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Enantioselective Synthesis of Imidazolines with Quaternary Stereocenters by Organocatalytic Reaction of *N*-(Heteroarenesulfonyl)imines with Isocyanoacetates

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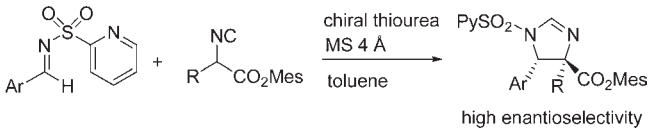
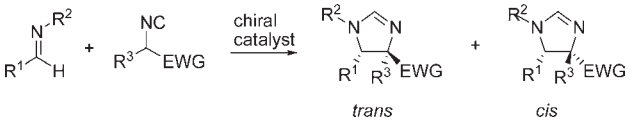
ABSTRACT



An organocatalytic enantioselective Mannich-type reaction of isocyanoacetate with *N*-sulfonylimines catalyzed by chiral thioureas derived from quinine yielded 2-imidazolines with high diastereo- and enantioselectivities (up to >99:1 dr. and 96% ee). This reaction provided a convenient route to access various imidazolines and related α,β-diamino acids having a quaternary carbon center in high enantiomeric purities.

The construction of optically active 2-imidazolines has received considerable attention because of their wide applications in the synthesis of biologically active compounds[1] and also their synthetic importance.[2] Furthermore, chiral imidazoline derivatives can be readily hydrolyzed to chiral 2,3-diamines, which are a constituent of several antibiotics as well as other biologically active compounds.[3] Therefore, their broad utility has prompted considerable interest to develop asymmetric methods for the preparation of imidazolines. One of the most efficient methods for the synthesis of chiral imidazolines is the catalytic enantioselective Mannich-type condensation of imines with isocyanides containing an electron-withdrawing group (EWG) at the α-carbon (Scheme 1).[4−6]

Scheme 1. Construction of Imidazolines through the Reaction of Imines with Isocyanoacetates



The first enantioselective reaction of sulfonylimines with isocyanoacetates was reported by Lin and co-workers

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(3) For reviews, see: (a) Viso, A.; de la Pradilla, R. F.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196. (b) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940–1948. (c) Viso, A.; de la Pradilla, R. F.; Tortosa, M.; Garca, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1–PR42 and references therein. See also: (d) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382–4385.

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(5) For organocatalytic enantioselective reactions of imines with isocyanides giving 5-aminooxazoles, see: Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717–6721.

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using Me_2SAuCl and a ferrocene-derived diphosphine ligand to afford imidazolines with up to 88% ee.[4a] Szabó and co-workers also reported the asymmetric synthesis of imidazolines using a chiral palladium-pincer complex in 98% yield with 86% ee for the cis isomer.[4b] Although pioneering work on the enantioselective formation of imidazolines using chiral transition metal catalysts has been done, there is only one report on the organocatalytic asymmetric reaction of imines with isocyanoacetates.[4c] Chan and co-workers reported that the reaction of methyl isocyanoacetate with *N*-(toluenesulfonyl)imines in the presence of 20 mol % of cinchona alkaloid catalysts afforded products with up to 70% ee. On the other hand, the construction of a stereogenic quaternary carbon center by the reaction of imines with α-substituted isocyanoacetates is highly desirable; however, the synthesis of optically active 2-imidazolines having a quaternary stereocenter has not been reported. Recently, we developed a highly enantioselective reaction using *N*-sulfonylimines having heteroarenesulfonyl groups, which act as highly functionalized activating groups, with various nucleophiles using bifunctional organocatalysts.[7] Herein, we report an efficient asymmetric synthesis of 2-imidazolines having a quaternary stereocenter from the reaction of *N*-(heteroarenesulfonyl) imines with α-substituted isocyanoacetates using bifunctional organocatalysts.

First, we examined the reaction of various *N*-(arenesulfonyl)-imines **1a**−**c** with isocyanoacetates **2a**−**c** in the presence of various chiral organocatalysts **4**−**7** (Figure 1). The results are shown in Table 1.

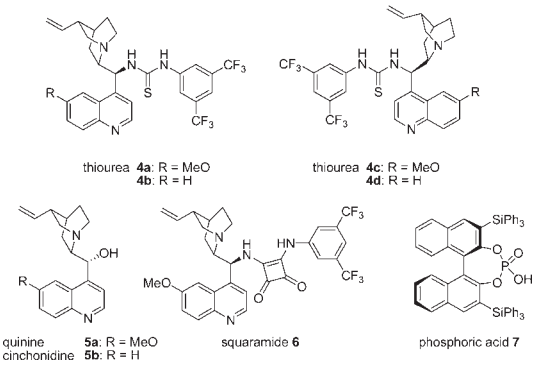
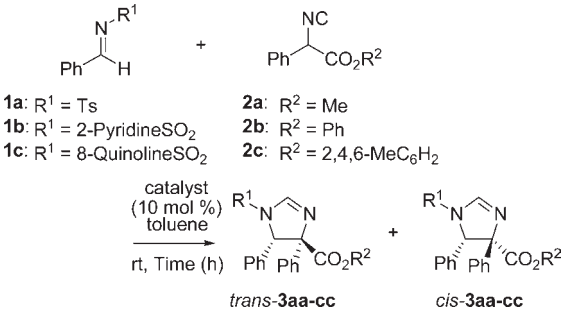


Figure 1. Structures of organocatalysts.

Table 1. Enantioselective Reaction of Imines and α-Substituted Isocyanoacetates Using Various Organocatalysts



run	1	2	catalyst	time (h)	yield (%)	dr[a] *trans*/*cis*	er (%)[b]
1	**1a**	**2a**	**4a**	0.5	99	71:29	59:41
2	**1b**	**2a**	**4a**	1	84	77:23	83:17
3	**1c**	**2a**	**4a**	1	86	82:18	78:22
4	**1b**	**2a**	**4b**	1	94	74:26	81:19
5	**1b**	**2a**	**4c**	1	85	69:31	22:78
6	**1b**	**2a**	**4d**	1	87	72:28	22:78
7	**1b**	**2a**	**5a**	1	99	80:20	60:40
8	**1b**	**2a**	**5b**	0.5	96	53:47	53:47
9	**1b**	**2a**	**6**	0.5	87	52:48	70:30
10	**1b**	**2a**	**7**	16	–	–	–
11	**1b**	**2b**	**4a**	0.5	96	79:21	87:13
12	**1b**	**2c**	**4a**	0.5	86	91: 9	86:14
13[c]	**1b**	**2c**	**4a**	0.5	98	85:15	91:9
14[c,d]	**1b**	**2c**	**4a**	0.5	98	99: 1	91:9
15[c,d]	**1a**	**2c**	**4a**	1	95	99: 1	79:21

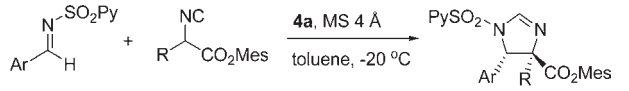
[a] Diastereomer ratio (dr) was determined by ^{1}H NMR analysis. [b] Enantiomer ratio (er) for major diastereomer was determined by HPLC analysis using a chiral column. [c] At −20 °C. [d] MS 4 Å was added.

(6) For a review on the enantioselective reaction of isocyanides, see: (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331. For organocatalytic enantioselective reactions of aldehydes with isocyanides, see: (b) Xue, M.-X.; Guo, C.; Gong, L.-Z. *Synlett* **2009**, 2191–2197. For organocatalytic enantioselective reactions of α,β-unsaturated carbonyl compounds with α-substituted isocyanides, see: (c) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jai, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947–2953. (d) Wang, L.-L.; Bai, J.-F.; Peng, L.; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.; Wang, L.-X. *Chem. Commun.* **2012**, *48*, 5175–5177. For organocatalytic enantioselective reaction of nitroolefins with isocyanide, see: (e) Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414–3417. For enantioselective reaction of aldehydes with isocyanides using chiral metal catalysts, see: (f) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406. (g) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215–6218. (h) Pastor, S. T..; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334. (i) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799–2802. (j) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron Lett.* **1992**, *48*, 1999–2012. (k) Soloshonok, A. V.; Kacharov, D. A.; Hayashi, T. *Tetrahedron* **1996**, *52*, 245–254. (l) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374–4379. (m) Motoyama, Y.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 1684–1696. (n) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Oganometallics* **2002**, *21*, 3408–3416. (o) Gosiewska, S.; in't Veld, M. H.; de Pater, J. J. M.; Bruijnincx, P. C. A.; Lutz, M.; Spek, A. L.; van Kotena, G.; Gebbinka, R. J. M. K. *Tetrahedron: Asymmetry* **2006**, *17*, 674–686. (p) Yoon, S. M.; Ramesh, R.; Kim, J.; Ryu, D.; Ahn, H. K. *J. Organomet. Chem.* **2006**, *691*, 5927–5934. (q) Wang, S.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, 4076–7080. (r) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Org. Lett.* **2007**, *9*, 3615–3618. (s) Gosiewska, S.; Herreras, S. M.; Lutz, M.; Spek, A. L.; Havenith, R. W. A.; van Klink, G. P. M.; van Koten, G.; Gebbink, R. J. M. K. *Organometallics* **2008**, *27*, 2549–2559. (t) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388–391. (u) Yue, T.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454–9457. (v) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384–8385. (w) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306–1309. (x) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713. For enantioselective reactions of α,β-unsaturated carbonyl compounds with α-substituted isocyanides using chiral metal catalysts, see: (y) Song, J.; Guo, C.; Chen, P.-H.; Yu, J.; Luo, S.-W.; Gong, L.-Z. *Chem.—Eur. J.* **2011**, *17*, 7786–7790. (z) Padilla, S.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2012**, *77*, 4161–4166. For enantioselective reaction of nitroolefins with isocyanide using chiral metal catalysts, see: (aa) Arróniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Sosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, 3755–3760.

Chiral thiourea **4a** derived from quinine can activate the reaction of **1a** with **2a** to give product **3aa** in high yield but with low diastereo- and enantioselectivity (entry 1).[8] The reaction of imines **1b,c** having heteroarenesulfonyl groups, such as a 2-pyridinesulfonyl- or 8-quinolinesulfonyl group, with **2a** afforded products **3ba**, **3ca** with good diastereoselectivity and moderate enantioselectivity (entries 2 and 3).[9] To improve the stereoselectivity, we next optimized the structure of organocatalysts. The reaction of **1b** with **2a** using various chiral thioureas **4b**−**d**, cinchona alkaloids **5a, b**, and squaramide **6** afforded product **3ba** with lower enantioselectivity than that using **4a** (entry 2 vs 4−9). Our previous studies on the Friedel−Crafts alkylation reaction of *N*-(2-pyridinesulfonyl)imines with pyrroles or indole showed that chiral phosphoric acid **7** is an effective organocatalyst;[7b] however the reaction of **1b** with **2a** using **7** did not give the product **3ba** (entry 10). Therefore, the chiral thiourea **4a** finally proved to be the catalyst of choice. We next examined the reaction using several alkyl or aryl 2-phenyl-1-isocyanoacetates **2b,c**. The reaction using a phenyl ester or 2,4,6-trimethylphenyl ester of isocyanoacetates **2b,c** afforded products **3bb, 3bc** in high yields with high diastereo- and enantioselectivities (entries 11 and 12). When the reaction was carried out at lower temperature, the enantioselectivity improved slightly more than that at room temperature (entry 13). The addition of 4 Å molecular sieves improved the diastereoselectivity of the reaction without a loss of enantioselectivity (entry 14). We examined the reaction of **1a** under the best reaction conditions to give the product **3ac** but with low enantioselectivity (entry15). This result provides evidence of the clear superiority of the 2-pyridinesulfonyl group as a stereocontrolling auxiliary. To our knowledge, this is the first example of the enantioselective synthesis of imidazoline having a quaternary stereocenter through the reaction of α-substituted isocyanoacetates with imines.

With these optimized conditions, the reaction of a series of *N*-(2-pyridinesulfonyl)imines **1b**−**m** and α-substituted isocyanoacetates **2c**−**i** using **4a** was examined (Table 2).

Table 2. Enantioselective Formation of 2-Imidazolines Using Various Imines **1b**−**m** and α-Substituted Isocyanoacetates **2c**−**i**



1b-m **2c-i** **8-20**

entry	Ar	R	product	yield (%)	dr *trans*/*cis*	er (%)[a]
1	Ph	Ph	**3bc**	98	99:1	91:9
2	4-MeC_6H_4	Ph	**8**	83	95:5	92:8
3	4-$MeOC_6H_4$	Ph	**9**	90	97:3	91:9
4	4-BrC_6H_4	Ph	**10**	87	98:2	94:6
5	4-ClC_6H_4	Ph	**11**	87	98:2	94:6
6	4-$NO_2C_6H_4$	Ph	**12**	99	99:1	98:2
7	2-BrC_6H_4	Ph	**13**	86	99:1	92:8
8	3-BrC_6H_4	Ph	**14**	83	99:1	95:5
9	1-Naphthyl	Ph	**15**	91	99:1	94:6
10	2-Naphthyl	Ph	**16**	87	98:2	94:6
11	2-Thienyl	Ph	**17**	71	81:19	87:13
12	Ph	*p*-ClPh	**18**	96	98:2	93:7
13[b]	Ph	*p*-FPh	**19**	84	91:9	91:9
14[c]	Ph	Me	**20**	90	83:17	89:11
15	Ph	CH_2Ph	**21**	79	99:1	90:10
16[c]	Ph	*i*Bu	**22**	85	73:27	94:6
17[c]	Ph	*i*Pr	**23**	–	–	–

[a] Enantiomer ratio for major diastereomer was determined by HPLC analysis using a chiral column. [b] At −40 °C. [c] At rt.

The reaction with both electron-donating and -withdrawing imines **1d**−**j** gave products **8**−**14** in high yield with high stereoselectivity (entries 2−8). The reaction of imines having a 1- or 2-naphthyl group or heteroaryl group also resulted in high enantioselectivity (entries 9−11). The absolute configuration of a major diastereomer of **10** (Ar = *p*-BrC_6H_4) was determined to be a (4*R*,5*S*)-isomer by X-ray crystallography analysis (see Supporting Information), and the stereochemistry of other products was tentatively assumed by analogy. The reaction of **1b** and various α-substituted isocyanoacetates **2d**−**h** using **4a** afforded products **18**−**22** in good yield with high diastereo- and enantioselectivity (entries 12−16). However, the reaction with isocyanide **2i** having a bulky isopropyl group did not afford the product (entry 17).

We next examined the deprotection of the pyridinesulfonyl group from the imidazoline product and the transformation of imidazoline to a chiral diamine. The recrystallization of product **10** afforded a diastereo- and enantiomerically pure compound. The pyridinesulfonyl group in **10** can be removed by magnesium in MeOH to give nonprotected 2-imidazoline **24** without a loss of diastereo- and enantiopurity (Scheme 2).

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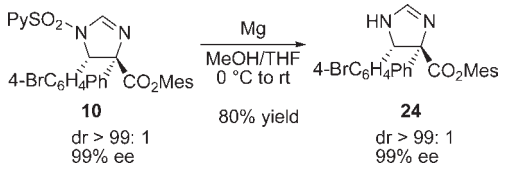
(8) For selected reviews for thiourea catalysts, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306. (b) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785–795. (c) Yu, X.; Wang, W. *Chem.—Asian. J.* **2008**, *3*, 516–532. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. (e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.

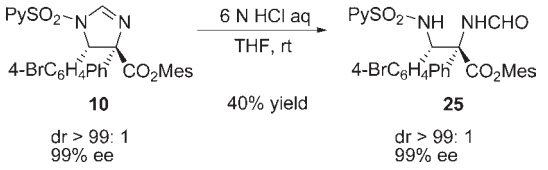
(9) We also tried the reaction of Boc-imine, however the product could not be obtained.

Scheme 2. Synthesis of *N*-Nonsubstituted Imidazoline **10**



The hydrolysis of imidazoline **10** using 6 N HCl afforded chiral diamine **25** without a loss of stereoselectivity (Scheme 3).

Scheme 3. Transformation of **10** to α,β-Diaminoacid **25**



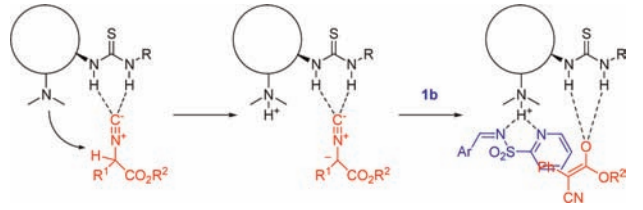


Figure 2. Proposed reaction mechanism for the reaction of *N*-(2-pyridinesulfonyl)imines with isocyanoacetates.

On the basis of the obtained results, we envisioned that catalyst **4a** could act in a bifunctional fashion, as previously proposed in the literature for chiral thiourea catalysts. The capacity to activate both substrates by a bifunctional catalyst in a cooperative manner would result in high catalytic activity and stereoselectivity. The proposed activating mechanism for the reaction of *N*-(2-pyridinesulfonyl)imines with isocyanoacetates using a chiral thiourea catalyst is shown in Figure 2. Thiourea functionalities in catalyst **4a** coordinates to the isocyano group in isocyanoacetate by hydrogen bonding to enhance the acidity of the α-proton on isocyanide.[10] Then, a basic site in catalyst **4a** deprotonates the acidic α-proton of isocyanide. Next, the generated α-isocyano carbanion converts to a more stable ester enolate.[11] Then, two nitrogens for pyridine and imine in *N*-(2-pyridinesulfonyl)imines coordinate to hydrogen in protonated **4a**. In this structure, the pyridyl group in **1b** plays an important role in stabilizing the hydrogen bonding. The addition of the α-carbanion of isocyanoacetate to the imine in the coordination sphere of chiral thiourea led to a chiral product.

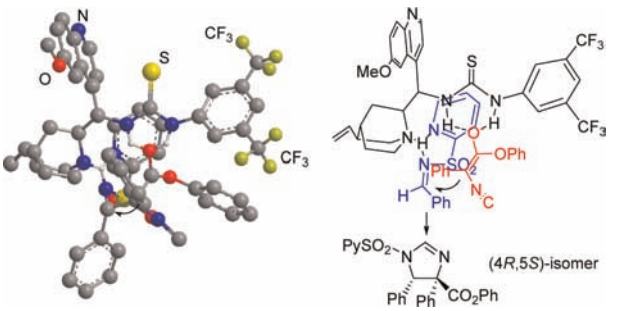


Figure 3. Proposed transition state for the reaction of *N*-(2-pyridinesulfonyl)imines **1b** with isocyanoacetate **2b**. H-atoms have been omitted for clarity.

From the above consideration and the absolute stereochemistry of the product, the proposed transition state for the enantioselective reaction of α-substituted isocyanoacetates with *N*-(2-pyridinesulfonyl)imines **1b** is shown in Figure 3. The *Z*-geometry of **1b** is preferred due to the steric repulsion between the quinuclidine ring in **4a** and phenyl group in **1b**. The enolate of isocyanoacetate approaches *N*-(2-pyridinesulfonyl)imines avoiding steric repulsion with the quinuclidine group; therefore the (4*R*,5*S*)-isomer is preferably formed. Therefore, the chiral thiourea **4a** would act as a dual activating organocatalyst. Further studies are required to fully elucidate the mechanistic detail of the reaction.

In conclusion, we developed the first highly enantioselective reaction of *N*-(heteroarenesulfonyl)imines with α-substituted isocyanoacetates. The obtained products can be converted to chiral nonprotected imidazolines. This process offers a simple and efficient route for synthesis of functionalized 2-imidazolines. Further studies are in progress to study the potential of *N*-(heteroarenesulfonyl)imines for other process.

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Supporting Information Available. Representative experimental procedures and NMR spectra of the products. This material is available free of charge via Internet at http://pubs.acs.org.

(10) For strong hydrogen bonding to carbon in isocyanide, see: Schleyer, P. V. R.; Allerhand, A. *J. Am. Chem. Soc.* **1962**, *84*, 1322–1323. Recently, the enhancement for acidity of isocyanoacetates by coordinating with achiral thiourea catalysts has been reported; see ref 6u.

(11) The possibility that the direct reaction between the generated α-isocyano carbainons and **1b** cannot be ruled out. This reaction pathway also affords the product with the same stereochemistry.

The authors declare no competing financial interest.