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Wei-Yang Ma, Coralie Gelis, Damien Bouchet, Pascal Retailleau, Xavier Moreau, et al.. Chiral Phosphoric Acid-Catalyzed Enantioselective Construction of 2,3-Disubstituted Indolines. *Organic Letters*, 2021, 23 (2), pp.442-448. 10.1021/acs.orglett.0c03947 . hal-03238222

HAL Id: hal-03238222

<https://hal.science/hal-03238222v1>

Submitted on 27 Jul 2021

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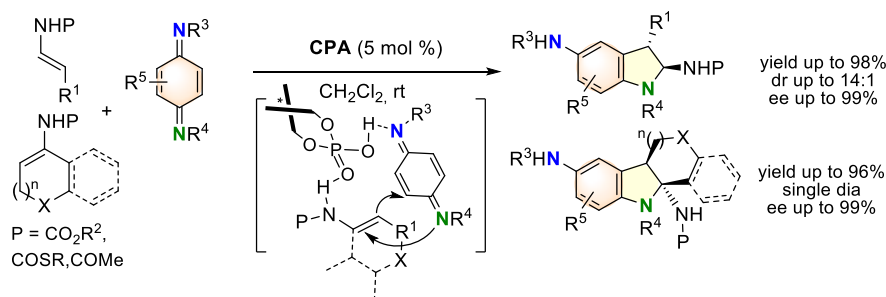
Chiral Phosphoric Acid Catalyzed Enantioselective Construction of 2,3-Disubstituted Indolines.

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Supporting Information Placeholder



ABSTRACT: Highly enantio- and regioselective selective (3 + 2) formal cycloaddition of β -substituted enes and thioenecarbamates as well as cyclic enamides with quinone diimides catalyzed by a BINOL- and SPINOL-derived phosphoric acid has been reported. A wide variety of 2-amino 2,3-disubstituted indolines, including polycyclic ones, were prepared in generally high yields (up to 98%) with moderate to complete diastereoselectivities and in most cases excellent enantioselectivities (up to 99% ee).

Chiral 2,3-disubstituted indolines are privileged heterocyclic rings frequently encountered in various natural bioactive alkaloids (such as (-)-physostigmine, (+)-aspidospermine and picrinine, Figure 1)¹ and biologically active drugs (such as pentopril and relcovaptan).² In addition, they have been successfully employed as chiral auxiliaries and organocatalysts in asymmetric synthesis.³ As a result, several asymmetric catalytic approaches have been established for the construction of indoline rings.⁴ Despite these elegant achievements, the development of novel asymmetric synthetic routes of 2,3-disubstituted indolines is still highly desirable.

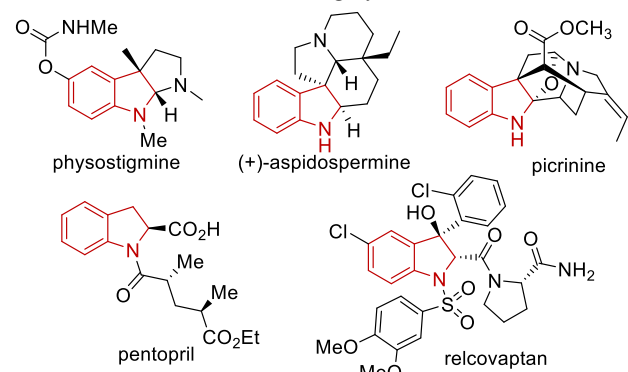
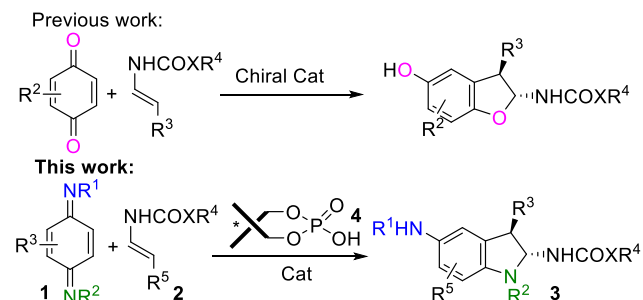


Figure 1. Representative bioactive indolines and its derivatives.

(3 + 2) Cycloaddition is one of the most convergent methods for the synthesis of five-membered heterocycles fused with aromatic rings.⁵ More specifically, (3 + 2) formal cycloaddition

of quinones (or quinone monoimines) with electron rich alkenes affords a convenient synthesis of dihydrofurans, oxygen analogue of indolines.^{4r,6,7} The aza variant⁸ of this reaction using quinone diimides⁹ to produce indolines has not been well explored. Furthermore, in these examples, there are few methods to synthesize 2,3-disubstituted indolines.^{8d,e} Indeed, while the chemistry of quinone diimides is rich, their unfriendly preparation (often relying on lead tetraacetate), their sensitivity towards hydrolysis of the carbon–nitrogen double bond, their redox properties leading to self-rearomatization or oxidative coupling¹⁰ hampers their wide use.¹¹ In this context, it is not surprising, that catalytic enantioselective transformation involving quinone diimides remains extremely rare.¹² To the best of our knowledge, only one example of enantioselective, cycloaddition involving *p*-quinone diimides has been recently reported.^{4x} We describe here the development of chiral

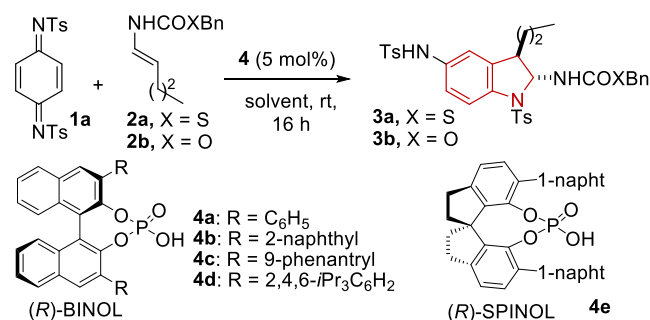
Scheme 1. Catalytic enantioselective formal (3+2) cycloaddition with quinone derivatives.



phosphoric acid (CPA)-catalyzed enantioselective (3 + 2) formal cycloaddition of quinone diimides and enecarbamates providing a simple and practical access to 2,3-disubstituted indolines (Scheme 1).

We have previously reported a CPA-catalyzed enantioselective (3 + 2) cycloaddition reactions of quinones with ene- and thioenecarbamates.^{7a} The reaction has a broad scope, offering 2,3-disubstituted 2-amino-2,3-dihydrobenzofurans with high enantioselectivity. The diastereoselectivity was highly dependent on the protecting groups on the nitrogen atom of the dipolarophiles: the thiocarbamates gave high selectivity in favor of *trans* isomer while the reactions with the enecarbamates were poorly diastereoselective. On the basis of our previous work,^{7a,13} we initially investigated the reaction between *p*-quinone di-*p*-toluenesulfonimide (**1a**) and (*E*)-thioenecarbamate **2a**, in presence of a CPA catalyst (Table 1).¹⁴

Table 1. Optimization of catalytic enantioselective synthesis of indolines.^a



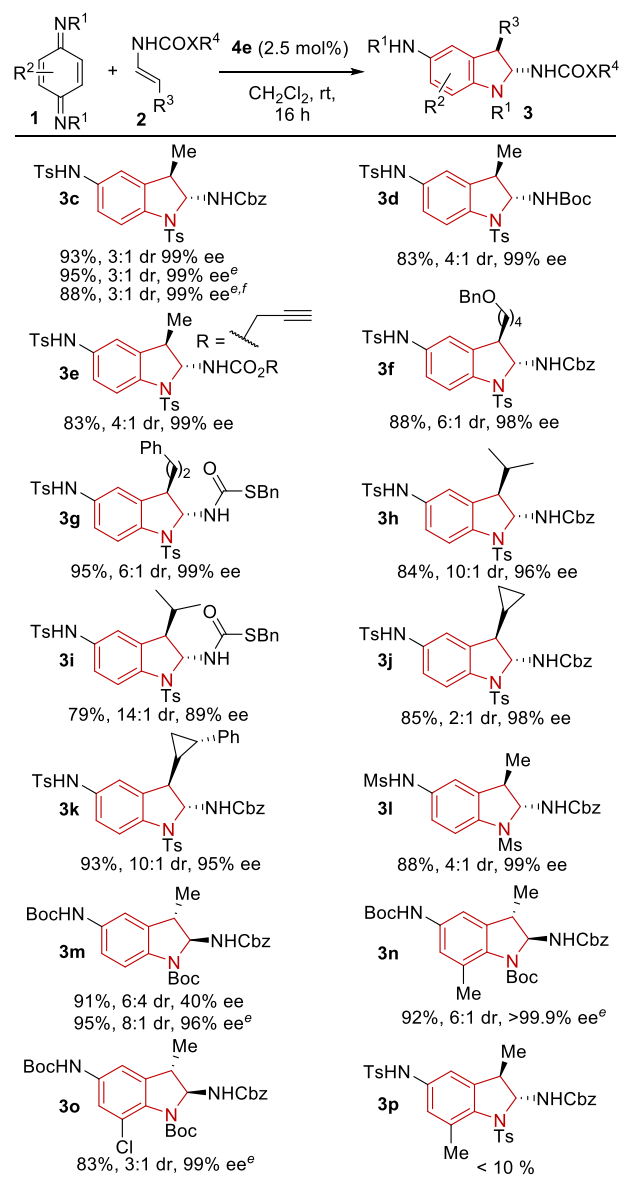
entry	cat	2	solvent	yield (%) ^b	dr ^c	ee (%) ^{d,e}
1	4a	2a	toluene	93	5:1	(+) 34
2	4b	2a	toluene	91	5:1	(+) 32
3	4c	2a	toluene	66	5:1	(+) 43
4	4d	2a	toluene	92	5:1	(+) 98
5	4e	2a	toluene	91	5:1	(-) 98
6	4d	2a	CH ₂ Cl ₂	98	6:1	(+) 98
7	4e	2a	CH ₂ Cl ₂	93	6:1	(+) 98
8	4d	2a	CH ₂ Cl ₂	72 ^f	6:1	(+) 98
9	4e	2a	CH ₂ Cl ₂	93 ^f	6:1	(-) 98
10	4e	2b	CH ₂ Cl ₂	94	6:1	(-) 94

^a General condition: **1a** (0.10 mmol), **2a** (0.12 mmol) and **Cat** (5 mol%) in solvent (0.1 M) at rt for 16 h. ^b Yield of isolated pure product after chromatography. ^c Determined by ¹H NMR. ^d (+) refers to absolute (2*S*, 3*S*) configuration, (-) refers to (2*R*, 3*R*) configuration, assigned by analogy to X-ray crystal-structure analysis of **3c** (see Supporting Information). ^e Determined by HPLC analysis on a chiral stationary phase. ^f With 2.5 mol% of **4**.

Pleasingly, the desired 2-amino-2,3-disubstituted indolines **3a** was obtained in high yield albeit with moderate selectivity by using 5 mol% of **4a** as the catalyst in toluene at room temperature for 16 h (entry 1). To increase both diastereo and enantioselectivity of this reaction, a series of CPA catalysts **4** were evaluated (entries 1-5). The catalyst **4d** bearing 2,4,6-triisopropylphenyl groups at the 3,3'-position of BINOL, as well as **4e** from SPINOL having a 1-naphthyl group at the 6,6'-position **4e** provided the desired product in much better enantioselectivity (98% ee, entries 4 and 5) but the

diastereomeric ratio was not significantly influenced by catalyst choice. A slight increase in the *trans*-diastereoselectivity was observed with CH₂Cl₂ as solvent (entry 6 vs 4). On one side, reducing catalyst loading of **4d** to 2.5 mol% leads to a reduction in yield (entry 8 vs 6). On the other side, no activity loss was noted when 2.5 mol% of **4e** was used (entry 9 vs 7), thereby providing conditions that were selected for further investigations. When we conducted the reaction with the enecarbamate **2b**, the corresponding cycloadduct **3b** was formed in similar diastereo- and enantioselectivity than **2a**, thus indicating (contrary to our previous work)^{7a} that the protecting group of **2** did not have too much influence on the stereoselectivity. Other solvents such as CHCl₃, CH₃CN, THF and toluene were evaluated to improve the diastereoselectivity.

Scheme 2. Scope of the enantioselective (3 + 2) formal cycloaddition.^{a-d}



^a General condition: **1** (0.10 mmol), **2** (0.12 mmol) and **4e** (2.5 mol%) in CH₂Cl₂ (0.1 M) at rt for 16 h. ^b Yield of isolated pure product after chromatography. ^c ee Determined by HPLC analysis on a chiral stationary phase. ^d dr determined by ¹H NMR. ^e With 5 mol% of **4d**. ^f With 1 mmol of **2**.

(See supporting information). Although a higher diastereomeric ratio was only found in THF (8:1), yield was reduced substantially.¹⁵ All attempts to separate the diastereomers were unsuccessful.

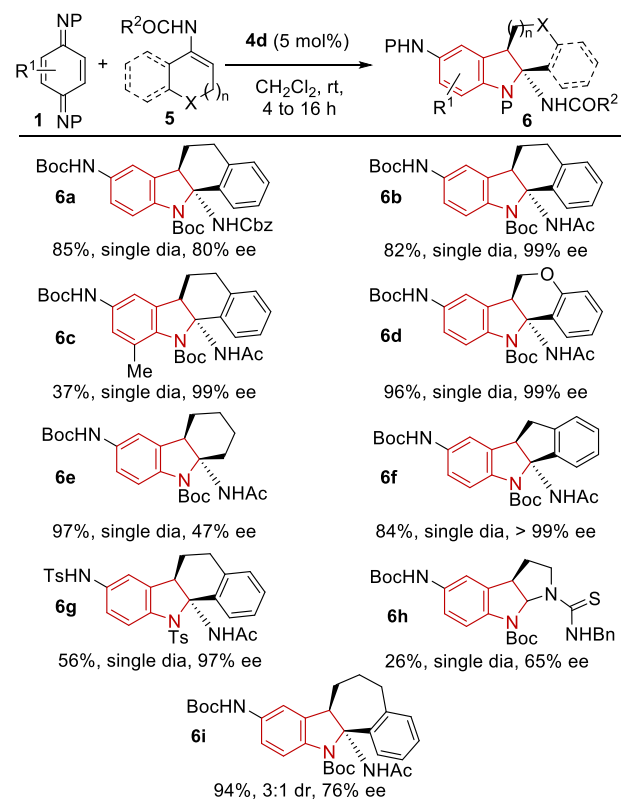
Having identified the optimum conditions (Table 1, entry 9), we explored the generality of the reaction by employing different enecarbamates. In general, the reactions worked well for selected protecting groups bonded to the nitrogen of **2**, including benzyloxy, prop-2-yn-1-yl and tert-butoxy carbamates. A range of linear β -substituted ene- and thioenecarbamates **2** reacted successfully, affording the corresponding 2-aminoindolines **3c-3k** in high yields with excellent enantioselectivities. The additional benzyl ether functional group was well tolerated on enecarbamate providing cycloadduct **3f** with good enantioselectivity. The enecarbamate bearing an ethyl-benzene side chain also furnished a high level of enantioselectivity (**3g**: 99% ee). To our satisfaction, ene- and thioenecarbamate substituted by isopropyl group at the β -position furnished compound **3h** and **3i** with an excellent diastereoselectivity (10:1 to 14:1) possibly revealing a significant substrate control effect. However, slight decrease of enantioselectivity was observed with the thioenecarbamate compared to the enecarbamate. Surprisingly, performing the reaction with a unsubstituted cyclopropyl side chain instead of an isopropyl group, lead to a drastic reduction in diastereoselectivity but enantioselectivity was kept high (**3j**, 2:1 dr, ee: 98%). Only trace of product was formed with enecarbamate bearing phenyl group at the C-2 position (data not shown). Presence of an enantiopure predefined chiral center on the enecarbamate moiety did not interfere with catalyst induction. Hence, compound **3k** was prepared in 93% yield and in 95% ee with a satisfactory 4:1 diastereoselectivity relatively to the 2 newly formed chiral centers.

Alternative quinone diimines bearing various protecting group and substituents were also investigated. On the one hand, dimethylsulfonamide uneventfully participated in the cycloaddition, giving **3l** with 99% ee. On the other hand, carboxybenzyl or acyl bis-protected diimines were not suitable partner for the transformation (data not shown).¹⁶ It was however possible to move away from sulfonyl-type protection as Boc-protected quinone diimine delivered compound **3m** in excellent yield. Regarding to enantioselectivity, SPINOL-derived CPA **4e** was far from ideal for such precursors. A brief optimization revealed that **4d** was suitable for high enantioselective induction (See Supporting Information). These Boc protected imines also tolerated substituent on the quinone core. As such, methyl and chlorine were fully tolerated delivering compound **3n** and **3o** as single regioisomers in good yields and enantioselectivities. This is particularly noteworthy as corresponding methyl bis-tosyl imine was reluctant in forming compound **3p**.¹⁶ Boc quinone diimides having stronger electron withdrawing group such as NO₂ group were not stable enough to perform the reaction (data not shown).¹⁶ We also demonstrated that the reaction could be easily performed on a 1.0 mmol scale, preparing cycloadduct **3c** with **4d** as catalyst in similar yield and selectivity than on a smaller scale, thus demonstrating the practicality of this process (Scheme 2).

Reaction could be further extended to the synthesis of polycyclic structures using cyclic enecarbamates and, tetrahydro-11a*H*-benzo[*a*]carbazol-11a-amide (**6a**) was obtained from the corresponding benzyl (3,4-dihydronaphthalen-1-yl)carbamate (**5a**) and Boc-protected

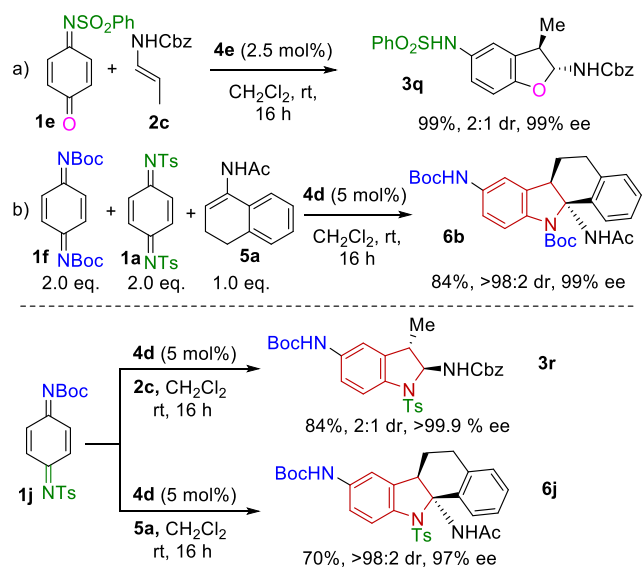
quinone diimine **1f** (Scheme 3). Refinement of reaction conditions, namely using 2.0 eq of Boc quinone diimide under otherwise identical settings, significantly improved the outcome of the reaction furnishing the desired product as a single diastereoisomer in 85% yield and 80% ee. Cyclic acetamides^{7e,17} derived from dihydronaphthalene, indene and 2*H*-chromene behaved particularly well in the transformation, furnishing compound **6b**, **6d** and **6f** in yields ranging from 82 to 96%, each time as a single diastereoisomer and with near perfect enantioselectivity ($\geq 99\%$). Presence of a ring-fusion in acetamides seems to be an important factor to achieve high enantioselectivity. Indeed, while *N*-(cyclohex-1-en-1-yl)acetamide allowed the synthesis of compound **6e** in excellent yield, only modest enantioselectivity was observed in this case. Achieving the synthesis of highly enantio-enriched adduct **6c** from methyl substituted Boc-quinone diimine, albeit in modest yield, is noteworthy since substitution on monoimide quinoids is reported to hamper reactivity.^{7e} Initial evaluation of tosyl-protected quinone diimine **1a** with cyclic enamide was sluggish and long. Solubility issue was identified as the main problem, and upon simple dilution (x4), **6g** could be isolated in satisfying yield. Furthermore, less reactive cyclic enethiourea^{13b} could also react with Boc quinone diimide to form a single diastereomer **6h** with excellent diastereoselectivity albeit with modest yield and enantioselectivity. Finally, the 7-membered cyclic enamide **5g** was successfully employed in the present reaction, affording the expected cycloadduct **6i** in 94% yield with 3:1 dr and 76% ee.

Scheme 3. Enantioselective (3 + 2) formal cycloaddition with cyclic enes.^{a-d}



^a General condition: **1** (0.10 mmol), **5** (0.20 mmol) and **4d** (5 mol%) in CH₂Cl₂ (0.1 M) at rt for 16h. ^b Yield of isolated pure product after column chromatography. ^c ee Determined by HPLC analysis on a chiral stationary phase. ^d dr determined by ¹H NMR.

Scheme 4. Chemoselectivity of the enantioselective (3 + 2) formal cycloaddition.^{a-d}



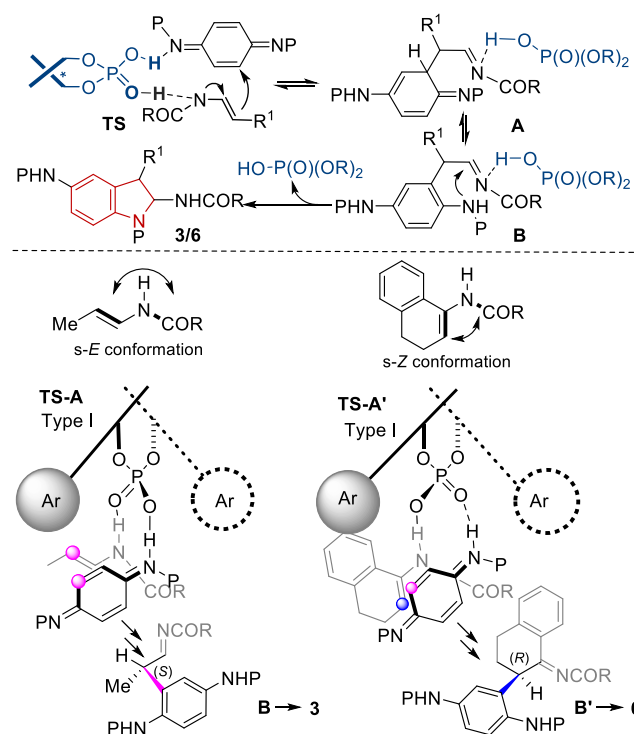
As we could expect, the dihydrofuran **3q** was obtained as sole regioisomer when reacting quinone monoimine **1e** with enecarbamate **2c** (Scheme 4, a),^{7b-d} Complete selectivity was also observed when opposing an equal amount of bis-Boc and bis-tosyl protected imines (**1f**, **1a**) to a limiting amount of cyclic enamide **5a**, furnishing exclusively compound **6b** (Scheme 4, b). Such a selectivity was not a simple consequence of solubility and could be further exploited for the selective synthesis of hetero protected compound **3r** and **6i** from the single hetero protected quinone diimine **1j**. While higher azaphilicity of phosphoric acids compared to oxaphilicity is well-known,^{7b,d,e,13e} these results also establish a relative affinity of such catalyst to differently *N*-protected species. To the best of our knowledge, it represents the first example in which CPAs were able to differentiate two common nitrogen protecting groups in enantioselective reaction.

Based on our^{7a} and other works,^{7b,d,e} a possible mechanism (Scheme 5) can be proposed, comprising the following steps: Michael addition, isomerization and intramolecular amination. This stepwise process is supported by the observation in the crude ¹H NMR spectra of aldehyde traces arising from hydrolyzed imine intermediate **6**. Then, we became interested in pursuing control experiments to propose a possible stereochemical model. No reaction occurred when either acyclic or cyclic tertiary enecarbamates (**2m** or **2n**, respectively) were employed as dipolarophile (Scheme 6). This suggests that the NH group of **2/6** plays a crucial role in the successful activation for the cycloaddition to proceed smoothly. In addition, the reaction of **1a** with β,β -disubstituted enecarbamate **2o** in the presence of **4e** affords the corresponding cycloadduct **3s** in nearly racemic form. This result rules out the possibility that catalyst maintained a hydrogen-bond with imine intermediate **B** to control the asymmetric induction of the hemiaminal stereogenic center.

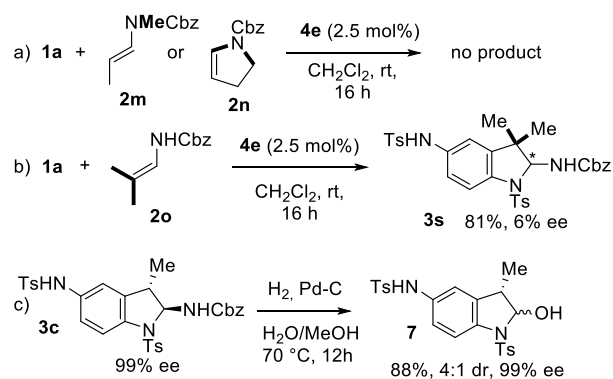
X-Ray diffraction of **3c** allowed us to determine the absolute configuration of both diastereoisomers obtained with (*R*)-**4d** catalyst. *Trans*-isomers with (2*S*, 3*S*) configuration was assigned for the major diastereoisomer while the one of minor *cis*-isomer was found to be (2*R*, 3*S*). Absolute configurations of **6b** and **6g** were also elucidated by X-ray analysis and found to

be (6*aR*, 11*aS*), thereby highlighting that protecting group did not change the sense of selectivity. Based on these results, two transition state model **TS-A** and **TS-A'** in which both substrates are activated at the same time by the catalyst, with the formation of a double hydrogen bonding, can be proposed. According to Goodman's proposal,¹⁸ electrophiles and nucleophiles can be placed following type I or type II arrangement. However, minimizing steric clash with geometrically defined enes and keeping in mind that reacting centers of the nucleophile and the electrophile must be in close proximity for reactivity, allows building two favorable arrangement of type I. (see also supporting information). As such, the acyclic enecarbamate would attack from quinone diimide *Re*-face, while cyclic derivative would attack from their *Si*-face using (*R*)-**4d**. Following a possible partial decomplexation, tautomerization would lead to intermediate **B/B'** in which aniline would attack the acyl iminium leading to final compound.

Scheme 5. Plausible reaction mechanism.



Scheme 6. Control experiments and further transformations.



Interestingly, selective deprotection Cbz group could be achieved. Indeed; hydrogenation of **3c** with Pd-C at 70°C in a mixture H₂O/MeOH solvent gave hemiaminal **7** in good yield with complete retention of enantioselectivity (Scheme 6).

To conclude, we have successfully developed the first enantioselective (3 + 2) cycloaddition of quinones diimides with β-substituted ene- and thioenecarbamates and with cyclic enamides using CPA catalysis. In addition, our work established the ability of phosphoric acid to differentiate selected nitrogen based on their individual protecting group. As such various indolines were obtained regio- and chemoselectively; and, in each case, with excellent yields and enantioselectivities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/...>

Experimental procedures, compound characterization data, ¹H, ¹³C, spectra and HPLC traces for all new compounds reported, and X-ray data for compound **3c**, **6b** and **6g** (PDF).

Accession Codes

CCDC 2016631, 2039802 and 2046101 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author Contribution

‡ W.-Y. Ma and C. Gelis contributed equally.

Note

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank ICSN for financial support. W-YM thanks China Scholarship Council for the doctoral fellowship. CG thank Paris-Saclay University for the doctoral fellowship. DB thanks CHARMMAT LabEx for the master fellowship.

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