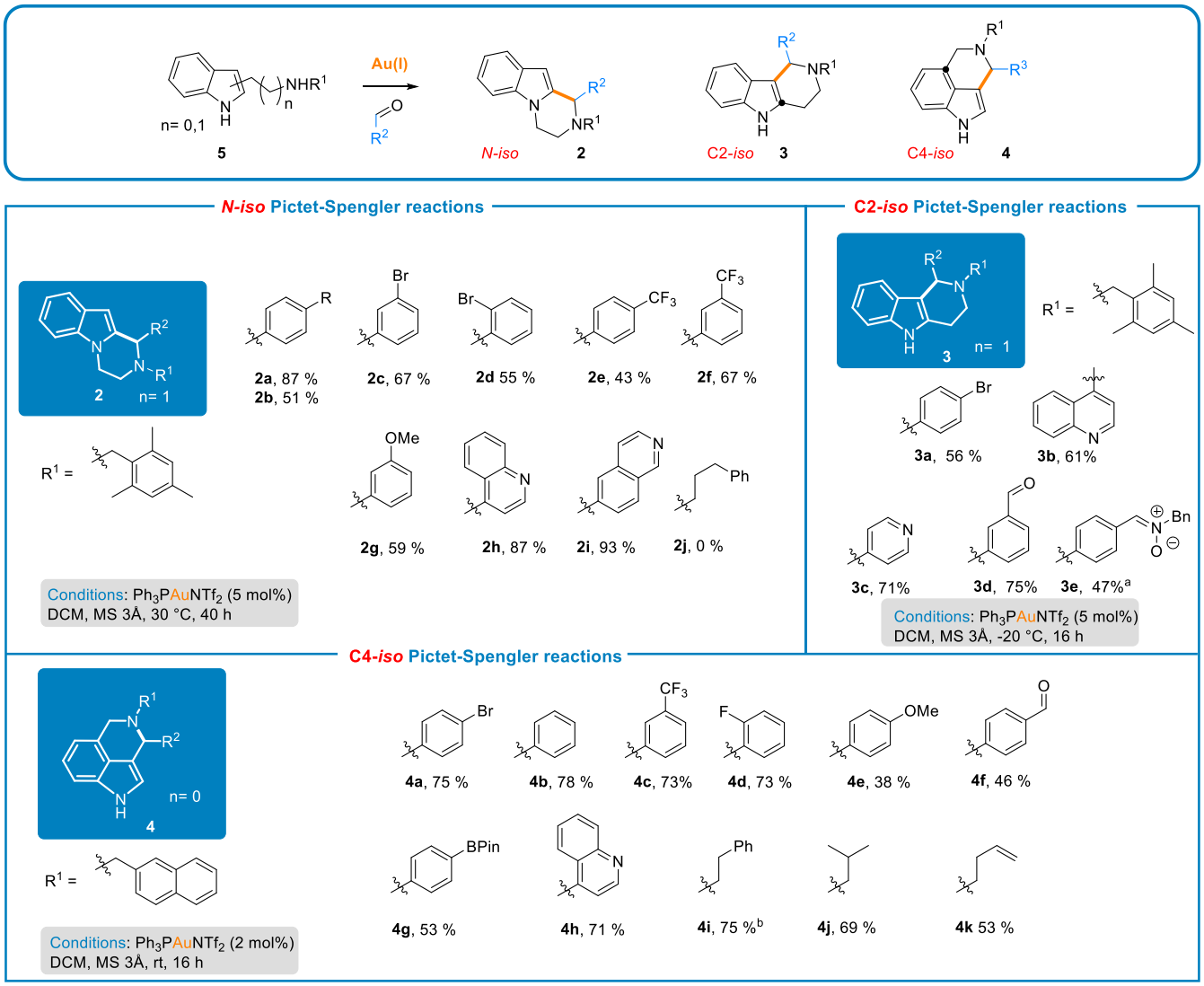
We next engaged a number of aromatic aldehydes in the reaction (Scheme 2, *N-iso* Pictet-Spengler reaction). The reactions performed with benzaldehyde and *p*-bromobenzaldehyde led to **2a** and **2b** in 87% and 51% yields, respectively. A bromide group was tolerated at the *meta* and *para* positions, leading to compounds **2c** and **2d** in good yields. The reaction also proved compatible with aldehydes bearing electron-withdrawing CF_3 groups at the *para* and *meta* positions. When *m*-methoxybenzaldehyde **8g** was used, the corresponding product **2g** was obtained in 59% yield. 4- and 6-quinoline carbaldehydes then furnished compounds **2h** and **2i** in 87% and 93% yields, respectively. However, the reaction showed a complete selectivity towards aromatic aldehydes, since 3-phenylpropanal did not lead to the expected compounds **2j**.

We switched to the gold-catalyzed C2-*iso*-Pictet-Spengler reaction, performed from isotryptamine **5b** and a range of aldehydes (Scheme 2, C2-*iso* Pictet-Spengler reaction). Of note, this reaction is characterized by a strong background reaction that can be suppressed by decreasing the temperature to -20 °C. At this temperature, the tetrahydro-γ-carboline **3a** was obtained in 54% yield when the reaction was performed in the presence of complex **b** (5 mol%), testifying for a solely Au(I)-catalyzed process. We screened a selection of functionalized arylaldehydes that could potentially result in reactivity issues if the reaction was acid-catalyzed. Compounds **3b** and **3c** bearing a 4-quinolynyl and 4-pyridyl chain, respectively, were obtained in good yields. Isophthalaldehyde led to the product **3d** in 75% yield as a single product (no trace of doubly functionalized compound). Remarkably, despite a lower conversion, the reaction also tolerated an aldehyde bearing a nitrone function, yet known to be activated by Au(I) complexes,[17] leading to compound **3e** in 47% yield.[18] Comparatively, this kind of aldehyde would not be suitable in related acidic-catalyzed reactions, because of the activation of the highly electrophilic nitrone.

We further moved toward the introduction of the alkylamine chain at C4 atom of the indole ring (Scheme 2, C4-*iso* Pictet-Spengler reaction). The reaction of **5c** with *p*-bromobenzaldehyde in DCM at room temperature in the presence of only 2 mol% of Gagosz catalyst led to the corresponding 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline **4a** in 75%.[19] Benzaldehyde and *m*-trifluoromethylbenzaldehyde also led to excellent yields in **4b,c**. A fluorine group at the *ortho* position was well tolerated, while a methoxy group at the *para* position led to a decrease of

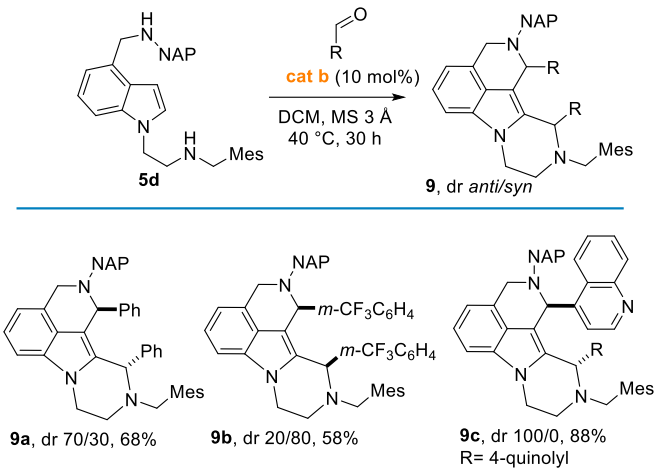
the reactivity (**4e**, 38% yield). The phthalaldehyde led to compound **4f** in 46% yield, this time accompanied by the dimeric product (ratio **4f**/dimer: 10/4). A boronate ester at the *para* position was tolerated, leading to **4g** in 53% yield, opening opportunities for subsequent cross-coupling functionnalizations. **4h**, bearing a quinolyl moiety was formed in 71% yield. Interestingly, aliphatic aldehydes were well converted to compounds **4i-k** in moderate to good yields. To date, this is the first time that we observed conversion in the course of any version of the four different Au(I)-catalyzed (*iso*)Pictet-Spengler reactions that we studied involving aliphatic aldehydes.

We next considered the possibility that an indole ring functionalized with two alkylamine chains at the *N*- and C4-position could undergo C2-C3 difunctionalization *via* a C4-*iso* and a *N*-*iso*-Pictet-Spengler cyclization cascade. For this purpose, we designed the diamine **5d**, keeping the same groups on the nitrogen atoms. Indeed, gold-catalyzed reaction of **5d** with benzaldehyde at 30 °C led to tetracyclic 2,3,8,9,10,11-hexahydro-1*H*-pyrazino[1',2':1,5]pyrrolo[4,3,2-*de*]isoquinoline **9a** in 68% yield and a 70/30 diatereomeric ratio, in favor of the *anti* diastereoisomer (Scheme 3).[20]



[a] Performed at rt. [b] Performed with 5 mol% of $Ph_3PAuNTf_2$.

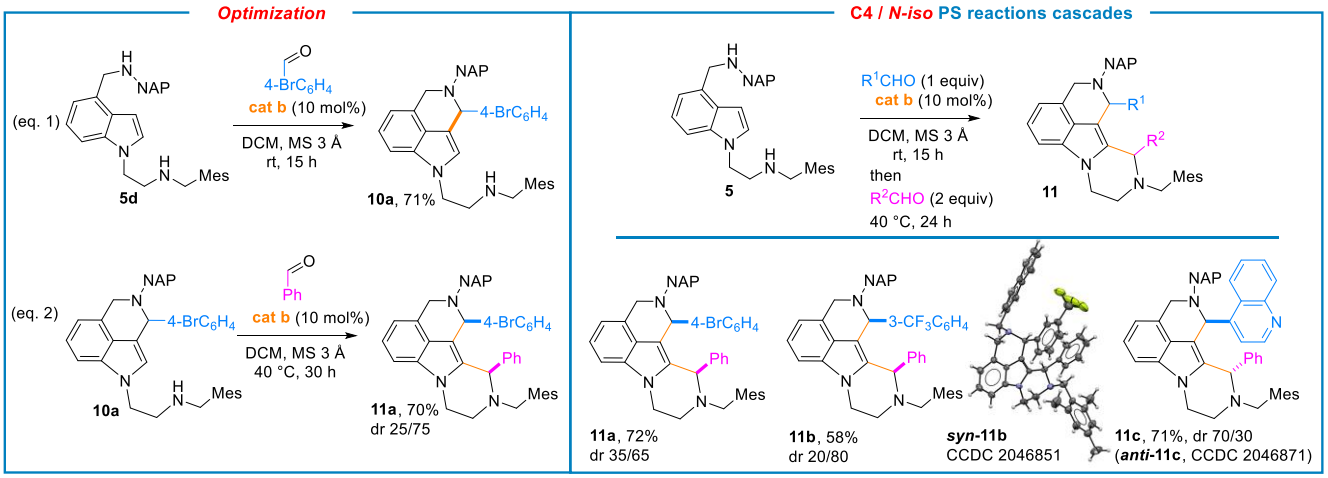
Scheme 2. Scope of the different versions of the *iso*-Pictet-Spengler reactions studied



Scheme 3. C4/*N-iso*-Pictet-Spengler reactions combined (the related stereochemistry indicated is that of the major diastereomer)

To the best of our knowledge, this scaffold has never been reported. When the *meta*-trifluoromethylbenzaldehyde was used, compound **9b** was obtained in 58% yield, with the diasteromeric ratio in favor of the *syn* isomer. 4-Quinoline carboxaldehyde led to the amine **9c** in 88% yield and full *anti*-diastereoselectivity.

We next reasoned that the C4-*iso* Pictet-Spengler reaction, operating with lower catalyst loading and temperature, should occur faster than the *N-iso* reaction, requiring higher catalyst loading and temperature. Indeed, when **5d** was engaged in the reaction with 1 equivalent of *p*-bromobenzaldehyde, the C4-*iso* Pictet-Spengler product **10a** was selectively obtained at room temperature in 71% yield (Scheme 4, eq. 1). It was then engaged in the *N-iso* Pictet-Spengler reaction with benzaldehyde that led to **11a** in 70% yield as a mixture of diastereomers (Scheme 4, eq. 2, dr 25/75).



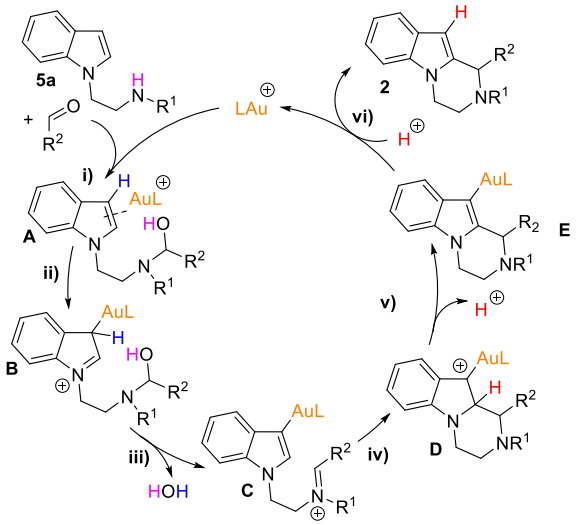
Scheme 4. Selective bis-functionnalization (the relative stereochemistry indicated is that of the major diastereomer)

We then developed the one-pot formation of compounds **11** by sequential addition of two different aldehydes from **5d** in the presence of 10 mol% of the gold complex **b** as catalyst (Scheme 4, right part). After 15 h of reaction in the presence of *p*-bromobenzaldehyde (1 equiv) at room temperature, benzaldehyde was added to the reaction mixture and further 24 h reaction led to compound **11a** in 72% yield (dr 35/65) in favor of the *syn* isomer. The same protocol was applied to another couple of aromatic aldehydes, leading to compound **11b** in good yields and good diastereoselectivity (dr 20/80). Gratifyingly, we obtained the Xray structure of the *syn*-diastereomer of **11b**. Beyond confirming its structure, it was helpful to further identify all other diastereomers of the series of compounds **9** and **11**. When 4-quinolinecarboxaldehyde was used in the first C4-*iso*-Pictet-Spengler step (requiring a

higher 40 °C temperature), followed by benzaldehyde for the *N-iso* step, compound **11c** was obtained in 71% yield and diastereoselectivity in favor of the *anti*-isomer. The diastereoselectivity of these reactions may be the result of electronic effects. Indeed, the Xray structure of the *syn*-**11b** shows a pretty good superposition of the phenyl and the trifluoromethylphenyl ring with a distance between the two aryl planes of ca. 3.30 Å. As reviewed by Iverson, interactions between electron-poor/electron rich aryls may be referred to the favored "aromatic donor-acceptor interactions" or polar/π model.[21] This would explain the general trend to lead to the *syn*-diastereomer with electron-poor aryl (**9b**, **11a**, **11b**) while destabilizing interactions operating with electron-rich aryl rings couples (phenyl, quinoline and their combination) lead mainly to the *anti*-isomer (**9a**, **9c**, **11c**).

Gratifyingly, no need for an addition batch of catalyst was required for the application of this protocol. The formation of these compounds, as the result of two successive *iso*-Pictet-Spengler reactions with different aldehydes, opens avenues for the synthesis of highly functionalized and complex compounds. This strategy potentially offers unique opportunities for the exploration of chemical space in biological studies.

The mechanistic hypothesis for these reactions relies on our previous gold-catalyzed "classical" Pictet-Spengler reactions[13a] and is illustrated below with the *N-iso*-version of the reaction (Scheme 5), with the following steps. (*i*) The spontaneous addition of the amine to the aldehyde leads to an hemiaminal (this step being potentially catalyzed by the Au(I) complex). (*ii*) The coordination of the indole ring leads to the η^2 and η^1-gold complexes **A** and **B**. (*iii*) The conversion of the latter to an iminium *via* an intramolecular abstraction of a proton and release of water generates **C**. (*iv*) the nucleophilic addition to the iminium via C2 forms complex0 **D**. (*v*) The elimination of a proton *via* **E** and protodeauration then leads to the product **2** and the regeneration of the cationic Au(I) complex. Similar mechanisms can be involved for the C2- and C4-*iso*-Pictet-Spengler reactions (see the supporting Information).



Scheme 5. Mechanistic pathway in *N-iso*-Pictet-Spengler reactions

To conclude, we have developed Au(I)-catalyzed *iso*-Pictet-Spengler reactions by introduction of the alkylamine chain around all the different positions of the indole ring allowing a trapping of the *in situ* generated iminium ion by either the C2 or C3 atom. This led to the isolation of numerous heterocyclic scaffolds. We have showed the high chemoselectivity enabled by Au(I) catalyzed processes in these reactions, in particular by design of the *in situ* sequential cascade of C4- and *N-iso*-Pictet-Spengler reactions leading to highly complex polycyclic indolic arrangements.

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(15) The same isotryptamine protected with a benzyl group on the amine function however reacts in this reaction in the presence of acid. The methylenemesityl group that we have used here, as in our previous study (see ref 13a), allows to guarantee a purely gold-catalyzed reaction.
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(18) The conversion rate was 65%. The same reaction without catalyst led to a lower 25% conversion over 60 h.
(19) The conversion was 77% after 7.5 h (5 mol% catalyst). The same reaction in the absence of catalyst lead to 8% conversion. See the Supporting Information.
(20) Both *syn* and *anti* diastereomers of the series have a typical footprint in ^{1}H NMR spectra. NOESY experiments and XRay obtained in other compounds of the series allowed the determination of the relative configurations of all the products by analogy.
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