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Chiral Phosphoric Acid-Catalyzed Enantioselective Formal [3+2] Cycloaddition of Azomethine Imines with Enecarbamates

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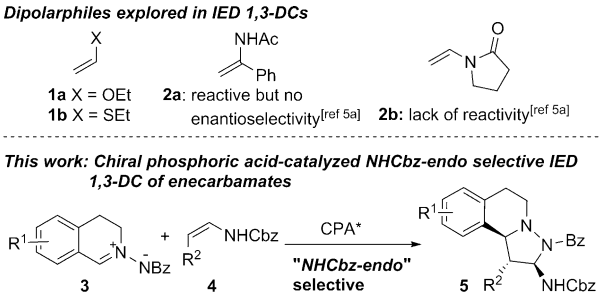
Abstract: The first catalytic asymmetric inverse electron demand 1,3-dipolar cycloaddition of azomethine imines with enecarbamates has been developed. Isoquinoline-fused pyrazolidines containing two or three contiguous stereogenic centers were obtained in high yields with excellent regio-, diastereo-, and enantioselectivities. The pyrazolidine ring can be opened to install an aminal, α-amino nitrile, or homoallylamine function with an excellent control of the newly generated stereogenic center. Access to aminobenzo[a]quinolizidine is also documented.

1,3-Dipolar cycloadditions (1,3-DCs) of azomethine imines with alkenes/alkynes are useful methods for the assembly of five-membered heterocycles.[1] The resulting dihydropyrazoles or pyrazolidines are structural motifs found in natural products and bioactive compounds.[2] Although enantioselective normal electron demand (NED) 1,3-DCs of azomethine imines with electron-deficient alkenes are well established,[3] the inverse electron demand (IED) cycloaddition between azomethine imines and electron-rich alkenes is far less developed.[4,5] Enol ether **1a** and enol thioether **1b** have been successfully employed as electron-rich olefins in the enantioselective IED 1,3-DCs, whereas enamides/enecarbamates have not been used thus far. Indeed, it has been reported that enamides **2a** and **2b**[6] were incompetent dipolarphiles in the attempted enantioselective [3+2] cycloadditions with *N*-acyl hydrazone (Scheme 1).[7] Assuming that the activation mode of azomethine imines might be different from that of *N*-acyl hydrazones, we set out to investigate the IED [3+2] cycloadditions between azomethine imines **3** and enecarbamates **4**. We report herein that in the presence of a chiral spinol-derived phosphoric acid,[8,9] heteroannulation between **3** and **4** occurs smoothly to afford the isoquinoline-fused aminopyrazolidines **5** in high yields with excellent regio-, diastereo-, and enantioselectivities (Scheme 1). Conditions for the cycloaddition involving β-substituted enecarbamates have also been optimized leading to cycloadducts with a penta-substituted pyrazolidine unit (R^2 = alkyl). The utility of this chemistry was further illustrated by the post-transformation of the resulting cycloadduct to functionalized tetrahydroisoquinolines and benzoquinolizidine. It is important to note that in Maruoka's chiral dicarboxylic acid-catalyzed heteroannulation of C,N-cyclic azomethine imines with *tert*-butyl vinyl ether, the reaction is *exo*-selective.[4a] However, our reaction is NHCbz-*endo* selective; therefore, indicating a significant mechanistic deviation from Maruoka's reaction.



Scheme 1. Enantioselective IED 1,3-DCs of electron-rich alkenes with azomethine imines.

The C,N-cyclic azomethine imine **3a** (R^1 = H) and benzyl *N*-vinyl carbamate **4a** (R^2 = H) were chosen as model substrates. After initial survey of the solvents, reaction temperatures, and concentrations using **6a** as a catalyst (0.1 equiv; Figure 1), we chose to perform the reaction in CH_2Cl_2 (0.1 M) at −20 °C for catalyst screening. As shown in Table 1, all chiral phosphoric

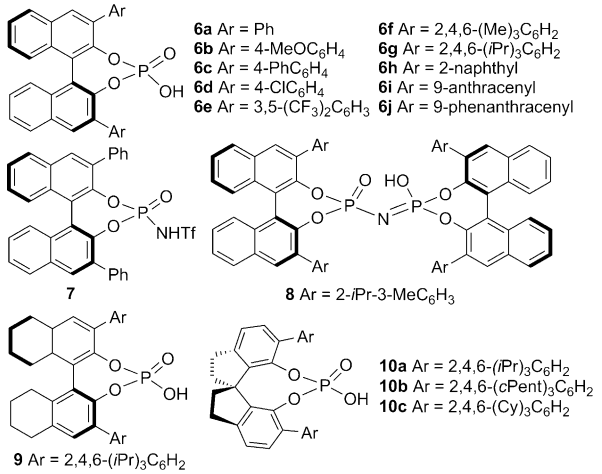


Figure 1. Structures of chiral phosphoric acids.

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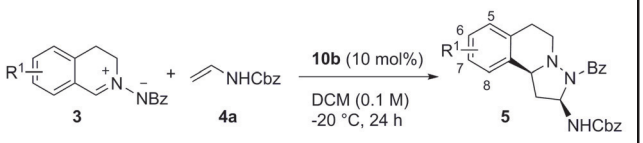
Table 1. Survey of reaction conditions.[a]

3a 4a 5a

Entry	Catalyst	*t* [h]	Conv. [%]	d.r.	e.r.[b]
1	**6a**	36	>99	>19:1	69.9:30.1
2	**6b**	20	>99	>19:1	68.1:31.9
3	**6c**	20	>99	>19:1	67.9:32.1
4	**6d**	20	>99	>19:1	65.3:34.7
5	**6e**	20	>99	>19:1	51.7:48.3
6	**6f**	20	>99	>19:1	57.9:42.1
7	**6g**	20	>99	>19:1	61.9:38.1
8	**6h**	20	>99	>19:1	64.1:35.9
9	**6i**	20	>99	>19:1	55.1:44.9
10	**6j**	20	>99	>19:1	65.1:34.9
11	**7**	20	>99	>19:1	53.3:46.7
12	**8**	20	>99	>19:1	53.3:46.7
13	**9**	20	>99	>19:1	80.0:20.0
14	**10a**	20	>99	>19:1	93.9:6.1
15	**10b**	**20**	**>99**	**>19:1**	**97.6:2.4**
16	**10c**	20	>99	>19:1	94.9:5.1

[a] Reaction conditions: **3a** (0.10 mmol), **4a** (0.20 mmol), and (*S*)-phosphoric acid (0.01 mmol) in DCM (*c* 0.1 M) at −20 °C. [b] Determined by SFC (supercritical fluid chromatography) analysis on a chiral stationary phase.

Table 2. Scope of asymmetric IED 1,3-DC with benzyl *N*-vinyl carbamate.[a]



3 4a 5

Entry	Product **5**	Yield [%][b]	d.r.	e.r.[c]
1	R^1=H (**5a**)	80	d.r.	97.6:2.4
2	R^1=5-Me (**5b**)	75	>19:1	95.3:4.7
3	R^1=6-Me (**5c**)	79	>19:1	98.6:1.4
4	R^1=7-Me (**5d**)	77	>19:1	94.9:5.1
5	R^1=8-Me (**5e**)	80	>19:1	94.2:5.8
6[d]	R^1=7-MeO (**5f**)	68	>19:1	97.5:2.5
7	R^1=7-F (**5g**)	83	>19:1	95.4:4.5
8	R^1=7-Cl (**5h**)	70	>19:1	95.1:4.9
9	R^1=5-Br (**5i**)	72	>19:1	95.4:4.6
10	R^1=6-Br (**5j**)	76	>19:1	98.3:1.7
11	R^1=7-Br (**5k**)	81	>19:1	96.5:3.5
12	R^1=5-CO_2Me (**5l**)	72	>19:1	97.8:2.2
13	R^1=6-CF_3 (**5m**)	76	>19:1	98.8:1.2

[a] Reaction conditions: **3a** (0.10 mmol), **4a** (0.20 mmol), and (*S*)-**10b** (0.01 mmol) in DCM (*c* 0.1 M) at −20 °C. [b] Isolated yield. [c] Determined by SFC analysis on a chiral stationary phase. [d] *t* = 48 h.

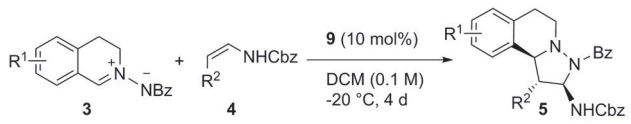
acids (CPAs) are capable of catalyzing the [3+2] cycloaddition between **3a** and **4a** to afford the desired adduct **5a** in excellent yield and diastereoselectivity (d.r. > 19:1). However, the enantioselectivity varied significantly depending on the backbone structure of CPAs. With (*S*)-binol-derived CPAs (**6a**–**6j**) having different steric and electronic properties as catalyst, **5a** was isolated with an e.r. of 69.9:30.1 at best (entries 1–10). The more acidic *N*-triflyl phosphoramide **7**[10] was also inefficient for this purpose (entry 11), so was the bulky imidodiphosphoric acid **8**[11] (entry 12). An improved enantioselectivity was observed with the octahydro-(*S*)-binol-derived CPA **9** (e.r.: 80:20; entry 13). A breakthrough came when STRIP (6,6′-bis(2,4,6-triisopropylphenyl)-1,1′-spirobiindan-7,7′-diyl hydrogenphosphate, **10a**) was employed as a catalyst to afford **5a** with an e.r. of 93.9:6.1 (entry 14).[12] Encouraged by this result, a series of (*S*)-spinol-derived CPAs were synthesized. Among them, the previous unknown CPAs **10b** and **10c** were found to be the most promising. With **10b** as a catalyst (0.1 equiv), the reaction of **3a** with **4a** afforded **5a** in 80% yield with an e.r. of 97.6:2.4 (entry 15).

With optimized conditions in hand (**10b** (0.1 equiv), CH_2Cl_2 (*c* 0.1 M), −20 °C, 24 h), the generality of the reaction was next examined (Table 2). A remarkably broad range of C,N-cyclic azomethine imines **3** could be converted to the corresponding cycloadducts **5** in excellent yields and enantioselectivities. Electron-donating (entries 2–6) and -withdrawing substituents (entries 7–13), irrespective of their positions on the aromatic ring, were well tolerated, providing the *endo* adducts with uniformly high diastereo- and enantioselectivities. It was nevertheless noted that a substituent at the C6-position of the azomethine imine gave in general a slightly higher e.r. of the cycloadducts (entries 3, 10, and 13). The absolute configuration of **5j** was determined by X-ray crystallographic analysis[13] and those of other adducts were assigned accordingly.

To further explore the scope of this novel catalytic enantioselective 1,3-DCs, both (*Z*)- and (*E*)-benzyl *N*-prop-1-en-1-yl carbamates (*Z*)-**4b** (R^2 = Me) and (*E*)-**4b** (R^2 = Me) were synthesized[14] and submitted to our standard conditions. Although the reaction of (*E*)-**4b** with **3a** afforded a mixture of two diastereomers, the reaction of (*Z*)-**4b** gave a single diastereomer, albeit with low conversion and a negligible e.r. (55.3:44.7). Therefore, screening of CPAs using (*Z*)-**4b** as dipolarphile was carried out that allowed us to identify H_8-binol-based CPA **9** as a suitable catalyst. Under optimized conditions (**3a** (0.1 mmol), (*Z*)-**4b** (0.2 mmol), **9** (0.01 mmol, 0.1 equiv), CH_2Cl_2 (*c* 0.1 M), −20 °C, 4 days), the cycloadduct **5n** was isolated as a single diastereomer in 91% yield with an e.r. of 96:4 (Table 3, entry 1). To the best of our knowledge, this represents the first example of IED 1,3-DCs between the C,N-cyclic azomethine imine and the electron-rich internal double bond.

As shown in Table 3, a wide range of C,N-cyclic azomethine imines containing electron-withdrawing or -donating substituents at different positions of the aromatic ring reacted with (*Z*)-**4b** to afford the corresponding cycloadducts **5o**–**5t** in excellent yields with excellent diastereo- and enantioselectivities (entries 2–7). Other β-substituted enecarbamates (*Z*)-**4c** (R^2 = Et), (*Z*)-**4d** (R^2 = *i*Pr), and (*Z*)-**4e** (R^2 = Bn) underwent 1,3-DC with **3j** to provide the corresponding cycloadducts in excellent yields and diastereoselectivities, albeit with slightly reduced enantioselectivities (entries 8–10). We note that increasing the size of R^2 substituent decelerated the reaction. Therefore, reactions involving (*Z*)-**4d** (R^2 = *i*Pr) and (*Z*)-**4e** (R^2 = Bn) had to be performed at room temperature that led to a decreased enan-

Table 3. Scope of asymmetric IED 1,3-DC of azomethine imines with (*Z*)-β-substituted enecarbamates.[a]



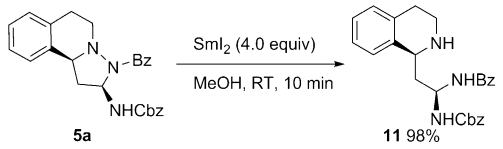
Entry	Product **5**	Yield [%][b]	d.r.	e.r.[c]
1[d]	R^1 = H; R^2 = Me (**5n**)	91	>19:1	96.0:4.0
2[e]	R^1 = 7-Me; R^2 = Me (**5o**)	89	>19:1	98.1:1.9
3	R^1 = 8-Me; R^2 = Me (**5p**)	93	>19:1	98.9:1.1
4	R^1 = 7-MeO; R^2 = Me (**5q**)	91	>19:1	97.5:2.5
5	R^1 = 5-Br; R^2 = Me (**5r**)	92	>19:1	97.8:2.2
6	R^1 = 6-Br; R^2 = Me (**5s**)	94	>19:1	98.6:1.4
7	R^1 = 7-Br; R^2 = Me (**5t**)	90	>19:1	97.0:3.0
8[f]	R^1 = 6-Br; R^2 = Et (**5u**)	93	>19:1	93.6:6.4
9[f,g]	R^1 = 6-Br; R^2 = *i*Pr (**5v**)	89	>19:1	89.6:10.4
10[f,h]	R^1 = 6-Br; R^2 = Bn (**5w**)	95	>19:1	90.0:10.0

[a] Reaction conditions: **3** (0.10 mmol), **4** (0.20 mmol), and (*S*)-**9** (0.01 mmol) in DCM (*c* 0.1 M) at −20 °C. [b] Isolated yield. [c] Determined by SFC analysis on a chiral stationary phase. [d] *t* = 5 d. [e] *t* = 48 h. [f] 3 Å MS was added. [g] RT, 48 h. [h] RT, 24 h.

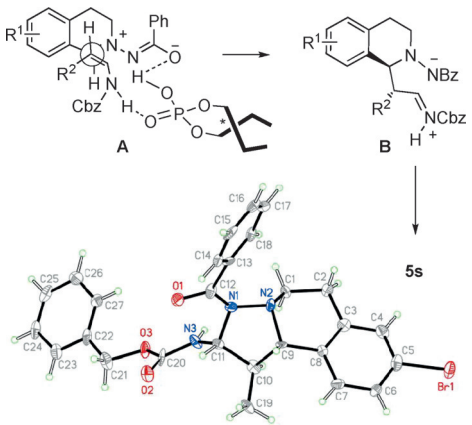
tioselectivity. Gratefully, addition of molecular sieves was found to be beneficial in these cases (entries 8–10).

The absolute configuration of **5s** was determined by X-ray crystallographic analysis. The fact that the reaction between (*E*)-**4b** and **3a** under optimized conditions afforded the cycloadduct in a lower yield with much reduced enantioselectivity (major isomer: yield 67%, e.r. 59:11; minor isomer: yield 25%, e.r. 81.5:18.5) excluded the possibility of the isomerization of (*Z*)-**4b** to (*E*)-**4b** before the annulation process. In addition, resubmitting the cycloadduct **5a** to the standard conditions did not cause the epimerization of the aminal stereogenic center. Therefore, the observed *trans* relationship between R^2 and the NHCbz groups in cycloadduct **5** indicated that the present IED 1,3-DCs between **3** and (*Z*)-**4b** most probably went through a stepwise mechanism. We assumed that the CPA acted as a bifunctional catalyst activating both the nucleophile and the electrophile via transition state **A** (Scheme 2). A pseudo-intramolecular attack of the enecarbamate to the *Si*-face of the azomethine imine would afford intermediate **B** that upon aminal formation afforded the cycloadduct **5**. In line with this hypothesis, benzyl *N*-methyl-*N*-vinyl carbamate, which lack the NH function, failed to react with **3a** under our standard conditions.

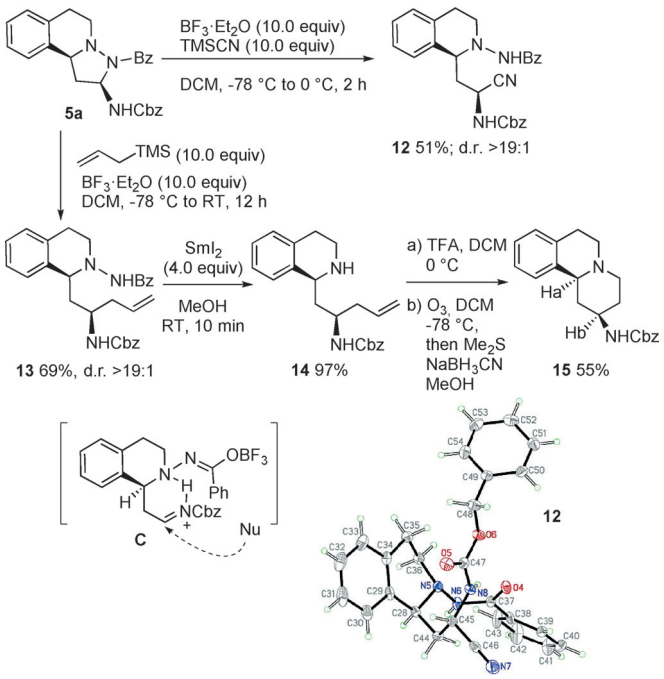
Post-functionalization of cycloadducts **5** was next investigated to illustrate the synthetic potential of this novel IED 1,3-dipolar cycloaddition. Treatment of **5a** with SmI_2 in MeOH at room temperature[15] afforded chiral aminal **11** (98%) as the only diastereoisomer through selective cleavage of the N–N bond (Scheme 3).[16] Taking advantage of the aminal function in **5**, its Lewis acid-mediated diastereoselective functionalization was examined. Reaction of **5a** with TMSCN (10.0 equiv) in the presence of an excess of $BF_3{\cdot}Et_2O$ afforded α-amino nitrile **12** in 51% yield with a d.r. of >19:1 (Scheme 4). The relative stereochemistry of **12** was determined without ambiguity by its X-ray crystallographic analysis. Using allyltrimethylsilane as nucleophile, allylamine **13** was similarly prepared in 69% yield with a d.r. of >19:1. Subsequent SmI_2-mediated reductive N–N bond cleavage[15] of **13** provided C1-substituted tetrahydroisoquinoline **14** with a 1,3-diamine unit in 97% yield.[17] The tetra-



Scheme 3. Reductive cleavage of the N–N bond of the cycloadduct.



Scheme 2. Stereochemical outcome and X-ray structure of **5s**.



Scheme 4. Synthetic transformations of the cycloadduct.

hydroisoquinoline bearing a stereogenic center at the C1-position represents a fundamental structural motif in many bioactive compounds.[18] In addition, **14** was readily converted in one operation to aminobenzo[*a*]quinolizidine **15** (Scheme 4), which has significant importance in the development of selective α2-adrenoceptor antagonist and DDP-IV inhibitor for the treatment of type II diabetes.[19] The observed strong NOE effect between H_a and H_b indicated that both protons are in *cis*-diaxial positions that allowed us to determine the relative stereochemistry of compound **15**, hence that of **13** and **14**. The high diastereoselectivity observed in these two nucleophilic addition reactions was tentatively explained by invoking the H-bonded 6-membered intermediate **C**. Addition of a nucleophile to the sterically more accessible *Re*-face of the imine would account for the observed stereoselectivity.

In summary, we have developed the first chiral phosphoric acid-catalyzed enantioselective inverse electron demand 1,3-dipolar cycloaddition reactions between C,N-cyclic azomethine imines and enecarbamates. The reaction afforded functionalized isoquinoline-fused pyrazolidines in high yields with excellent regio-, diastereo-, and enantioselectivities. The utility of this transformation was illustrated by the subsequent conversion of the resulting cycloadducts to a diverse set of C1-substituted tetrahydroisoquinolines and benzoquinolizidine.

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Keywords: azomethines · carbamates · cycloaddition · organocatalysis · tetrahydroisoquinolines

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