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Enantioselective Aza Michael-Type Addition to Alkenyl Benzimidazoles Catalyzed by a Chiral Phosphoric Acid

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Abstract: *Highly enantioselective Michael-type addition (MTA) reactions between N-protected alkenyl benzimidazoles and either pyrazoles or indazoles as nitrogen nucleophiles are accomplished for the first time using chiral phosphoric acid catalyst. Theoretical studies elucidated the reaction pathway and the origin of the stereochemical outcomes, where the catalyst substituent and the N-protecting group of benzimidazole contributed to the resulting high enantioselectivity.*

The construction of aromatic N-heterocyclic motifs bearing complex side chains, particularly chiral ones in an enantioenriched form, is of paramount significance and great interest in the synthetic community because they are ubiquitously found in natural products and biologically active compounds (e.g., pharmaceutical substances and agrochemicals). These structures are commonly constructed by forming N-heterocycles using chiral precursors.[1] Another synthetic methodology, the direct enantioselective functionalization of prochiral heterocyclic compounds, is an attractive alternative strategy in terms of its atom and step economy. An ideal example of this type of construction is the conjugate addition to an alkenyl moiety, having an electron-deficient aromatic N-heterocycle (azaarene), a reaction which is an analogue of the classical Michael addition to an α,β-unsaturated carbonyl compound. This particular transformation is often seen in biosynthesis,[2] and has also been developed by synthetic chemists into a beneficial synthetic method.[3] However, asymmetric conjugate addition to alkenyl azaarenes has been less exploited and remains a challenging task.[4] Indeed, to promote these processes, harsh reaction conditions are usually required because energetically less favorable intermediates are generated through a transient dearomatization step.

Chiral phosphoric acids[5] have emerged as versatile catalysts for various enantioselective transformations,[6] and thus have the potential of meeting the aforementioned challenge. In fact, they have been used in dearomatization processes such as the catalytic asymmetric hydrogenation of heteroarenes,[7] in which an endocyclic double bond undergoes nucleophilic addition in an enantioselective fashion. However the LUMO-decreasing activation of a double bond attached to the azaarene, which enables 1,4-conjugate addition to alkenyl azaarenes, has not yet been realized using chiral phosphoric acids. The proposed transformation has an intrinsic problem associated with the conformational flexibility of the acyclic system, where control of the newly generated stereogenic center is rather difficult. Our project is focused on the development of enantioselective Michael-type addition (MTA) to alkenyl azaarenes catalyzed by a chiral phosphoric acid (**1;** Figure 1 a).

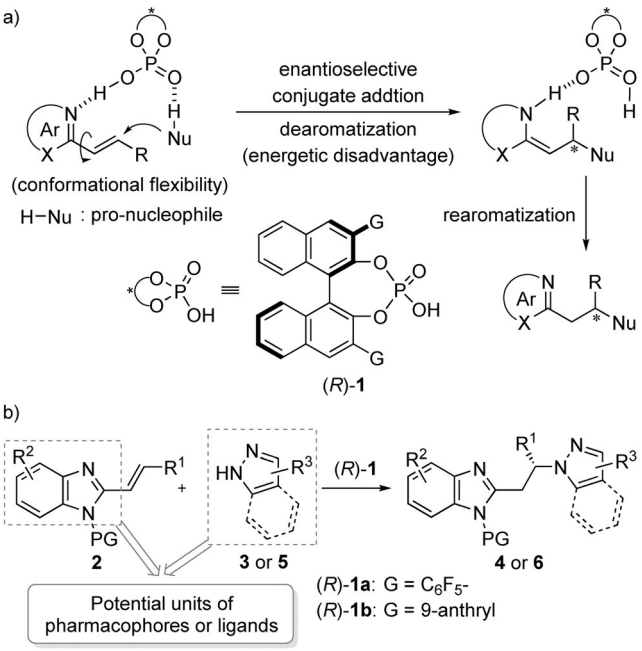

Figure 1. a) Enantioselective MTAs to alkenyl azaarene catalyzed by chiral phosphoric acid. b) The aza MTA between either pyrazoles or indazoles and alkenyl *N*-protected benzimidazoles.

To validate the transformation envisaged, we employed benzimidazole as the aromatic N-heterocyclic unit for the alkenyl azaarene. While many five- or six-membered aromatic N-heterocycles (e.g., thiazole, pyridine, and pyrimidine) have been reported as basal units of the alkenyl azaarenes for Michael-type additions,[3] the alkenyl benzimidazoles **2** (Figure 1 b) have never been used in the proposed MTA, despite benzimidazoles being typical elements of biologically active

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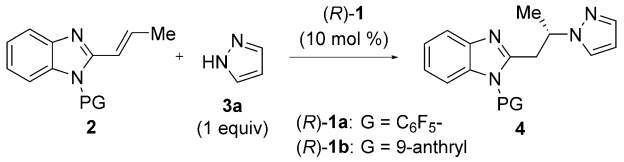
compounds.[8] The reactivity of **2** as well as the stereochemical outcome of the addition products could be tuned through the choice in the protecting group at the nitrogen atom of the benzimidazole moiety. A further consideration is the type of nucleophile employed. By taking account of the synthetic importance of C–N bond formation as well as the potential utility of the addition products, we selected pyrazoles (**3**) and indazoles (**5**) as nitrogen nucleophiles[9] to establish the reaction system. Herein, we report the development of an aza MTA between either **3** or **5** and the N-protected **2**, catalyzed by **1**. The reaction is an efficient method for coupling two aromatic N-heterocycles, which are potential pharmacophores or ligands, into one molecule (Figure 1b).

At the outset of our studies, the reaction of the pyrazole **3a** with a series of alkenyl benzimidazoles (**2**) was investigated (Table 1). These reactions were performed using the

Table 1: Optimization of the reaction conditions.[a]



Entry	2 (PG)	1	Reaction conditions	4	Yield [%][b]	*ee* [%][c]
1	**2a** (H)	**1a**	$CHCl_3$, 25 °C, 48 h	**4a**	< 5	–
2	**2b** (Bn)	**1a**	CH_2Cl_2, 25 °C, 48 h	**4b**	95	2
3	**2c** (Boc)	**1a**	CH_2Cl_2, 25 °C, 18 h	**4c**	99	51
4	**2c**	**1b**	CH_2Cl_2, 25 °C, 18 h	**4c**	99	73
5	**2c**	**1b**	toluene, 25 °C, 18 h	**4c**	99	78
6	**2c**	**1b**	THF, 25 °C, 18 h	**4c**	99	82
7[d]	**2c**	**1b**	THF, −40 °C, 48 h	**4c**	99[e]	98
8[d]	**2d** (Cbz)	**1b**	THF, −40 °C, 48 h	**4d**	99[e]	98
9[d]	**2e** (Ts)	**1b**	THF, −40 °C, 48 h	**4e**	96[e]	99

[a] Unless otherwise noted, reactions were carried out with (*R*)-**1** (0.01 mmol), **2** (0.1 mmol), and **3a** (0.1 mmol) in 1.0 mL of the indicated solvent (0.1 M). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] Determined by chiral stationary phase HPLC analysis. [d] With (*R*)-**1b** (0.02 mmol), **2** (0.2 mmol), and **3a** (0.2 mmol) in 1.0 mL THF (0.2 M). [e] Yield of isolated product. PG = protecting group, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

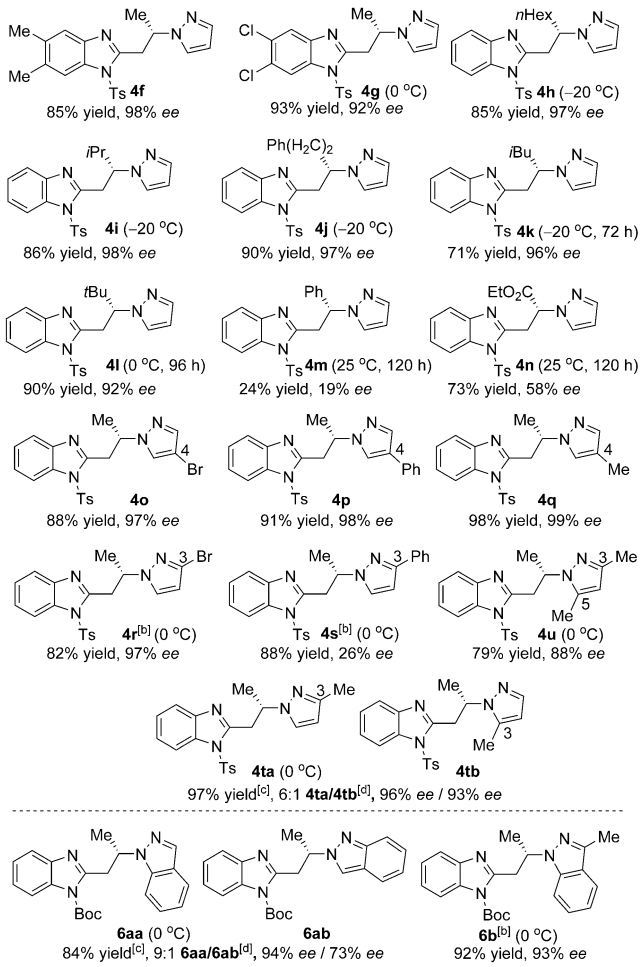
chiral phosphoric acid catalyst **1a** (10 mol%) at room temperature. The reaction of the unprotected **2a** did not proceed under these reaction conditions (entry 1). In contrast, substrates protected by either an electron-donating group (EDG) or an electron-withdrawing group (EWG) afforded the desired addition products in excellent yield (entries 2 and 3). Of particular interest is that the reaction of the *N*-*tert*-butoxycarbonyl (Boc)-protected **2c** was faster than that of *N*-benzyl (Bn)-protected **2b**. The more basic **2b** would be protonated at the nitrogen atom more strongly by **1a**, however the less-basic **2c,** which has a higher electrophilicity than **2b**, exhibited the higher reactivity. These results suggest that the inherent electrophilicity of **2** is the dominant factor governing the reactivity, rather than the basicity at the nitrogen atom of **2**. More interestingly, moderate enantiomeric excess (*ee*) was observed in **2c**, while an almost racemic mixture was obtained when using **2b**. Considering the favorable reactivity and stereochemical outcome using **2c**, we employed EWG-protected benzimidazoles (**2**) in the following studies.

To enhance the *ee* value of the product **4c**, we thoroughly screened the reaction conditions.[10] As shown in Table 1, **1b**, having a 9-anthryl group at the 3,3′-positions, exhibited better *ee* values than that of **1a** (entry 4 versus 3). THF was the best of the solvents screened for the reaction of **2c** when using **1b**, thus giving rise to **4c** in 82% *ee* (entries 4–6).[11] It is unusual that a higher *ee* value was achieved in the more polar THF than in the less polar CH_2Cl_2 or toluene, which have been commonly used in chiral phosphoric acid catalyzed reactions. The temperature effect was next explored. Lowering the temperature to −40 °C dramatically improved the *ee* value (98% *ee*), and a long reaction time ensured a good yield. Delightfully, the reactions of **2d** and **2e**, which are protected by other common EWGs (Cbz and Ts, respectively), also gave similarly excellent *ee* values, and the result using **2e** (Ts protected) was slightly better than the others (entries 7–9). The Ts group of the addition product **4e** could be readily removed in accordance with a known procedure, affording deprotected products without any loss of the enantiomeric purity.[12] Hence *N*-Ts-protected benzimidazoles were employed for further investigations.

With the optimal reaction conditions in hand, the scope of the present transformation was demonstrated in the reaction between a series of *N*-protected benzimidazoles (**2**) and either pyrazoles (**3**) or indazoles (**5**). The results are summarized in Table 2. For some less reactive substrates, higher temperatures and longer reaction times were required to ensure acceptable yields (*T*: temperature, *t*: time). The electron-donating dimethyl substituent on the benzimidazole ring of **2** did not compromise the *ee* value of **4f**. The absolute configuration of **4f** was determined to be *S* by single-crystal X-ray diffraction analysis.[13] The higher temperature was required for the reaction of the electron-withdrawing chloro-substituted benzimidazole because of the solubility of the substrate in THF, and resulted in a slight reduction of the *ee* value of **4g**. Further investigations showed that different alkyl substituents attached to the vinyl terminus of **2** led to excellent enantioselectivities (**4h–l**), irrespective of the substituent. Nevertheless, a phenyl group was an unsuitable substituent given the low yield and *ee* value observed with **4m**. Intriguingly, introducing an ester group to vinyl terminus of **2** led to the addition reaction at the α-position of the ester functionality, thus affording **4n** in moderate *ee* value. This result indicates that EWG-protected benzimidazole greatly polarizes the C=C bond rather than the carbonyl group under the influence of the phosphoric acid, and hence functions as a strong directing group. The alkenyl azarene bearing an imidazole, instead of benzimidazole, is also an applicable substrate, albeit leading to the addition product in moderate yield and *ee* value.[14]

The scope with respect to the nucleophiles, **3** and **5**, was further investigated (Table 2). Varying the substituent at the C4-position of **3** was tolerated (**4o**, **4p**, **4q**) and both the electron-withdrawing bromide (**4r**) and electron-donating methyl (**4t**) worked well at the C3-position. In contrast,

Table 2: Scope with respect to substrates.[a]



[a] Unless otherwise specified, reactions were carried out with (*R*)-**1b** (0.02 mmol), **2** (0.2 mmol), and either **3** or **5** (0.2 mmol) in 1.0 mL THF (0.2 M) at −40 °C for 48 h. If other conditions (*T*, *t*) were used see data within parentheses. Yields of isolated products are given. The *ee* value was determined by chiral stationary phase HPLC analysis. [b] No N2 adducts were observed in these cases. [c] Combined yield of two regioisomers. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture.

introduction of a sterically hindered phenyl group at the C3-position led to a marked decrease in the *ee* value of **4s**. Furthermore, the formation of two regioisomers, N1 and N2 adducts, would be expected, when using C3-substituted pyrazoles. 3-Methylpyrazole underwent the reaction at the N1 and N2 positions to afford a regioisomers **4ta** and **4tb** in 6:1 mixture, however in the reactions of 3-bromo- and 3-phenyl-pyrazole, the N1-adducts **4r** and **4s** were formed exclusively. 3,5-Dimethyl-substituted pyrazole is also applicable, despite showing a slight decrease in yield and *ee* value of **4u**. Finally, the indazole **5** was employed as a nucleophile and the corresponding products **6** were obtained in good yields with high enantio- and regioselectivities, although the *ee* value of the minor product **6ab** was only moderate.

The present aza MTA to alkenyl benzimidazole exhibited extremely high enantioselectivity in most cases. In addition, it can be considered that the products **4** and **6** were formed through the energetically less favorable process of a transient dearomatization step. These findings prompted us to study further the mechanism of this intriguing transformation. We therefore conducted computational analysis to acquire mechanistic insights into the present reaction. The catalyst **1b**, **2e**, and **3a** were used for the theoretical studies and all calculations were performed with the Gaussian 09 package.[15] The geometries of transition states were fully optimized and characterized using frequency calculations at the B3LYP density-functional theory[16] with the 6-31G* basis set. Relative Gibbs free energies were obtained by single-point energy calculations of the optimized structures at the M06-2X/6-31G* level[17] with the SCRF method based on CPCM ($\varepsilon = 7.4257$ for THF)[18] followed by the addition of thermal corrections which were calculated at the geometrical optimization by B3LYP/6–31G* level.[19]

Three-dimensional (3D) transition structures of the stereodetermining C–N bond-forming step are illustrated in Figure 2.[20] The transition-state **TS-s** [affords (*S*)-**4e**] is more stable than **TS-r** [affords (*R*)-**4e**] by 4.4 kcal mol^{-1} at the B3LYP/6-31G* level (1.5 kcal mol^{-1} for the free energy) using the catalyst (*R*)-**1b**, and is consistent with the experimental

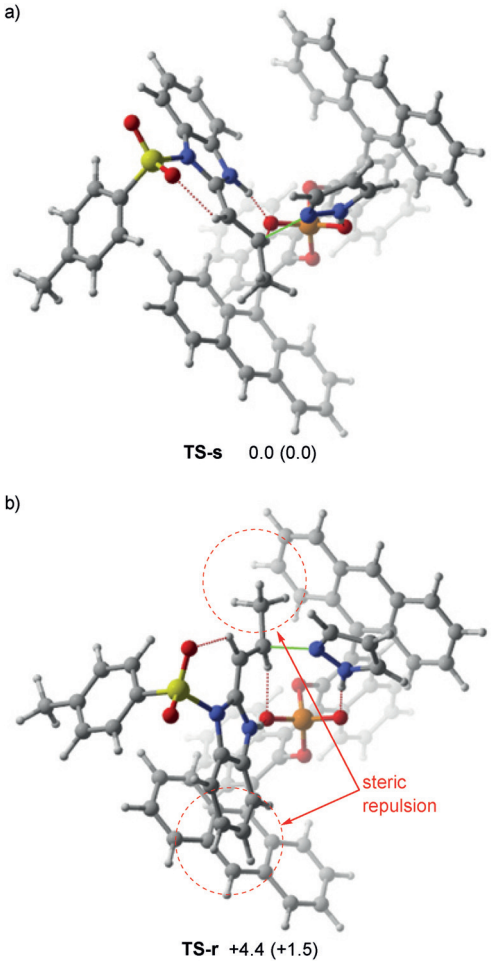


Figure 2. 3D structures of the transition states a) **TS-s** and b) **TS-r**. Relative energies at the B3LYP/6-31G* level are shown in kcal mol^{-1}. Relative Gibbs free energies (in kcal mol^{-1}) at the CPCM (THF)/M06-2X/6-31G* level are shown within parentheses.[19]

results. Further structural analysis of **TS-s** and **TS-r** allowed identification of the major factors contributing to the efficient enantioselection. In both transition structures, **2e** and **3a** interact with the chiral phosphoric acid **1b** through two hydrogen bonds. Furthermore, the alkenyl moiety and the benzimidazole core of **2e** lie in the same plane. This coplanar fragment is almost parallel to the anthryl plane of the catalyst substituent to avoid steric congestion in the energetically more-favorable **TS-s** (Figure 2a). In contrast, in the less favorable **TS-r**, the coplanar fragment is inserted perpendicularly between two anthryl planes (Figure 2b), in which the methyl group of the alkenyl moiety and the tail-end of the benzimidazole core are located close to the top and bottom anthryl substituents. This arrangement leads to steric repulsion between the substrate and the catalyst (dashed red circles in Figure 2b), which would destabilize **TS-r**. More interestingly, to avoid steric repulsion between the alkenyl moiety of **2e** and the *N*-Ts group, the alkenyl moiety is oriented to the opposite side of the *N*-Ts group. In addition, this conformation would be further stabilized by the intramolecular C–H···O hydrogen bond between the α-vinyl proton and the oxygen atom of the sulfonamide moiety (dashed red lines in Figure 2).[21] In fact, the distances between the α-vinyl proton and the oxygen atom (2.27 Å in **TS-s**, 2.22 Å in **TS-r**) are considerably shorter than the sum of the van der Waals radii of hydrogen and oxygen atoms (ca. 2.7 Å). The observed high enantioselectivity also stems from the conformational fixation of the alkenyl moiety by the Ts group.

As illustrated in Figure 3,[22] the reaction energy profile shows that the intermediate complex **CP2**, consisting of the initial product **INT** and (*R*)-**1b**, forms prior to the product **4e. CP2** is energetically comparable to **CP1** which is the precursor of the C–N bond-forming step. However subsequent energetically favorable rearomatization of **INT** via **TS-rearom** suppresses the retro-aza Michael-type reaction to **CP1**. The rearomatization is accomplished through tautomerization of the *exo* double bond of **INT** aided by the chiral phosphoric acid **1b**, which eventually yields the thermodynamically more stable product **4e**.

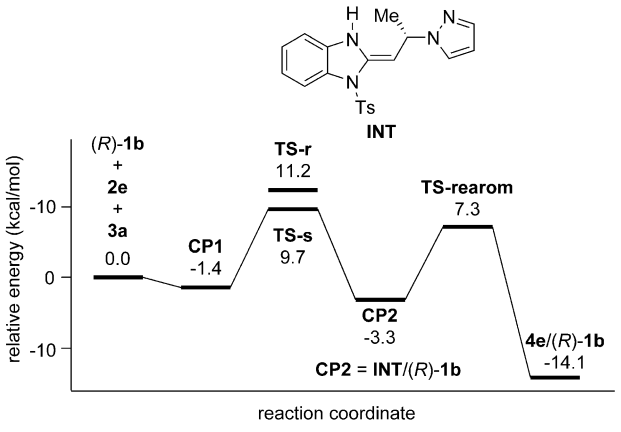


Figure 3. Energy profile of the aza-MTA to **2e** with **3a** catalyzed by (*R*)-**1b**. The energy of the sum of (*R*)-**1b**, **2e**, and **3a** is set to zero and relative Gibbs free energies at the CPCM (THF)/M06-2X/6-31G* level are shown in kcal mol^{-1}.[19]

In conclusion, we accomplished the first enantioselective aza MTA of pyrazoles and indazoles to alkenyl benzimidazoles using a chiral phosphoric acid catalyst. The reaction affords the corresponding products with both benzimidazole and pyrazole (indazole) units, which are ubiquitous elements of biomolecules and pharmacophores, in excellent enantioselectivities in most cases. Theoretical calculations elucidated the origin of the stereochemical outcomes and the reaction pathway. Structural analysis of the transition states at the C–N bond-forming step revealed that not only the catalyst substituent but also the *N*-protective group of benzimidazole contributed to the resulting high enantioselectivity. Moreover, the energy profile formulated by the theoretical studies indicates that the reaction proceeds through a transient dearomatization process. Further studies on the development of enantioselective transformations using other types of alkenyl azaarenes and nucleophiles are underway in our laboratory.

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Keywords: enantioselectivity · heterocycles · Michael additions · organocatalysis · synthetic methods

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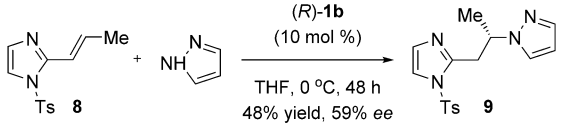
[14] The observed difference in reactivity between **2** and **8** implies that the benzo moiety of **2** aided the present transient dearomatization process, presumably by stabilizing the energetically less favorable intermediates.



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[22] See the Supporting Information for the 3D structures of **CP1**, **CP2**, **TS-rearom**, and **4e**/(*R*)-**1b**.

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