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N-Heterocyclic Carbene-Catalyzed [3+4] Cycloaddition and Kinetic Resolution of Azomethine Imines

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Supporting Information

ABSTRACT: The first *N*-heterocyclic carbene (NHC)-catalyzed [3+4] cycloaddition of azomethine imines and enals is disclosed. Oxidative catalytic remote activation of enals affords 1,4-dipolarophile intermediates that react with 1,3-dipolar azomethine imines to generate dinitrogen-fused seven-membered heterocyclic products with high optical purities. Our approach also provides effective kinetic resolution of azomethine imines, in which the substrate chiral center that is remote from the NHC catalyst can be well resolved.

Pyrazolones and the related dinitrogen-fused heterocyclic derivatives have interesting medicinally significant biological activities.[1] For example, seven-membered dinitrogen-fused heterocyclic derivatives are promising candidates as insecticides, acaricides, herbicides, and acetyl-CoA carboxylase inhibitors (Figure 1a)[2] Since the use of stable azomethine

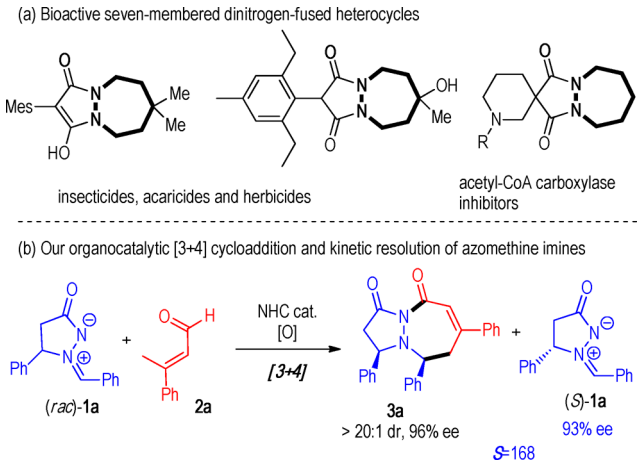


Figure 1. Bioactive dinitrogen-fused heterocycles and our organocatalytic preparation method.

imines (e.g., **1**) as 1,3-dipolar reagents reported by Dorn and Otto[3] in 1968, cycloaddition reactions of azomethine imines **1** have become one of the most efficient strategies for the construction of dinitrogen-fused heterocyclic derivatives. In 2003, Fu and co-workers developed an asymmetric Cu-catalyzed [3+2] cycloaddition and kinetic resolution of azomethine imines **1** with alkynes.[4] In addition to alkynes,[4,5] electron-deficient alkenes[6] have also been found as effective dipolarophiles to react with azomethine imines for [3+2] cycloadditions under metal catalysis. The [3+3] cycloadditions of azomethine imines have been reported by the Hayashi[7] and Toste groups[8] using Pd and Au metal catalysis respectively. Outside of transition metal catalysis,[9] organocatalytic cycloadditions of azomethine imines have also been developed. Chen and co-workers developed amine-catalyzed [3+2] cycloadditions of azomethine imines with α,β-unsaturated aldehydes and cyclic enones.[10] Kwon and Guo et al. reported a phosphine-catalyzed [3+2] annulation of azomethine imines and allenoates.[11] Scheidt described an *N*-heterocyclic carbene (NHC)-catalyzed diastereoselective [3+3] cycloaddition of azomethine imines **1** with enals.[12] Recently, the Wang group reported a Et_3N-catalyzed [3+3] annulation of azomethine imines and 3-isothiocyanatooxindoles.[13]

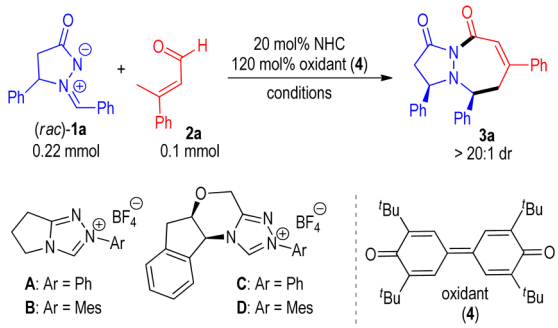
The above [3+2] and [3+3] cycloadditions afford five- and six-membered dinitrogen-fused heterocyclic products and have received considerable studies. The related [3+4] cycloadditions of azomethine imines that can form seven-membered dinitrogen-fused heterocyclic derivatives (Figure 1a), on the other hand, are much less studied. Elegant relevant work in this direction include Hayashi's Pd-catalyzed decarboxylative formation of 1,4-dipolarophile intermediates to react with 1,3-dipolar nitrones.[14] Kwon and Guo observed [3+4] cycloaddition adducts with impressive yet still low yields in their phosphine organocatalysis approach.[11,15] Here we disclose NHC-catalyzed enantioselective and diastereoselective [3+4] cycloaddition of azomethine imines with enals (Figure 1b).[16] Oxidative γ-carbon activation of enals via NHC catalysis afford vinyl enolates[17] as the reactive 1,4-dipolarophile. Racemic azomethine imine substrates (0% ee) are used and the seven-membered [3+4] adducts are obtained with excellent diastereoselectivity and over 90% ee. Using the same catalytic approach, kinetic resolution of azomethine imine substrates is also achieved.

Key results of condition searching and optimization are summarized in Table 1. The reaction between azomethine imine **1a** (0.22 mmol) and enal **2a** (0.1 mmol) was chosen as a model reaction and quinone **4**[18] was used as an oxidant. Studies on NHC catalysts revealed that when triazolium-based catalyst **A**[19] with an *N*-phenyl substituent was used, the desired [3+4] cycloaddition product **3a** was formed, albeit with a very low yield (entry 1). Additional studies found that a switch to the corresponding *N*-mesityl-substituted triazolium catalyst **B**[19] led

Received: November 6, 2013
Published: January 14, 2014

   dx.doi.org/10.1021/ja411110f | *J. Am. Chem. Soc.* 2014, 136, 1214−1217

Table 1. Condition Optimization[a]



entry	conditions	yield 3a (%)[b]	ee 3a (%)[c]
1	**A**, Cs_2CO_3, THF, 12 h	trace	–
2	**B**, Cs_2CO_3, THF, 12 h	38	–
3	**C**, Cs_2CO_3, THF, 72 h	trace	–
4	**D**, Cs_2CO_3,THF, 72 h	47	93
5	**D**, K_2CO_3, THF, 72 h	64	96
6	**D**, K_2CO_3, CH_2Cl_2, 72 h	75	92
7	**D**, K_2CO_3, CH_2Cl_2/THF[d], 72 h	72	94

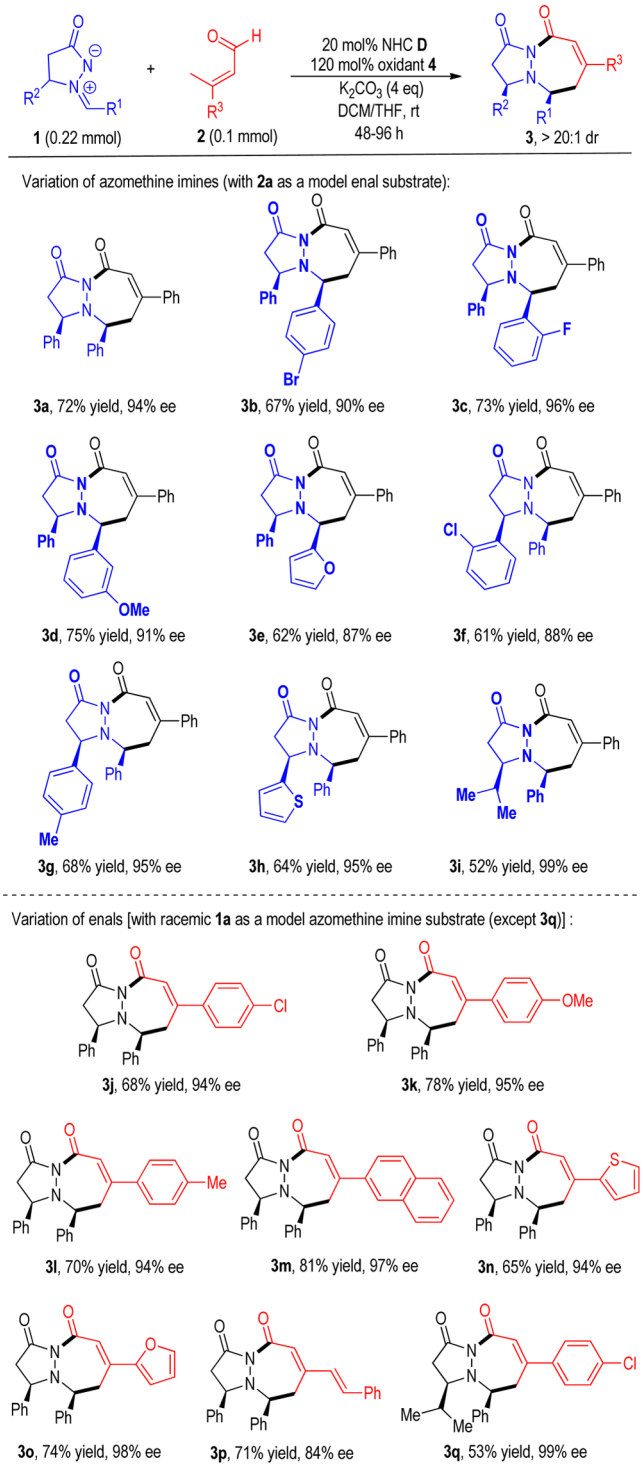
[a]Reaction conditions: **1a** (0.22 mmol), **2a** (0.1 mmol), NHC **D** (0.02 mmol), **4** (0.12 mmol), base (0.05 mmol Cs_2CO_3 or 0.4 mmol K_2CO_3), solvent (2 mL), 4 Å molecular sieves. [b]Isolated yield based on **2a** after chromatography. [c]Enantiomeric excess of **3a** determined via chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned on the basis of X-ray structure of **3j**[21] (see Chart 1 and SI). [d]Ratio of CH_2Cl_2/THF = 1:1 v/v.

to **3a** with encouraging 38% yield (entry 2). Chiral triazolium precatalysts were then evaluated (entries 3 and 4) and the use of indanol-derived catalyst **D**[20] with an *N*-mesityl substituent afforded **3a** with 47% yield and 93% ee. A switch of base from Cs_2CO_3 (0.5 equiv, entry 4) to K_2CO_3 (4.0 equiv, entry 5) led to a better yield (64%) and comparable ee (96%). As a note, using more than 0.5 equiv of Cs_2CO_3 or less than 4.0 equiv of K_2CO_3 both led to lower yields. Solvent CH_2Cl_2 (entry 6) was then found to perform better than THF (entry 5) with respect to reaction yield. The 92% ee for reaction in CH_2Cl_2 (entry 6) was slightly lower than that in THF (entry 5). At last we found the use of CH_2Cl_2/THF solvent mixture could consistently afford the cycloaddition product with good yield and excellent ee (entry 7).

Examples of azomethine imines and enals that work effectively under the optimal condition (Table 1, entry 7) are illustrated in Chart 1. With **2a** as the model enal substrate, azomethine imines derived from (hetero)aryl aldehydes bearing various substituents all worked well, affording the corresponding [3+4] reaction adducts **3a**–**e** with good yields, excellent dr's (>20:1 dr) and ee (86–96% ee). Azomethine imines derived from various pyrazolidinones containing different aryl (**3f**–**h**) and alkyl (**3i**) substituent at the 5-position also reacted well. With respect to the enals, replacing the phenyl substituent of enal **2a** to various (hetero)aryl (**3j**–**o**) were all tolerated in this reaction (>20:1 dr, 94–98% ee). When a vinyl substituent (**3p**) was used instead of *β*-phenyl substituent, the enantioselectivity was slightly decreased (84% ee) while maintaining a high diastereoselectivity (>20:1).[22]

The fact that optically pure [3+4] reaction products could be obtained from racemic azomethine imine substrates (Table 1, entry 7; Chart 1) reveals that the two enantiomers of azomethine imines have different reactivities under asymmetric NHC catalysis. Therefore, a kinetic resolution for azomethine

Chart 1. Substrates Scope[a]



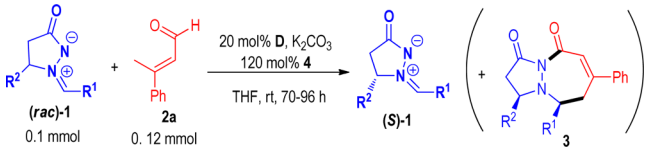
[a]Reaction conditions as in Table 1, entry 7. Yields are isolated yields. The ratio of **1** and **2** is 2.2:1 because the reactions selectively consume half of **1**.

imines using our organocatalytic [3+4] reaction strategy should be feasible. In our early study (Table 1, entry 7) of reacting 0.22 mmol azomethine imine **1a** with 0.1 mmol enal **2a**, when the cycloaddition product **3a** (>20:1 dr, 94% ee) was obtained in 72% yield (yield based on enal **2a**), the azomethine imine **1a** was recovered in 58% yield (yield based on **1a** initially used)

dx.doi.org/10.1021/ja411110f | J. Am. Chem. Soc. 2014, 136, 1214–1217

and 51% ee. Since optically enriched azomethine imines are useful building blocks for a range of reactions,[23] we decided to optimize our conditions for their kinetic chiral resolutions. Prior to our work, the only related study we can find in the literature is Fu's Cu-catalyzed [3+2] cycloaddition to resolve azomethine imines with an *S*-factor of 15−96.[4b] In short, by increasing the relative equivalents of enal (**2a**) (see SI for details), a variety of azomethine imines could be resolved with high selectivity factors (S = 60−339) and good yield and ee (Table 2). It is worth noting that previously NHC organocatalysis has mainly been used for the kinetic resolution of alcohols and amines through the formation of esters and amides, respectively.[24] In those reported reactions, the alcohol/amine reactive sites are close to the chiral NHC catalysts. In our kinetic resolution of azomethine imines, the substrate reactive sites are remote (multiple bonds away) from the NHC catalysts. Our results suggest that resolving the remote chiral centers via NHC organocatalysis can be developed as a useful strategy for challenging substrates.

Table 2. Kinetic Resolution of Azomethine Imines 1[a]



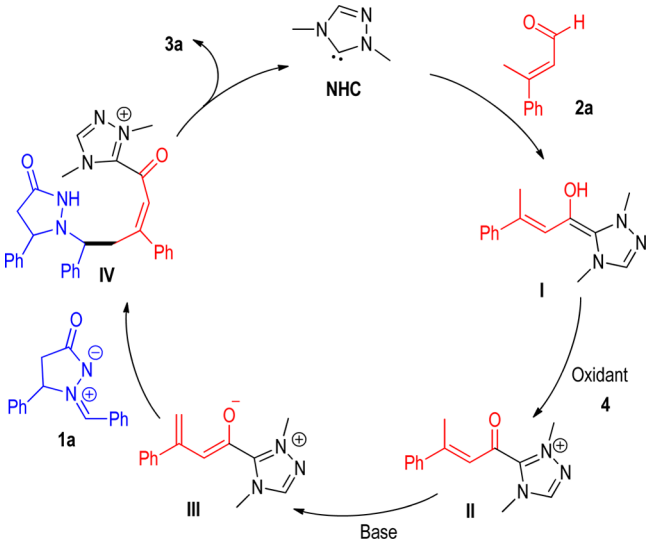
			(*S*)-**1**		**3**		
entry	**1**	conv[b] (%)	yield[c] (%)	ee (%)	yield[c] (%)	ee (%)	*S*[d]
1	**1a**	49	38	93	41	96	168
2	**1b**	44	40	73	37	93	60
3	**1d**	50	39	96	44	96	194
4	**1g**	49	42	91	40	93	88
5	**1i**	35	51	53	26	99	339

[a]Reaction conditions: (*rac*)-**1** (0.1 mmol), **2a** (0.12 mmol), NHC **D** (0.02 mmol), **4** (0.12 mmol), K_2CO_3 (0.4 mmol), THF (2 mL), 4 Å molecular sieves. [b]Conversions of (*rac*)-**1**, conv = $ee_1/(ee_1 + ee_3)$. [c]Isolated yield based on **1** after chromatography; note maximum possible yield of (*S*)-**1** is 50%. [d]*S*-factor = $\ln[(1 - conv)(1 - ee_1)]/\ln[(1 - conv)(1 + ee_1)]$.

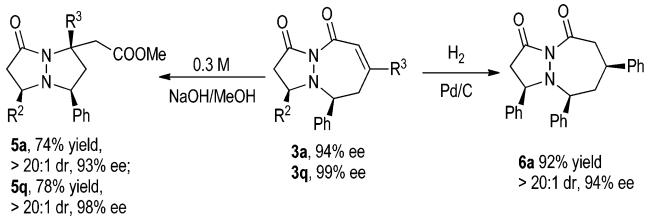
A postulated reaction pathway is illustrated in Scheme 1. Reaction of enal **2a** with NHC catalyst forms Breslow intermediate **I**. Oxidation of the Breslow intermediate converts **I** to a NHC-bound ester intermediate **II**. Base-mediated deprotonation on the γ-carbon of the NHC-bound α,β-unsaturated ester intermediate **II** successfully gives vinyl enolate intermediate **III**.[17] This vinyl enolate intermediate behaves as a 1,4-dipolarophile to react with azomethine imine **1a** to eventually form the formal [3+4] cycloaddition adduct **3a** with a regeneration of the NHC catalyst. The kinetic resolution originates from the reactivity difference between the chiral vinyl enolate intermediate **III** and the two enantiomers of the azomethine imine substrate.

The synthetic transformations of the seven-membered [3+4] cycloaddition adducts were then evaluated (Scheme 2). Under a simple protocol of NaOH in methanol, opening of the seven-membered lactam ring of **3a** (or **3q**) followed by an intramolecular Michael addition gave a dinitrogen-fused five-membered heterocyclic compound **5a** (or **5q**) bearing a quaternary carbon center. No apparent erosion of product ee occurred and **5a** (or **5q**[21]) was obtained with >20:1 dr and 93% ee (or 98% ee). The unsaturated carbon−carbon double bond in **3a** could be selectively reduced under H_2 with Pd/C catalyst to give **6a** with 92% yield, > 20:1 dr, and 94% ee.

Scheme 1. Postulated Reaction Pathway



Scheme 2. Transformation of Compound 3



In summary, we have developed a NHC-catalyzed highly diastereoselective (>20:1 dr) and enantioselective (84−99% ee) [3+4] cycloaddition of azomethine imines and enals. NHC-catalyzed remote activation of enals under oxidative conditions affords vinyl enolate intermediates as 1,4-dipolarophiles. Racemic azomethine imines (0% ee) can be used as 1,3-dipolar substrates to afford dinitrogen-fused seven-membered heterocyclic compounds with high optical purities (up to 99% ee). In this catalytic process, the NHC catalyst enables highly effective kinetic resolution of azomethine imines (*S*-factor up to 339). The fact that the substrate's chiral center which is remote to the NHC catalysts can be effective resolved is impressive. Further exploration of NHC organocatalysis for unusual cycloadditions and kinetic resolutions is under progress in our laboratory. In particular, kinetic resolution of challenging substrates bearing remote chiral centers is of our ongoing interest.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support for this work is provided by Singapore National Research Foundation, Singapore Economic Development Board, GlaxoSmithKline, and Nanyang Technological University (NTU). We thank Dr. Y. Li and Dr. R. Ganguly (NTU) for X-ray structure analysis.

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(21) CCDC 968788 (**3j**) and CCDC 968789 (racemic **5q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(22) When R^1 or R^3 is an alkyl unit (e.g., when R^1 is a cyclohexyl substituent or R^3 is a methyl group), or when R^2 is a proton, the cycloaddition products are not obtained. In these cases, amide formation between the azomethine imine and the oxidized enal substrate is a major side reaction.

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