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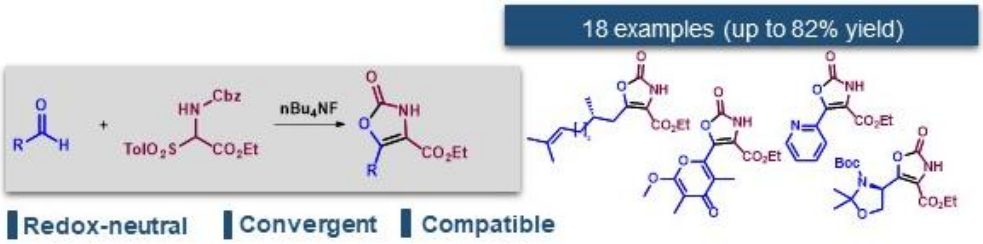
Convergent Synthesis of 2-Oxazolone-4-carboxylates Esters by Reaction of Aldehydes with Ambivalent *N*-Cbz-α-Tosylglycinate Ester

Masahiro Abe,[a] Baptiste Picard,[a] Michaël De Paolis[a,*]

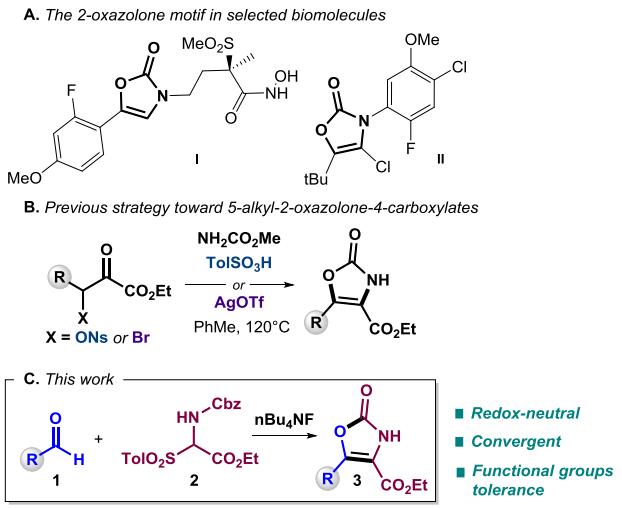
[a] *Normandie Univ, UNIROUEN, COBRA, INSA Rouen, CNRS, COBRA, 76000 Rouen, France. michael.depaolis@univ-rouen.fr, Supporting Information Placeholder*



ABSTRACT: *N*-Cbz-α-tosylglycinate ester was combined with aldehydes in a redox-neutral sequence leading to 2-oxazolone-4-carboxylates with high functional groups tolerance. While the scope of the method was delineated to primary and secondary aliphatic aldehydes as well as aromatics, no racemization occurred with chiral aldehydes such as Garner's. Hitherto unknown, this process relies on the ambivalent role of *N*-Cbz-α-tosylglycinate ester acting as pronucleophile.

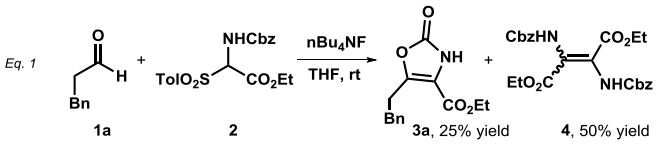
Combining nitrogen and oxygen in a 5-membered aromatic ring, 2-(3*H*)oxazolones (2-oxo-2,3-dihydrooxazoles) are pertinent molecules in the fields of medicinal chemistry and agrochemistry,[1] as illustrated with **I** and **II** (Scheme 1A) with respectively antibacterial[1a] and herbicidal activities.[1b,2] As planar and aromatic derivatives of amino acids such as serine and threonine, electron-poor 2-(3*H*)oxazolone-4-carboxylates esters have much promise in the aforementioned fields (Scheme 1B). However, the known strategy toward 5-substituted-2-(3*H*)oxazolone-4-carboxylates requires two limiting steps.

Scheme 1.



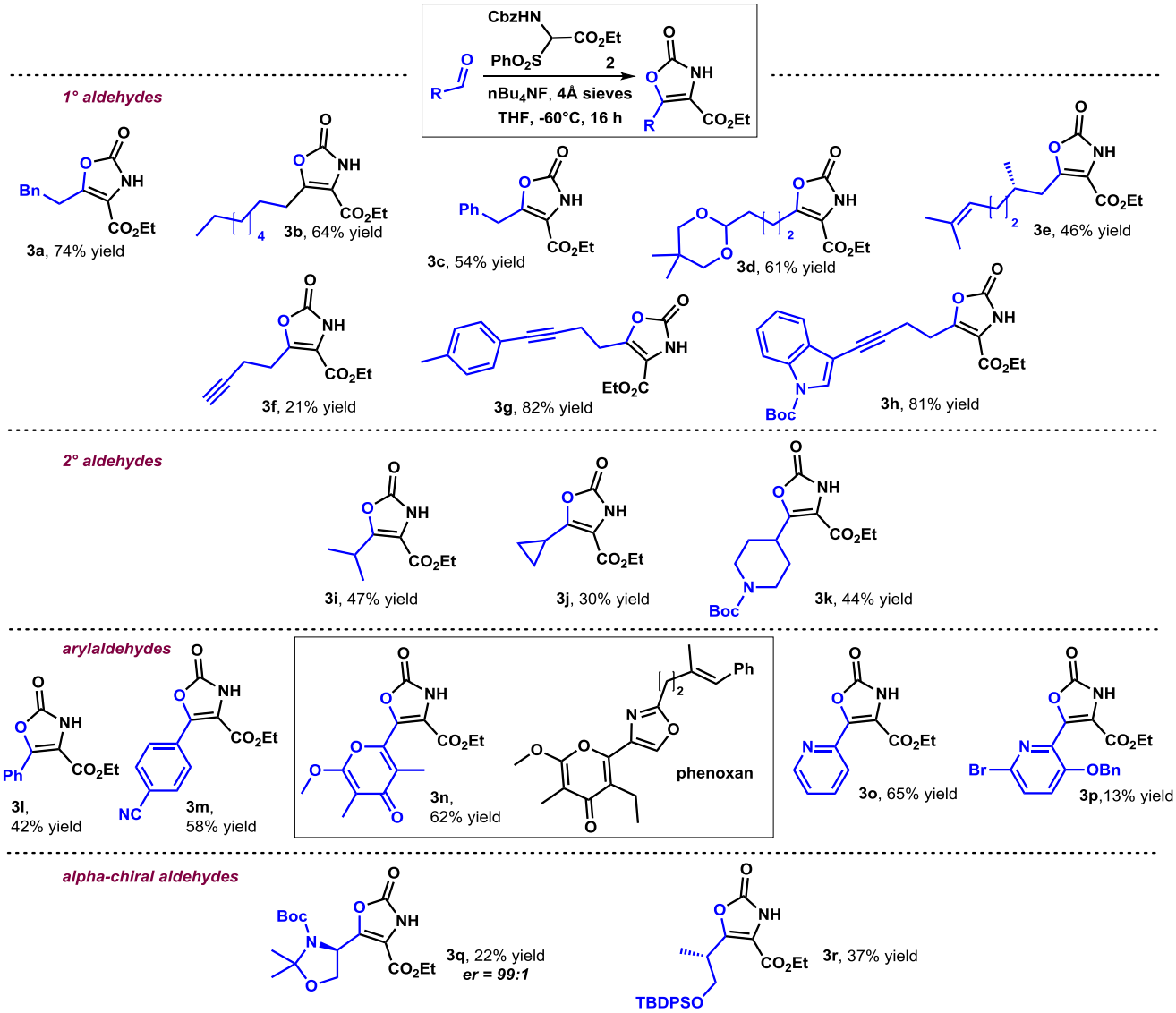
First, α-ketoesters are oxidized into α-nosyloxy or α-bromo-β-ketoesters, then the nitrogen nucleus is introduced with methyl carbamate by nucleophilic addition in harsh conditions, upon activation with *p*-toluenesulfonic acid or silver triflate, in refluxing toluene.[3] Within this strategy, alternative routes were described by combining either α-amino-β-ketoesters with triphosgene[1b] or α-diazo-β-ketoesters with methyl carbamate.[1c] Beside the limited functional group tolerance displayed by these methods, the assemblage and/or oxidation of the acyclic compounds remain impediments to broader molecular diversity.

At the inception of this study was an attempt to promote the Mannich coupling between dihydrocinamaldehyde **1a** and *N*-Cbz-α-tosylglycinate ester **2** which inadvertently led to 2-(3*H*)oxazolone **3a** in 25% yield (Eq. 1).



Simply promoted by nBu_4NF, the redox-neutral and convergent domino sequence gave 5-alkyl and 5-aryl-2-(3*H*)oxazolone-4-carboxylates from **2** and functionalized, aliphatic and aromatic, aldehydes (Scheme 1C). The role of **2** in this sequence was puzzling, reacting usually as a proelectrophile.[4,5] Interestingly, this study illustrates the ambivalent reactivity of **2** as a pronucleophile.

Scheme 2. Scope of the method



From the initial experiment (Eq.1), we set out to diminish the amount of **4** [6] and, to that end, the temperature of reaction was decreased (SI contains the detailed optimization). Pleasingly, operating at -60°C gave **3a** in 65% yield by reacting **1a** (1.5 equiv.) with **2** (1 equiv.) in the presence of nBu_4NF (2.5 equiv.). This result was improved by conducting the experiment with molecular sieves (4Å) and nBu_4NF (3 equiv.), yielding **3a** in 74% (Scheme 2). Switch to a less polar solvent (toluene) or modulating the ratio **1a/2** negatively or only marginally affected the efficiency of the sequence. As for the promotor, instead of nBu_4NF, a stronger base such as LiHMDS caused the decomposition of the reagents, whereas tetrabutylammonium difluorotriphenylsilicate (TBAT) left the starting materials unchanged.[7]

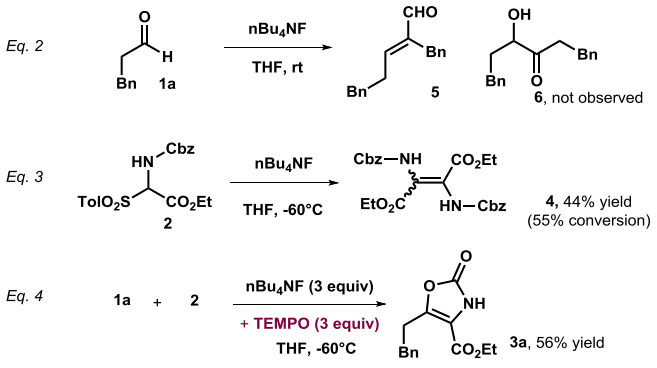
With a protocol in hand, we examined the scope of the method starting with primary aldehydes such as nonaldehyde and phenylacetaldehyde which were converted into **3b** (64%) and **3c** (54%). For the latter, it is noteworthy that the acidity of the aldehyde only moderately impacted the efficiency of the coupling compared to dihydrocinnamaldehyde (74% vs 54% yield). Further, oxazolone **3d** featuring an acid-sensitive acetal functional group was prepared in 61% yield from the monoprotected glutaraldehyde derivative. Since no oxidant is required to form the heterocycle, electron-rich functional groups are compatible as demonstrated with the preparation of **3e** (46%) from (*S*)-citronellal, containing a prenyl appendage. While 4-pentynal was found less compatible, the corresponding oxazolone **3f** was isolated in 21% yield,[8] electron-rich alkynylaryls such as 5-(*p*-tolyl)pent-4-ynal and the alkynylindole were efficiently combined with **2** into **3g** (82%) and **3h** (81%). In spite of the higher steric hindrance of secondary aldehydes, they still reacted with **2** as demonstrated with isopropyl and cyclopropyl substituted 2-(3*H*)oxazolones **3i** (47%) and **3j** (30%). The more functionalized *N*-Boc-4-piperidinecarboxaldehyde was converted into **3h** in 44% yield, an alkaloid of pharmaceutical pertinence.[1c] A limit was reached with tertiary aldehyde, as pivalaldehyde was found unreactive and, instead of the heterocycle, the sole production of **4** was noted. On the other hand, aromatic aldehydes reacted

well with **2** as observed with benzaldehyde and 4-cyanobenzaldehyde giving **3i** (42%) and **3j** (58%).[9] Interestingly, since the motif is easily hydrolyzed in acidic conditions, α-carboxaldehyde-α'-methoxy-γ-pyrone[10] was efficiently combined with **2** into **3n** (62%), a heterocycle sharing structure similarity with phenoxan, a natural product with anti-HIV and fungicide properties.[11] Moreover, a basic aromatic ring such as pyridine was smoothly combined with **2** into **3o** (65%). However, hindered and electronically-rich pyridines were less reactive and **3p** was assembled in 13% yield from **2** and the corresponding aldehyde.[8]

Eventually, α-chiral aldehydes were examined to assess the risk of racemization induced by the conditions of reaction. To that end, Garner's aldehyde was selected due to its tendency to racemize in presence of base. Pleasingly, 2-(3*H*)oxazolone **3q** was isolated without racemization (er = 99:1) in 22% yield after exposure of Garner's aldehyde to **2** in the standard conditions.[8] Although low, the unoptimized yield remains synthetically useful and reflects the challenge of forming C-C bonds from sterically hindered reagents. A less hindered chiral aldehyde, deriving from the Roche's ester, was more easily combined with **2** since 2-(3*H*)oxazolone **3r** was isolated in 37% yield. Incidentally, the bulky tButyldiphenylsilyl protecting group (TBDPS) was not removed in these conditions thus proving its compatibility with the method.

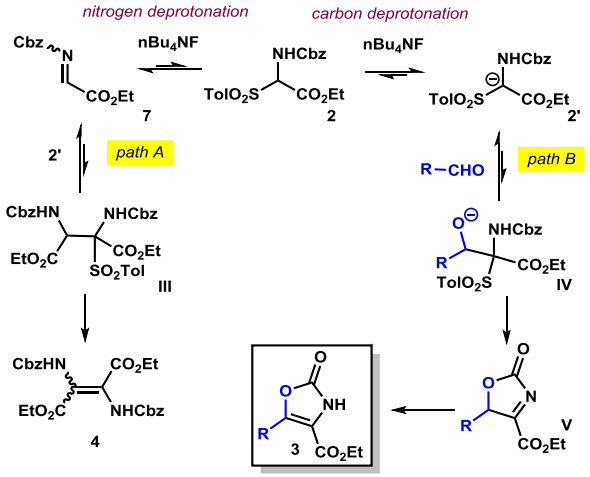
To gain an insight into the mechanism, **1a** was exposed to nBu_4NF in the absence of **2** (Scheme 3, Eq. 2), which led to enal **5** resulting from the self-aldolization/crotonisation process. Since the α-hydroxyketone **6** was not observed, an umpolung mechanism in which **1a** would act as nucleophile was thus ruled out. Moreover, exposure of **2** to these conditions (Eq. 3) led to **4** (44% yield, 55% conversion) demonstrating the ambivalent reactivity of **2**. To examine the possibility of a radical mechanism, we performed the coupling of **1a** with **2** (Eq. 4) in the presence of nBu_4NF (3 equiv.) and of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 3 equiv.), a scavenger of radical species. Since the outcome was not significantly impacted (65% vs 56% yield in **3a**), we surmised that an anionic mechanism was likely.

Scheme 3. Mechanistic perspective



Accordingly, **2** would act a nucleophile after carbon deprotonation into **2'**, a process in competition with the usual nitrogen deprotonation of **2** leading to imine **7** (Scheme 4). As observed in the presence of tertiary aldehyde, the coupling between **2'** and **7** becomes the major pathway (path A) leading to **4** via the Mannich adduct **III**. In the cases of primary and secondary aldehydes (path B), an aldolization occurs with **2'** forming the alcoholate **IV**, which after *p*-tolylsulfinate elimination and intramolecular addition of the alcoholate to the carbonyl of the Cbz group would give 2-(5*H*)oxazolone **V**. Subsequent isomerization of **V** would follow, ultimately affording 2-(3*H*)oxazolone **3**. The success of the whole sequence probably relies on the addition of the alcoholate to the carbamate shifting the series of equilibrium to **V**, this step being facilitated by the non-coordinating nature of the quaternary ammonium.[12] The fact that the process failed when the Cbz group of **2** was replaced by the more hindered Boc group gives credit to this assumption.[13] As an illustration of the competition between the paths A and B, a small amount of **4** was observed when primary aldehydes were reacted while the production of **4** was significant with secondary aldehydes and predominate when a tertiary aldehyde was engaged.

Scheme 4. Postulated mechanism



Simpler and advanced synthetic processes are urgently and continuously sought for and, in this context, a convergent synthesis of various 5-alkyl and 5-aryl-2-(3*H*)oxazolone-4-carboxylates was developed. Within the competition between *C*- or *N*-deprotonation of **2** with nBu_4NF, the unprecedented sequence begins with the aldolization reaction of **2'** which, despite being sterically hindered, reacted with a good variety of aldehydes, the main limitation of the method being the steric hindrance of the electrophile. Since no oxidation step or acidic conditions are needed, aldehydes with electron-rich, acid-sensitive or pyridinyl appendages were successfully converted into 2-(3*H*)oxazolones from **2**, which can be prepared in large scale and in one step. Furthermore, because 2-(3*H*)oxazolones are known intermediates en route to oxazoles[14] or oxazolidinones,[3a] this method may have a bearing on the synthesis of these motifs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General procedure and characterizations of each compounds, as well as optimization of the procedure, variations of the reagents and copies of ^{1}H, ^{13}C NMR spectra and HPLC, GC traces. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **3a-r** and **4b**.

AUTHOR INFORMATION

Corresponding Author

* Michael.depaolis@univ-rouen.fr

Authors

Masahiro Abe – *current address, School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, 11-68, 9-Bancho, Koshien, Nishinomiya, Hyogo 663-8179, Japan*

Baptiste Picard – *Normandie Univ, UNIROUEN, COBRA, INSA Rouen, CNRS, COBRA, 76000 Rouen, France*

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[7] KHMDS, DMAP, DABCO and NaH were also tested as promoter with various outcomes. See SI for details.

[8] Unoptimized yield. The conversion of **2** was total and compound **4** was the major product of the reaction.

[9] Cinnamaldehyde, *trans*-2-bromo-3-(2-nitrophenyl)acryl aldehyde and 2-nitrobenzaldehyde were found unreactive, as well as $PhCOCF_3$.

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[12] Why nBu_4NF gave the best results in the series of bases was not investigated, but combined effects may explain the superiority of the promotor. Hence, while the mild basicity of the reagent is important, the reactivity of anionic species such as **2'** and alcoholate **IV** is also enhanced by non-coordinating organic cations such as nBu_4N^+.

[13] Other pronucleophiles with modulations of the substituents were tested without success, see SI for details.

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