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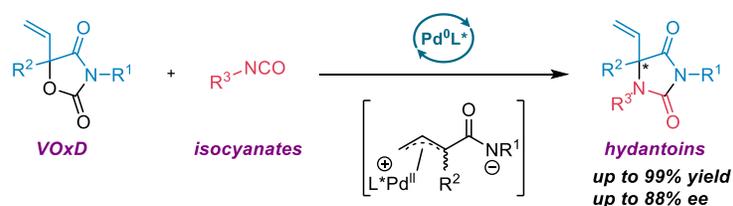
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Cycloadditions of 5-Vinylloxazolidine-2,4-diones: A Straightforward Access to the (thio)Hydantoin Scaffold

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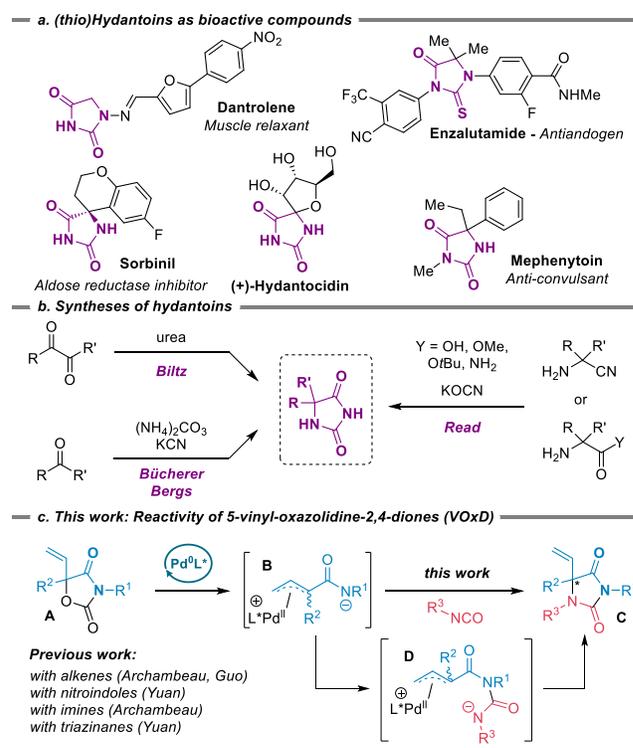
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ABSTRACT: A palladium-catalyzed (3+2) cycloaddition between 5-vinylloxazolidine-2,4-diones (VOxD) and (thio)isocyanates is described. Under optimized conditions, an array of (thio)hydantoin was readily prepared and an enantioselective version of this transformation was then studied. To illustrate the importance of this method, a concise synthesis of two bioactive compounds, nirvanol and mephenytoin, was carried out. This work emphasizes the synthetic potential of VOxD as useful precursors of zwitterionic aza- π -allylpalladium^{II} intermediates.

Hydantoin is a ubiquitous structure in medicinal chemistry and their imidazolidine-2,4-dione skeleton is encountered in natural products (hydantocidine, parazoanthine...) and many small molecules drugs displaying a variety of biological activities such as mephenytoin (anticonvulsant), dantrolene (muscle relaxant), or sorbinil (aldose reductase inhibitor).¹ Thiohydantoin skeletons are also encountered within marketed API and enzalutamide display antiandrogen activities (Scheme 1a).² Besides these important properties, hydantoin has also found application in synthetic chemistry and can notably act as interesting substrate to access α -amino acids.³ As a widely encountered scaffold,⁴ 5- and 5,5'-substituted hydantoin can be accessed through various synthetic pathways such as the Bücherer-Bergs (from aldehydes or ketones),⁵ Read (from amino acid derivatives)⁶ or Biltz (from 1,2-diketones) transformations (Scheme 1b).⁷ To access 5,5'-substituted hydantoin, substitution at the C₅ position is also a reliable strategy which has recently aroused curiosity among several organic chemists.⁸ Despite these developments, the known enantioselective methods very often apply to the preparation of monosubstituted 5-(thio)hydantoin, often relying on the hydrogenation of exocyclic alkenes.^{8d,9} On the opposite, strategies displaying the *de novo* preparation of enantioenriched 5,5'-hydantoin from small, linear and achiral precursors are still scarce.¹⁰

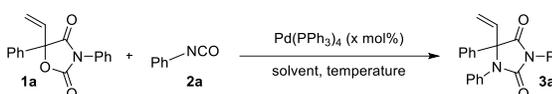
Scheme 1. Relevance and preparation of hydantoin



Having made these observations, we anticipated that cycloaddition of zwitterionic π -allylpalladium^{II} intermediates could be a reliable strategy to access these important scaffolds. After the seminal work of Trost and Tsuji on Pd⁰-catalyzed cycloadditions of trimethylenemethanes¹¹ and vinylcyclopropanes,¹² respectively, this approach has proven to be a dependable pathway toward numerous carbo- and heterocycles.¹³ Furthermore, the installation of chiral ligands on the metal center unlocked access to enantioenriched structures. In this way, numerous precursors of zwitterionic aza- π -allylpalladium^{II} intermediates have been devised by several research groups such as vinylbenzoxazinones,¹⁴ vinylcarbamates,¹⁵ trimethylenecarbamates,¹⁶ or vinylaziridines.¹⁷ Recently, Guo and our group concomitantly disclosed 5-vinyl-oxazolidine-2,4-diones **A** (VOxD) a promising precursor of intermediate **B**, acting as a C–C(=O)–N synthon in cycloadditions with electrophilic alkenes.¹⁸ We then extended this reactivity to electrophilic imines¹⁹ and the group of Yuan reported the cycloaddition of other partners such as triazinanes²⁰ and nitroindoles.²¹ In this manuscript we report the preparation of 5,5'-disubstituted (thio)hydantoin **C** by (3+2) cycloaddition of VOxD with electrophilic isocyanates.

To begin this study, VOxD **1a** (R¹ = Ph, R² = Ph) and phenylisocyanate **2a** were selected as test substrates. Using Pd(PPh₃)₄ (10 mol%) as a catalyst, we were pleased to observe the formation of hydantoin **3aa** in a satisfactory yield of 82% with acetonitrile as the solvent (Table 1, Entry 1, 70 °C). While screening various solvents, we identified THF (40 °C, 94%) and DCM (rt, 93%) as suitable solvents for this transformation, furnishing the expected hydantoin in excellent yields even at lower temperatures (Table 1, Entries 3-7). Our next endeavor was to lower the catalyst loading and we quickly discovered that 2 mol% of Pd(PPh₃)₄ were sufficient to afford the desired heterocyclic product, albeit in lower yields (Table 1, Entries 8-11). However, increasing the temperature to 70 °C in THF led to a smooth conversion (3 h) of the starting materials while maintaining a high yield of 91% (Table 1, Entry 12).

Table 1. Optimization of a racemic version.^a



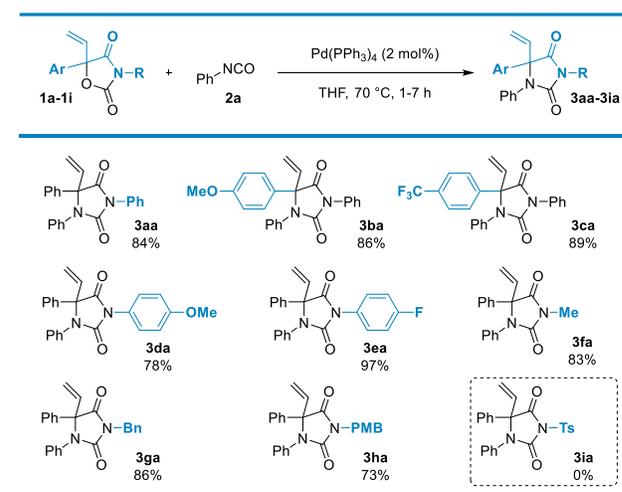
Entry	(x)	Solvent	T (°C)	t	Yield ^b
1	10	MeCN	70	1 h	82
2	10	DCE	70	1 h	98
3	10	DCM	40	1 h	98
4	10	DCM	rt	2 h	93
5	10	THF	70	1 h	99
6	10	THF	40	0.5 h	94
7	10	THF	rt	2 h	79
8	5	DCM	rt	21 h	90
9	5	THF	40	2 h	88
10	2	DCM	rt	23 h	23
11	2	THF	40	21 h	65
12	2	THF	70	3 h	91

^aReaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), Pd catalytic system in solvent (0.5 mL). ^bNMR yields using 1,3,5-trimethoxybenzene as internal standard.

With these optimized conditions in hand, we pursued with the investigation of the reactivity of several VOxD nucleophilic cycloaddition partners **1** with phenyl isocyanate **2a**. These reactions were run on a 0.2 mmol scale and hydantoin **3aa** was then isolated in a satisfactory yield of 84%. Substitution of the phenyl group located at the allylic position by a methoxy electron-donating group or a trifluoromethyl electron-withdrawing group afforded the corresponding hydantoins **3ba** (86%) and **3ca** (89%) with very little influence on the outcome of the cycloaddition. Similarly, the phenyl group attached to the nitrogen atom was replaced by an electron-rich (*p*-OMe-C₆H₄) or an electron-poor (*p*-F-C₆H₄) aromatic ring and hydantoins **3da** (78%) and **3ea** (97%), respectively, were obtained in good yields.

The mechanism described in Scheme 1 highlights the importance of this R¹ group carried by the nitrogen atom of the VOxD. Indeed, a more electron-donating group will decrease the rate of the decarboxylation step while allowing the formation of a more nucleophilic zwitterionic intermediate **B**. Under the same reaction conditions, we were glad to observe the smooth formation of hydantoins **3fa** (83%), **3ga** (86%) and **3ha** (73%) bearing a methyl, benzyl and *para*-methoxybenzyl group, respectively. Conversely, the decarboxylation step is favored when R is electron-withdrawing but the resulting intermediate is now less electrophilic. This observation could rationalize why VOxD **1i** (R = Ts) proved unreactive under these conditions (Scheme 2).

Scheme 2. Scope of the VOxD partner.^a

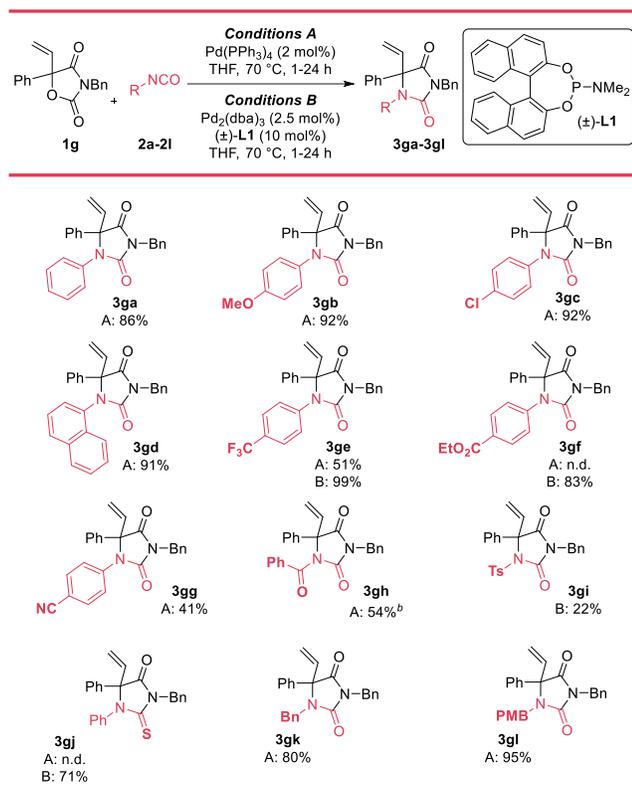


^a**1** (0.2 mmol), **2** (0.24 mmol), Pd(PPh₃)₄ (2 mol%), THF (2 mL, 0.1M), 70 °C.

We then turned our attention to the reactivity of various isocyanate electrophilic cycloaddition partners **2** with the same VOxD **1g** (*N*-Bn). In addition to phenyl isocyanate, other aryl isocyanates were tolerated and aryl isocyanates **2b** (R = *p*-OMe-C₆H₄) and **2c** (R = *p*-Cl-C₆H₄) were smoothly converted to the corresponding hydantoins **3gb** (92%) and **3gc** (91%). These reactions conditions also accommodated sterically hindered aryl group and hydantoin **3gd** (R = 1-naphthyl) was isolated in 92% yield. However, a sluggish reactivity was observed when electron-deficient aryl isocyanates were submitted under the same reaction conditions (conditions A). The transformation of **2e** (R = *p*-CF₃-C₆H₄) afforded hydantoin **3ge** in a moderate yield of

51% and remaining starting materials were still present in the crude mixture. After further optimization, we were glad to observe the efficient formation of **3ge** (99%) when using an achiral phosphoramidite (\pm)-**L1** and Pd₂dba₃ as the metal source (conditions B). The same behavior was observed with the ester-substituted hydantoin **3gf** which could only be prepared using conditions B. Surprisingly, although conditions A allowed the preparation of **3gg** (R = *p*-CN-C₆H₄) in a moderate yield (41%), no conversion of **2g** was noted under conditions B. However, conditions B were necessary to prepare *N*-Bz (5 mol% of catalyst) and *N*-Ts hydantoin **3gh** (79%) and **3gi** (22%), respectively, although this latter was isolated in a low yield. Our method also proved efficient to access 2-thiohydantoin **3gj** (71%) from phenyl isothiocyanate. Finally, electron-rich isocyanates were also tolerated. Under conditions A, hydantoin **3gk** (76%) and **3gl** (95%) derived from benzyl isocyanate and *p*-methoxybenzyl isocyanate were generated in very good yields.

Scheme 3. Scope of the isocyanate partner.^a

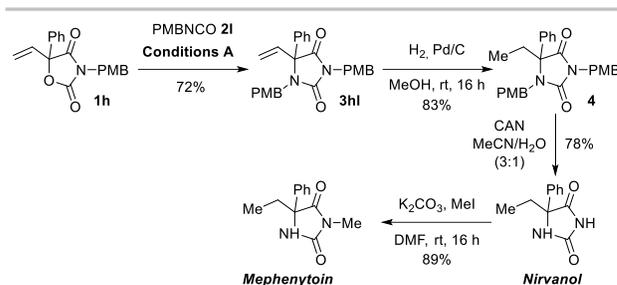


^aReaction conditions A: **1** (0.2 mmol), **2** (0.24 mmol), Pd(PPh₃)₄ (2 mol%), (2 mL, 0.1M), 70 °C. Reaction conditions B: **1** (0.2 mmol), **2** (0.24 mmol), Pd₂(dba)₃ (2.5 mol%), ligand (\pm)-**L1** (10 mol%), THF (2 mL, 0.1M), 70 °C. ^b5 mol% of Pd(PPh₃)₄ was used.

To highlight the synthetic potential of our methodology, we performed a straightforward synthesis of nirvanol and mephenytoin, two molecules with anticonvulsant activities.²² VOxD **1h** was treated under conditions **A** in the presence of *p*-methoxybenzylisocyanate **2i** to afford hydantoin **3hi** whose two nitrogens are substituted by a PMB group. This latter was submitted to a catalytic hydrogenation (H₂, Pd/C) to generate **4** after reduction of the terminal alkene group. It is worth pointing out that the two *p*-methoxybenzyl groups proved resistant to these conditions (the same behavior was observed with benzyl

groups) and a double deprotection under oxidative conditions (CAN, MeCN/H₂O) afforded (\pm)-nirvanol. Finally, (\pm)-mephenytoin was prepared from nirvanol after a selective methylation (K₂CO₃, MeI) of the most acidic N-H group (Scheme 4).

Scheme 4. Further synthetic transformations toward bioactive compounds.

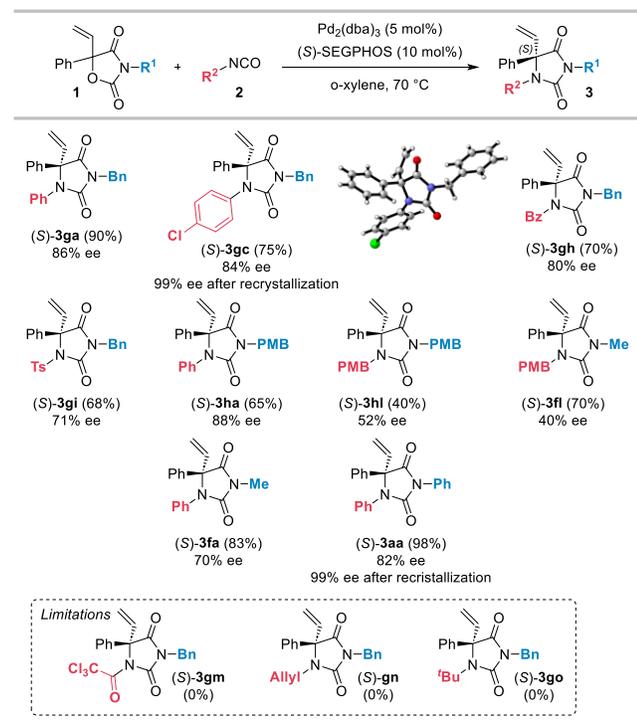


An asymmetric version of this transformation was tested out using chiral ligands of the palladium. After an optimization of the reaction conditions,²³ we managed to isolate (*S*)-**3ga** in excellent yield and good enantioselectivity (86% *ee*) using Pd₂(dba)₃ as the Pd⁰ source and (*S*)-SEGPHOS as the chiral ligand (*o*-xylylene, 70 °C). The absolute (*S*) configuration of the newly formed stereocenter was assigned by XRD analysis after preparation of hydantoin (*S*)-**3gc** bearing a *para*-chlorophenyl group on the N₃ atom.²⁴ This (3+2) cycloadduct was prepared with a satisfactory 84% enantiomeric excess but the major isomer could be isolated after recrystallization in Et₂O (99% *ee*). *N*-benzyl VOxD **1g** was treated under the same conditions in the presence of electron-poor benzoyl and tosyl isocyanates **2h** and **2i**. The corresponding hydantoin **3gh** (70%, 80% *ee*) and **3gi** (68%, 71% *ee*), respectively, were generated in moderate to good enantiomeric excess. Through our synthesis of nirvanol and mephenytoin, we demonstrated the synthetic potential of *para*-methoxybenzyl groups as they can be removed using usual oxidative conditions. The cycloaddition of VOxD **1h** (R¹ = PMB) with phenylisocyanate yielded the corresponding hydantoin in a good yield (65%) and enantiomeric excess (88% *ee*). The putative hydantoin precursors of nirvanol and mephenytoin (*S*)-**3hi** (40%, 52% *ee*) and (*S*)-**3fi** (70%, 40% *ee*) could be prepared in moderate to good yields but unfortunately with unsatisfactory enantiomeric excess. In the presence of the same catalytic system, phenylisocyanate can also react with VOxD **1f** (R¹ = Me) and **1a** (R¹ = Ph) to access hydantoin (*S*)-**3fa** (70% *ee*) and (*S*)-**3aa** (82% *ee*) with good enantioselectivity. Interestingly, the major enantiomer of the latter hydantoin could be isolated (99% *ee*) after recrystallization in Et₂O. We also encountered the limitations of this method as no cycloaddition product was observed when VOxD **1g** (R¹ = Bn) was treated with trichloroacetyl, allyl or tert-butyl isocyanate.

It is worth pointing out that our method furnishes hydantoin (3+2) cycloadducts in lower enantioselectivity when compared with our previous work regarding the cycloaddition of activated alkenes or imines.^{18,19} This observation could be explained when having a closer look at the stepwise mechanism of this transformation. After a ring-opening oxidative addition of Pd⁰ and decarboxylation, the nucleophilic zwitterionic intermediate **B** is formed and can then add to the electrophilic cycloaddition partner to access the new zwitterion **D** (Scheme 1). In the case of activated alkenes, imines or 3-nitroindoles, this addition is

reversible and several diastereomers could be obtained and the equilibrium between the different reaction intermediates allows for an excellent enantioselectivity.²⁵ The situation is different in the case of isocyanates. When the stereodetermining step is obviously still the cyclization step, the irreversibility of the initial nucleophilic addition likely hampers the efficiency of this DYKAT process.

Scheme 5. Development of an enantioselective version.^a



^a1 (0.2 mmol), 2 (0.3 mmol), Pd₂dba₃ (5 mol%), (S)-SEGPHOS (10 mol%), *o*-xylene (2 mL, 0.1M), 70 °C.

To conclude this study, we established VOxD as suitable precursors of the C-(C=O)-N synthon for the straightforward preparation of various (thio)hydantoin heterocycles. This cycloaddition with isocyanates generally proceeds in good yields and allows the preparation of various substituted heterocycles. An asymmetric version of this transformation was proposed.

ASSOCIATED CONTENT

Supporting Information

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

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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