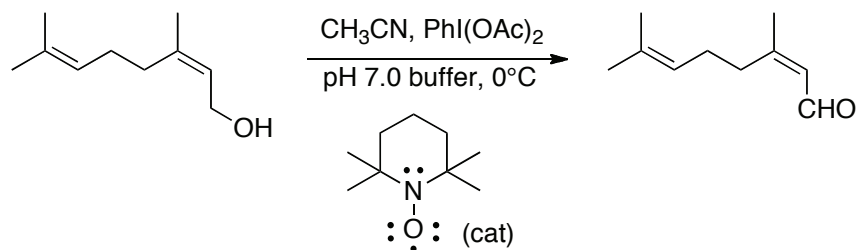


## Discussion Addendum for: Oxidation of Nerol to Neral with Iodosobenzene and TEMPO



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The oxidation of alcohols with IBD (iodosobenzene diacetate) with catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), developed by Piancatelli, Margarita, and co-workers,<sup>2</sup> has become an established and effective protocol that has been continuously and successfully utilized, as reported in numerous literature reviews.<sup>3</sup> The methodology is characterized by a significantly high level of selectivity for the oxidation of primary alcohols to aldehydes<sup>4</sup> without over-oxidation to carboxylic acids, and a high chemoselectivity in the presence of secondary alcohols or other oxidizable functional groups.<sup>5</sup> The protocol has the additional benefits of being operationally simple and avoiding the use of heavy metals, odoriferous reagents, or expensive reagents.<sup>3,5</sup> Its robust nature is also described in a standardized protocol for the oxidation of nerol to neral in *Organic Syntheses*.<sup>6</sup>

### Application in Total Synthesis

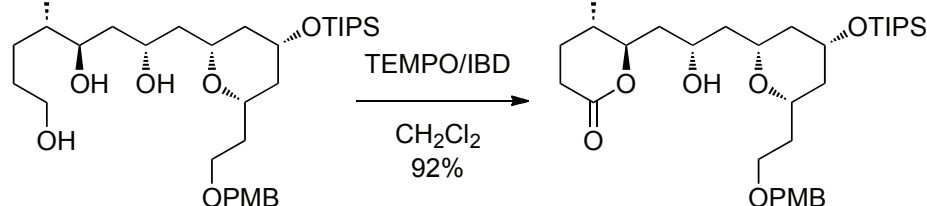
Beside the wide range usage of the Piancatelli/Margarita oxidation for classic reactions, it has become a standard method for efficient and clean conversion of alcohols to the aldehydes during the total synthesis of complex molecules. Some applications in this field will be highlighted.

A novel and chemoselective  $\delta$ -lactonization was described in the stereocontrolled total synthesis of leucascandrolide A, a cytotoxic 18-membered macrolide (Scheme 1). This was conveniently achieved by

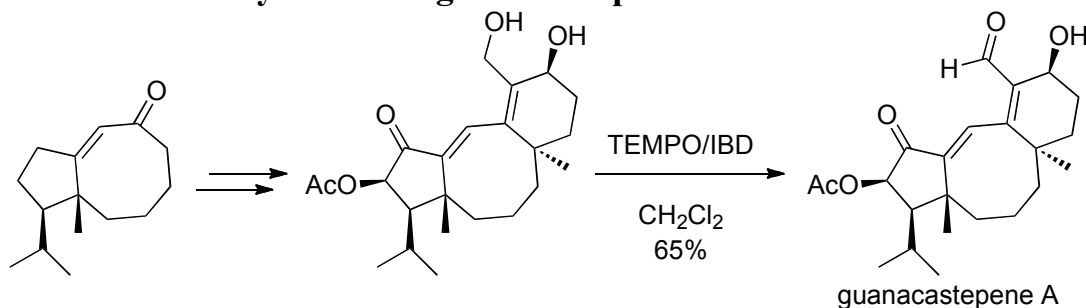
selective oxidation of the primary alcohol to the lactol and further oxidation to generate the  $\delta$ -lactone in 92% yield.<sup>7</sup>

Danishefsky completed the total synthesis of guanacastepene A by applying the highly selective properties of the IBD/TEMPO in the final step. The primary allyl alcohol was selectively oxidized in preference to the secondary one (Scheme 2).<sup>8</sup>

### Scheme 1. Selective oxidation and $\delta$ -lactonization

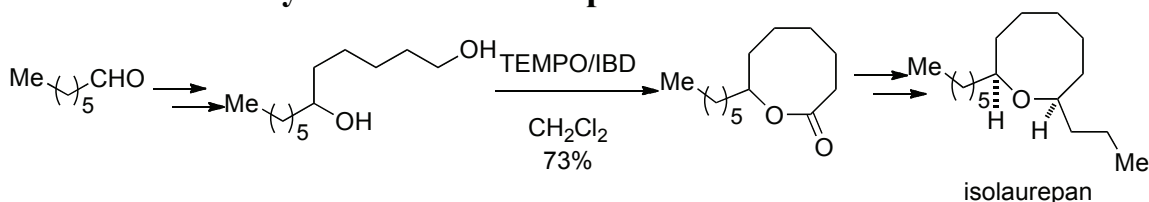


### Scheme 2. Total Synthesis of guanacastepene A



The TEMPO/IBD reagent combination allowed the oxidative lactonization of 1,6- and 1,7-diols, which formed seven- and eight-membered lactones, respectively, in good yields. These reactions have been performed in non-extreme-dilution conditions and on a large scale (up to 15 g) with high yields and without the formation of dimers or oligomers. In addition, the TEMPO/IBD-oxidative lactonization strategy avoided the use of protective groups, as well as separate oxidation steps. The TEMPO/IBD-mediated oxidative lactonization strategy was applied efficiently to the synthesis of isolaurepan (Scheme 3).<sup>9</sup>

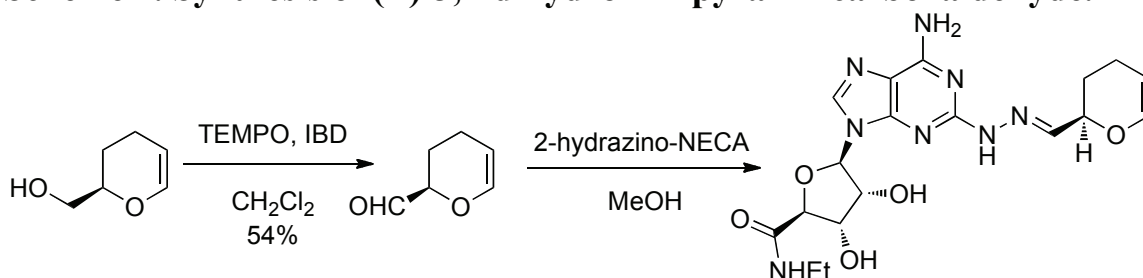
### Scheme 3. Total synthesis of isolaurepan.



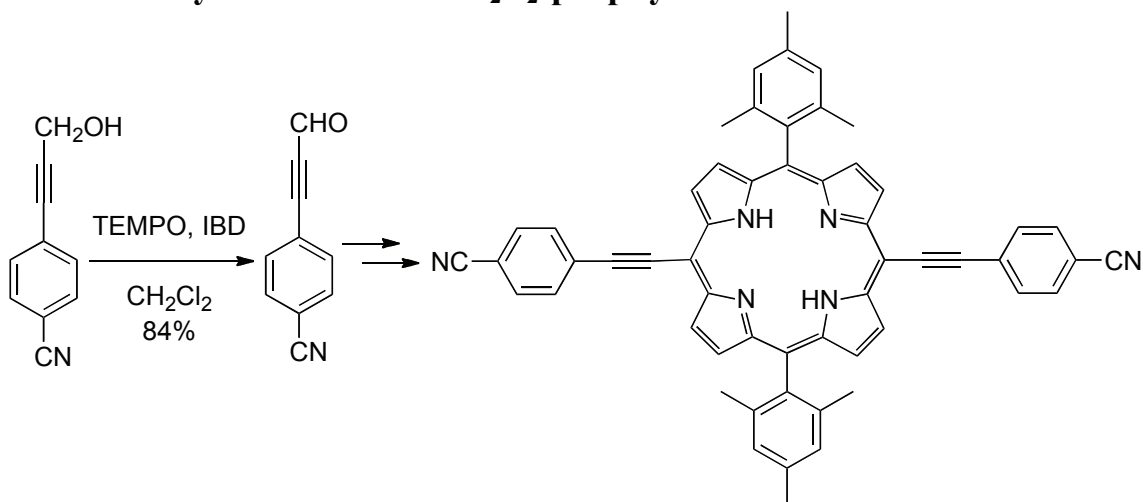
After testing several oxidation agents, the TEMPO/IBD protocol was selected for its efficiency and cleanliness in the preparation of (*R*)-3,4-dihydro-2*H*-pyran-2-carbaldehyde, a compound that is useful for the synthesis of potent adenosine agonist (Scheme 4).<sup>10</sup>

The selective oxidation of phenyl-substituted propargylic alcohols was attempted under many reaction conditions before the TEMPO/IBD methodology was identified as providing the best results in terms of stability, availability, reaction time and reaction yield. The aldehydes resulting from this reaction were used as building blocks in the preparation of porphyrins (Scheme 5).<sup>11</sup>

**Scheme 4. Synthesis of (*R*)-3,4-dihydro-2*H*-pyran-2-carboxaldehyde.**

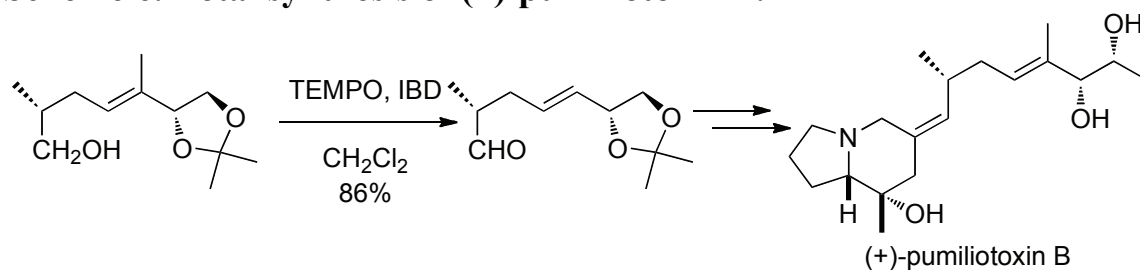


**Scheme 5. Synthesis of *trans*-A<sub>2</sub>B<sub>2</sub>-porphyrins.**



Capitalizing on the mild reaction conditions, the TEMPO/IBD procedure was successfully applied to the oxidation of a chiral primary alcohol. Other oxidants caused extensive and highly problematic epimerization of the aldehydes  $\alpha$ -stereocenter. The resulting chiral aldehyde was a key intermediate in the synthesis of (+)-pumiliotoxin B (Scheme 6).<sup>12</sup>

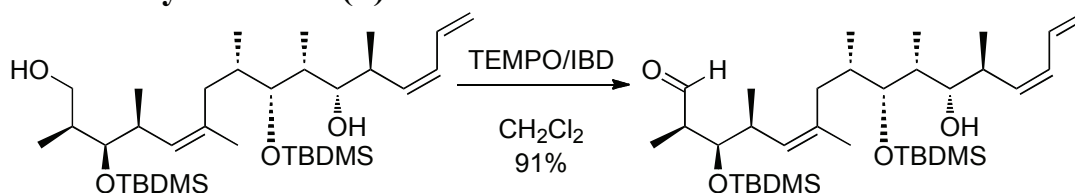
### Scheme 6. Total synthesis of (+)-pumiliotoxin B.



### Industrial Applications

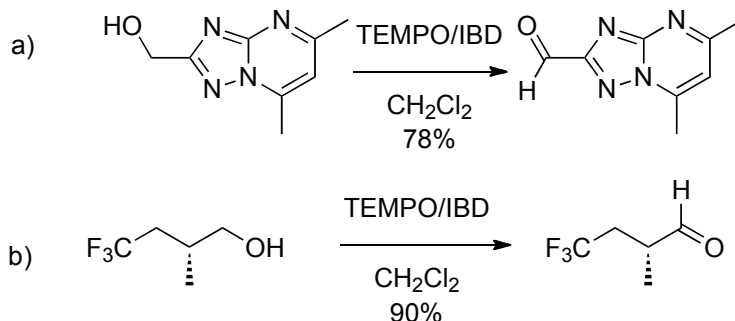
Paterson, together with Novartis Pharma, performed the oxidation of a polyol with TEMPO/IBD system to form an aldehyde in the course of a large-scale synthesis of the anti-cancer marine natural product (+)-discodermolide, (Scheme 7). The authors found that addition of a small amount of water resulted in the dramatic acceleration of the oxidation reaction and the formation of the product in high yields, which allowed scale-up of the reaction.<sup>13</sup>

### Scheme 7. Synthesis of (+)-discodermolide.



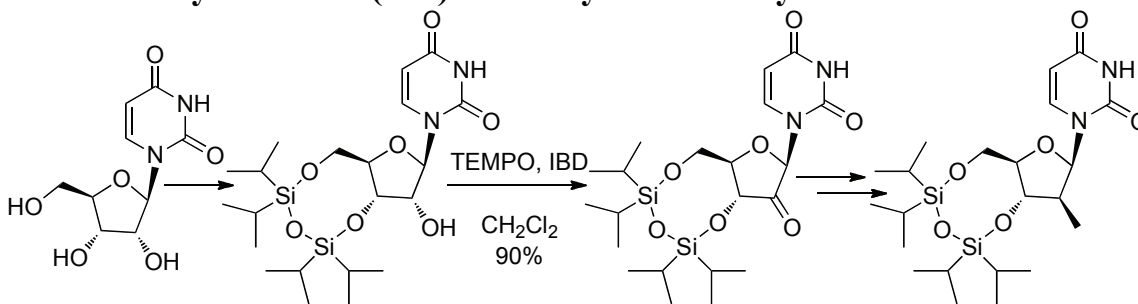
A group at Pfizer demonstrated that the oxidation process could be performed at a kg scale during their synthesis of the hepatitis C polymerase inhibitor (Scheme 8a).<sup>14a</sup> Similarly the IBD/TEMPO oxidation was employed industrially with a volatile aldehyde without workup and by telescoping to the next step (Scheme 8b).<sup>14b</sup>

### Scheme 8. Multi-kilogram-scale synthetic application of the IBD/TEMPO oxidation methodology.



A Johnson and Johnson group, searching for a more scalable procedure for oxidation of a secondary alcohol, selected the TEMPO/IBD procedure (Scheme 9). For the product purification a simple switch of the solvent from dichloromethane to heptane, followed by cooling, produced a crystalline keto-derivative, an intermediate in the synthesis of (2'*R*)-2'-deoxy-2'-*C*-methyluridine, in 85-88.5% yield on scales that ranged from 100 g up to 10 kg.<sup>15</sup>

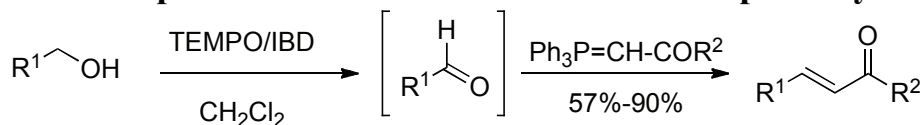
**Scheme 9. Synthesis of (2'*R*)-2'-deoxy-2'-*C*-methyluridine.**



**Development reactions**

Interestingly, the mild reaction conditions and the tolerability of complex functional moieties have opened the route to combination reactions following the oxidation of alcohols. For example, Vatele has shown that the IBD/TEMPO system, in combination with stabilized phosphoranes, constitutes a mild and stereoselective one-pot method for the conversion of a variety of primary alcohols into their corresponding  $\alpha,\beta$ -unsaturated esters (Scheme 10). The procedure was described by the author as having significant advantages over the existing ones for its chemoselectivity (oxidation of primary alcohols over secondary ones), general applicability to a broad range of complex molecules, and the employment of commercially available and safe reagents.<sup>16</sup>

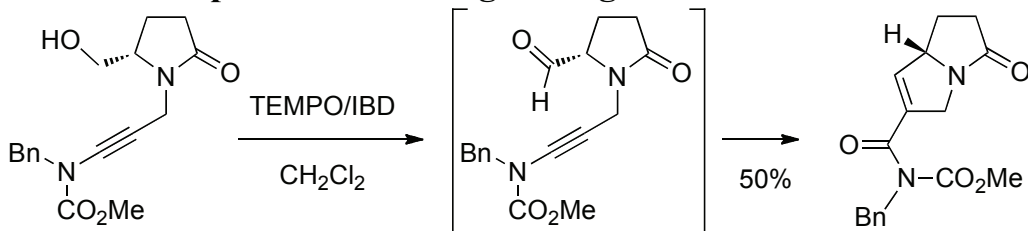
**Scheme 10. One-pot selective oxidation/olefination of primary alcohols.**



An additional example that demonstrates multiple one-pot reactions is the oxidation, under classical IBD/TEMPO conditions, of a primary alcohol

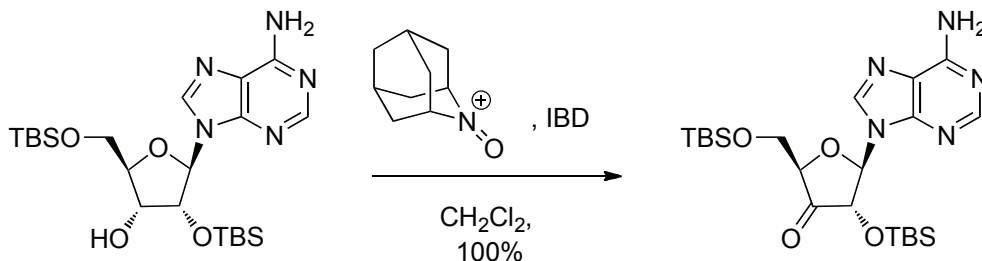
in presence of an ynamide; the formation of the aldehyde triggers the ring-closing yne-carbonyl metathesis as a cascade reaction (Scheme 11).<sup>17</sup>

**Scheme 11. One-pot oxidation/ring closing metathesis.**



Modifications of the nitroxide catalyst, as in the use of 2-azaadamantane *N*-oxyl, have resulted in the ability to oxidize highly hindered alcohols, as well as the demonstration of enhanced catalytic efficiency (Scheme 12);<sup>18a</sup> meanwhile, C2-symmetric and bridgehead nitroxides have demonstrated that, together with IBD, stereoselective oxidations of secondary alcohols are at least conceptual feasibility.<sup>18b</sup>

**Scheme 12. Oxidation with structurally less hindered class of nitroxyl radicals.**



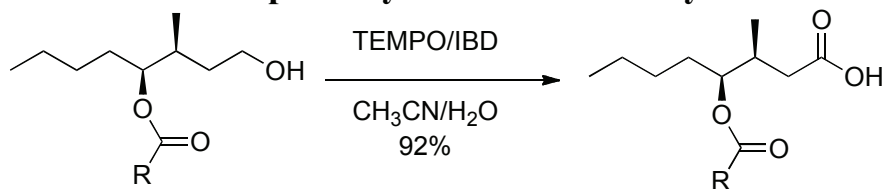
The simplicity of the reaction conditions have also triggered development of supported reagents (silica or polymer-based) or fluoros-tagged reagents, both for TEMPO and phenyliodoso acetate derivatives. The modifications improve the greenness of the oxidation process with more easily recoverable variations.<sup>19</sup>

**Oxidation to Acids**

Depending on the reaction conditions, primary alcohols can be oxidized to the corresponding carboxylic acids, usually in high yields.<sup>3c</sup> Observed initially by Epp and Widlansky in 1999,<sup>20</sup> this method has found its way into several natural product syntheses. For example, Sefton and coworkers reported that the oxidation of the primary alcohol with TEMPO

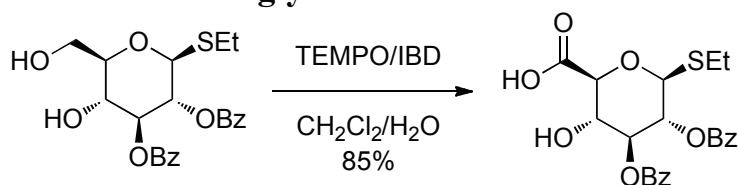
and IBD in aqueous acetonitrile led directly to the acid in very high yields (Scheme 13).<sup>21</sup>

**Scheme 13. Oxidation of primary alcohol to carboxylic acid.**



Van der Marel and his group disclosed TEMPO/IBD-mediated chemo- and regioselective oxidation of partially protected thioglycosides as a powerful means to obtain the corresponding thioglycuronic acids. The reaction was carried out in a mixture of dichloromethane and water (2:1) and proceeded in excellent yields. Interestingly, this oxidation protocol can be applied to alcohols containing thio and selenoethers (Scheme 14).<sup>22</sup>

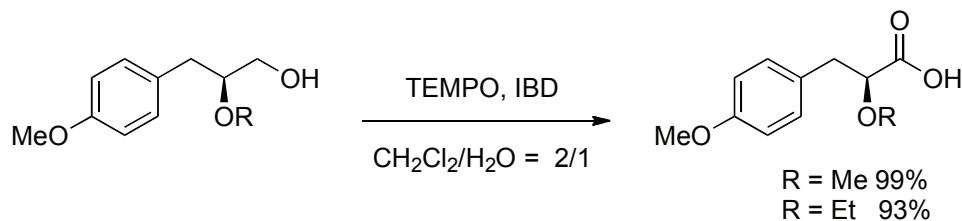
**Scheme 14. Oxidation of thioglycosides.**



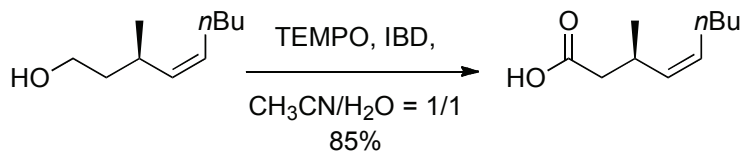
Optically active alcohols were oxidized to the corresponding acid with IBD in the presence of a catalytic amount of TEMPO in quantitative yields and without loss of enantiomeric purity (Scheme 15). These acids are key intermediates in the synthesis of several drugs, such as Tesaglitazar and Navaglitazar.<sup>23</sup>

After many attempts with other well-known oxidation procedures, the problematic oxidation of a primary alcohol to a carboxylic acid was achieved cleanly and in a good yield only when applying the TEMPO/IBD protocol. A series of 4,5-disubstituted  $\gamma$ -lactones, including whisky and cognac lactones (Scheme 16), were produced.<sup>24</sup> Further applications in this field are described in the reference 25.

**Scheme 15. Stereospecific synthesis of Tesaglitazar and Navaglitazar precursors.**



**Scheme 16. Oxidation of primary alcohol to carboxylic acid.**



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Roberto Margarita is the Business Development Director for Corden Pharma managing marketing, sales and strategic business planning. He previously held a similar position at Bristol Myers Squibb. He also developed a background in manufacturing as API Business Unit Director and in pharmaceutical development in the CMC area, including preparation of NDAs. His educational background includes a Ph.D. in Chemical Sciences from the University of Rome “*la Sapienza*”, a Post-Doctoral experience at the Université de Montreal, Montreal, Quebec, Canada and a Diploma in General Management from the Henley Management College in Henley–UK. He is author of more than 20 publications.



Francesca Leonelli was born in Rome in 1974. She graduated in Chemistry at the University of Rome “*La Sapienza*” in 1999 and she received her Ph.D. in Chemistry in 2003 at the same university. Since 2008 she has been a researcher in the Chemistry Department in the same University. Francesca Leonelli’s research is principally focused on the natural compound synthesis and on the preparation of molecules of biological interest.