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Catalytic Asymmetric Construction of Chiral Hydropyridazines *via* Conjugate Addition of *N*-Monosubstituted Hydrazones to Enones

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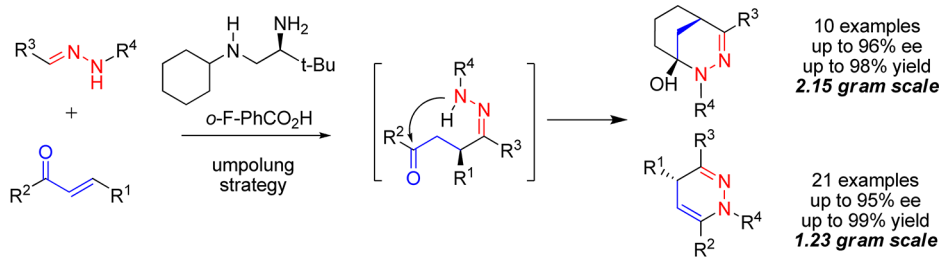
ABSTRACT



The first example of a highly enantioselective and scalable formal diaza–ene reaction between N-monosubstituted hydrazones and enones catalyzed by a simple chiral primary-second diamine salt has been developed. The catalytic process provides a highly practical and stereoselective synthetic method for chiral hydropyridazines.

The chemistry of hydropyridazine derivatives has been extensively studied reflecting their wide range of pharmacological activities, performing as anti-inflammatory and cardiovascular agents, antidepressants, and GABA antagonists.[1] Tetrahydropyridazine derived molecules levosimendan and pimobendan were used as an ionotropic agent and cardiotonic vasodilator, respectively. 1,4-Dihydropyridazine derivatives acted as vasodilators, coronary therapeutic agents, and spasmolytic agents, particularly when the substituent at C4 was aromatic.[2] Despite this, only limited asymmetric methodologies have been realized for the synthesis of hydropyridazines.[3,4] Motivated by the variable and significant biological activities observed in tetrahydropyridazines and 1,4-dihydropyridazines, we envisioned that the hydropyridazine skeleton

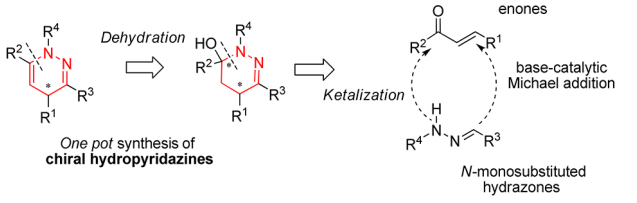


Figure 1. Design approaches for chiral hydropyridazines.

(1) (a) Heinisch, G.; Kopelent-Frank, H. In *Progress in Medicinal Chemistry*, Vol 29; Ellis, G. P.; Luscombe, D. K. Elsevier: Amsterdam, 1992. (b) Joule, J. A.; Mills, K. *Hetreocyclic Chemistry*, 5th ed.; Blackwell Science, Oxford, 2000. (c) Kolar, P.; Tiler, M. In *Advances in Heterocyclic Chemistry*, Vol. 75; Katritzky, A. R. Academic Press: San Diego, 2000. (d) Testa, R.; Leonardi, A.; Tajana, A.; Riscassi, E.; Magliocca, R.; Sartani, A. *Cardiovasc. Drug Rev.* **1997**, *15*, 187–219.

(2) (a) Frankowiak, G.; Meyer, H.; Bossert, F.; Heise, A.; Kazda, S.; Stoepel, K.; Towart, R.; Wehinger, E. U.S. Patent 1982, No. 4348395. (b) Scarsdale, B. L.; Ossining, H. J.; Shroff, J. R.; Conn. R. U.S. Patent 1984, No. 4,435,395. (c) Riehen, A. V. U.S. Patent 1985, No. 4491581.

(3) For selected examples on the synthesis of achiral hydropyridazines: (a) Nair, V.; Mathew, S. C.; Biju, A. T.; Suresh, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2070–2073. (b) Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. *V. Angew. Chem., Int. Ed.* **2010**, *49*, 6139–6142. (c) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550–2551.

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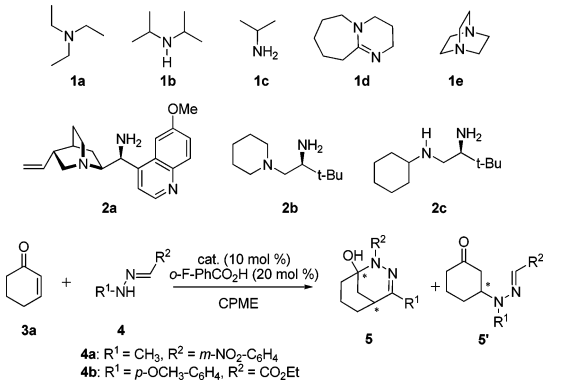
could be constructed through sequential base-catalytic asymmetric conjugate reactions between enones and *N*-monosubstituted hydrazones using an umpolung strategy,[5] intramolecular aminal formation, and subsequent dehydration in one pot (Figure 1), which could enrich asymmetric access to this type of chiral diaza-heterocycle.[6]

Hydrazones, which show very diverse reactivity, can be used as formyl anion equivalents in organic synthesis, where they participate in nucleophile−electrophile interactions.[7] Conventionally, *N*,*N*-dialkylhydrazones were applied in the total synthesis of natural products as practical chiral auxiliary reagents[8] and have been reported as useful ligands and catalysts[9] in asymmetric reactions. Besides, differing from the reactions where they acted as electrophiles,[10] conjugate additions where *N*,*N*-dialkylhydrazones were used as nucleophiles have been realized recently.[11−13] In comparison, asymmetric conjugate addition of *N*-monosubstituted hydrazones in organocatalysis still remains problematic and challenging due to the competitive aza-Michael addition[14] and carbo-Michael addition[15] (formal diaza-ene reaction). The site selectivity was dependent on the *N*-monosubstituted hydrazones used in each organocatalytic reaction.

Herein, our ongoing interest was extended to an efficient and highly enantioselective formal diaza−ene reaction between *N*-monosubstituted hydrazones with broad substrate variables and enones, avoiding a competitive reversible[16] aza-Michael reaction simultaneously, which have not been reported to the best of our knowledge.

Table 1. Reaction Optimization[a]



entry	cat.	4a/4b	*T* (°C)	time (h)	yield (%)[b]	5/5′	ee of 5/5′(%)[c]
1	**1a**−**1e**	**4a**	rt	24	44−58[d]	<1/99	n.d./0
2	**2a**	**4a**	rt	24	96	3/97	n.d./0
3	**2b**	**4a**	rt	24	97	<1/99	n.d./0
4	**2c**	**4a**	rt	24	96	40/60	90/0
5	**2c**	**4a**	rt	3	96	7/93	89/0
6[e]	**2c**	**4a**	rt	24	95	38/62	90/0
7[f]	**2c**	**4a**	rt	24	95	42/58	90/0
8[g]	**2c**	**4a**	rt	48	94	93/7	96/n.d.
9	**2c**	**4a**	rt	72	95	80/20	90/0
10	**2c**	**4a**	0	72	94	27/73	92/0
11	**2c**	**4a**	−40	72	90	2/98	n.d./0
12[h]	**2c**	**4b**	rt	72	94	>99/1	90/n.d.

[a] Reaction conditions: 0.20 mmol of **3a**, 0.30 mmol of **4a**, catalyst (10 mol %), and acid (20 mol %) were stirred in CPME (C = 0.5 M) at rt. [b] Yield was determined after chromatography. [c] Enantiomeric excess was determined by chiral HPLC. [d] Yields for catalysts **1a**−**1e** are 44%, 55%, 58%, 51%, 58% respectively. [e] 10 mol % acid. [f] 30 mol % acid. [g] 160 mol % acid. [h] 20 mol % catalyst and 40 mol % acid. The ratio of the two products was determined by ^{1}H NMR of the crude reaction and confirmed by chiral HPLC. All products' dr were >20/1. CPME = Cyclopentyl methyl ether.

We initiated our studies by exploring the nucleophilic character of *N*-monosubstituted hydrazones **4**. Choosing the model reaction between compounds **3a** and **4a**, we focused our studies on a series of achiral amines with

(4) For selected examples on asymmetric synthesis of hydropyridazines: (a) Shen, L.-T.; Sun, L.-H.; Ye, S. *J. Am. Chem. Soc.* **2011**, *133*, 15894–15897. (b) Xu, X.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9829–9833. (c) Das, A.; Volla, C. M. R.; Atodiresei, I.; Bettray, W.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 8008–8011.

(5) For reviews on umpolung strategies, see: (a) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357–402. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258. (c) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.

(6) For selected examples on the synthesis of chiral diaza-heterocycles catalyzed by a transition metal, see: (a) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710–10711. (b) Yamashita, Y.; Kobayashi, K. *J. Am. Chem. Soc.* **2004**, *126*, 11279–11282. (c) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276–8277. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174–2175. For selected examples on synthesis of chiral aza-heterocycles catalyzed by an organocatalyst, see: (e) Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9975–9978. (f) Müller, S.; List, B. *Synthesis* **2009**, 2171–2178. (g) Mahé, O.; Dez, I.; Levacher, V.; Brière, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7072–7075. (h) Campbell, N. R.; Sun, B.; Singh, R. P.; Deng, L. *Adv. Synth. Catal.* **2011**, *353*, 3123–3128.

(7) For reviews, see: Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629–5660.

(8) For excellent reviews on hydrazones used as practical chiral auxiliary reagents in total synthesis: (a) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329. (b) Samment, K.; Gastl, C.; Baro, A.; Laschat, S.; Fischer, P.; Fetting, I. *Adv. Synth. Catal.* **2010**, *352*, 2281–2290.

(9) For an excellent review on hydrazones used as ligands and catalysts: Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386–1434.

(10) For reviews, also see ref 7and: (a) Enders, D.; Bolkenius, M.; Vázquez, J.; Lassaletta, J. M.; Fernández, R. *J. Prakt. Chem.* **1998**, *340*, 281–285. (b) Fernández, R.; Lassaletta, J. M. *Synlett* **2000**, 1228–1240.

(11) (a) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Pareja, C. *Tetrahedron Lett.* **1996**, *37*, 5787–5790. (b) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Vázquez, J.; Díez, E.; Monge, A.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3428–3430. (c) Pareja, C.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 8846–8854. (d) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Lassaletta, J. M. *J. Org. Chem.* **2001**, *66*, 5201–5207. (e) Crespo-Peña, A.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Chem.—Asian J.* **2011**, *6*, 2287–2290.

(12) Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303–3306.

(13) (a) Dixon, D.; Tillman, A. L. *Synlett* **2005**, 2635–2638. (b) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065–1068. (c) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556–7557.

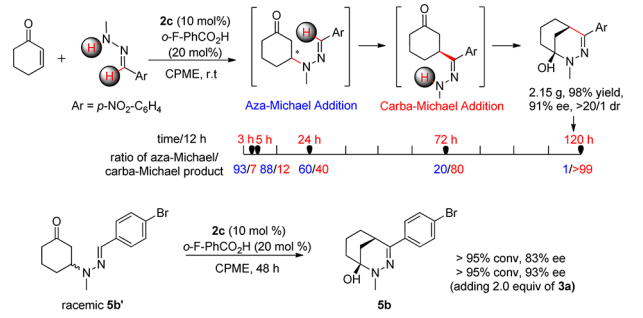
(14) (a) Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565–3568. (b) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249–2252.

(15) (a) Crespo-Peña, A.; Monge, D.; Martín-Zamora, E.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 12912–12915. (b) Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872–11875.

(16) For examples on the reversible addition step of the NH group of aza-Michael reactions, see refs 6e−6h and 14; for reviews, see: (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513–518. (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058–11076.

various pK_a values. Only the aza-Michael addition product was detected when the reaction was catalyzed by **1a**–**1e**'s *o*-fluorobenzoic acid (OFBA) salt with a 44% to 58% yield (Table 1, entry 1). Next, we turned our attention to bifunctional chiral diamine catalysts. Using 9-amino(9-deoxy)-*epi*-quinine's OFBA salt as the catalyst, the aza-Michael product was detected with a 96% yield while 3% trace formal diaza-ene reaction product was detected (entry 2). To our delight, 40% of the desired product with 90% ee was observed catalyzed by diamine **2c** derived from a chiral amino acid[17] in the presence of OFBA after stirring for 24 h (entry 4), while only a racemic aza-Michael addition product was detected catalyzed by **2b** (entry 3). With these distinct results in hand, we attempted to study the competitive reaction between aza/carba-Michael additions. The aza-Michael reaction completed in 3 h catalyzed by **2c** with 7% of the formal diaza–ene reaction product (entry 5). After testing the amount of the acidic additives, it was found that the results were basically the same (entries 6–7). Considering the reversible aza-Michael reaction step, the reaction time was extended to 72 h and the ratio of the two products was raised to 80/20 (entry 9). Moreover, when 160 mol % of OFBA was added, the reaction was completed in 48 h and 93% of the formal diaza–ene reaction product was obtained with 96% ee (entry 8). Lowering the reaction temperature could selectively synthesize the aza-Michael product but with poor enantioselectivity (entries 10–11). On the other hand, only the formal diaza–ene reaction product was observed using monosubstituted *N*-aryl hydrazone **4b** with a 94% yield and 90% ee without the aza-Michael reaction product (entry 12).

Scheme 1. Competitive Aza-Michael and Carba-Michael Reactions and Control Experiments

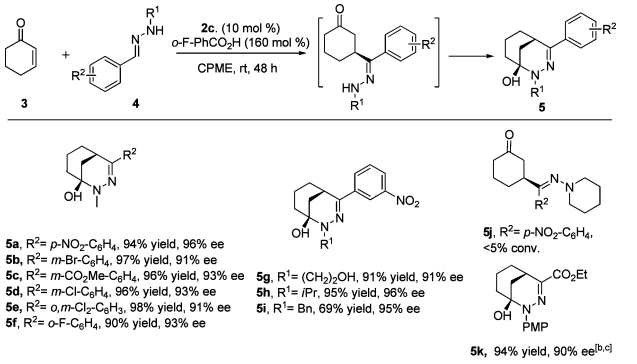


(17) (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505. (b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. (c) Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2008**, *14*, 10888–10891. (d) Li, J.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 1747–1750. (e) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wong, K.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 11105–11108. (f) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3232–3235. (g) Hu, S.; Zhang, L.; Li, J.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2011**, 3347–3352. (h) Yu, F.; Hu, H.; Gu, X.; Ye, J. *Org. Lett.* **2012**, *14*, 2038–2041. (i) Wu, W.; Huang, H.; Yuan, X.; Zhu, K.; Ye, J. *Chem. Commun.* **2012**, *48*, 9180–9182. (j) Wu, W.; Li, X.; Huang, H.; Yuan, X.; Lu, J.; Zhu, K.; Ye, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1743–1747. (k) Huang, H.; Wu, W.; Zhu, K.; Hu, J.; Ye, J. *Chem.—Eur. J.* **2013**, *19*, 3838–3841.

As shown in Scheme 1 (top), the ratio of aza-Michael/carba-Michael reaction products slowly changed from 93/7 to 1/>99 along with extending the reaction time (for details, see Supporting Information (SI)). To prove the validity of the proposed reaction process, control experiments were carried out (Scheme 1, bottom). Full conversion of the carba-Michael reaction product with 83% ee was obtained when racemic aza-Michael product **5b′** was used as the only substrate catalyzed by **2c** and starting materials **3a** and **4b** were detected in the process of the reaction. The enantioselectivity was raised to 93% by adding 2 equiv of cyclohex-2-enone.

After the optimal conditions had been established, the substrate scope was investigated. As summarized in Scheme 2, electron-withdrawing aromatic aldehyde related monosubstituted *N*-alkyl hydrazones were found to be tolerant of the reaction, affording the products **5a** to **5f** with excellent yields and 91–96% ee. 2-Hydrazinylethanol, isopropylhydrazine, and benzylhydrazine related hydrazones were also tested, leading to the products (**5g** to **5i**) with excellent enantioselectivities. Less than 5% of conversion was detected when *N*,*N*-dialkylhydrazones were used as the substrate (**5j**). When the reaction between monosubstituted *N*-aryl hydrazone **4b** and cyclic enones was evaluated, the formal diaza–ene reaction product was detected when cyclohex-2-enone was employed with a 94% yield and 90% ee (**5k**).

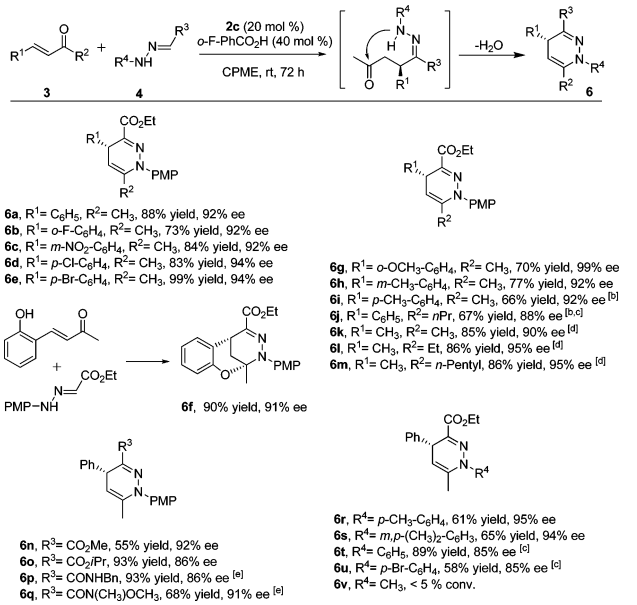
Scheme 2. Asymmetric Enantioselective Reaction of *N*-Monosubstituted Hydrazones To Synthesize Bicycle 1,4,5,6-Tetrahydropyridazines[a]



[a] Reaction conditions: 0.20 mmol of **3**, 0.30 mmol of **4**, catalyst **2c** (10 mol %), and *o*-F-PhCO$_2$H (160 mol %) were stirred in CPME (C = 0.5 M) at rt for 48 h. [b] **2c** (20 mol %) and *o*-F-PhCO$_2$H (40 mol %). [c] For 72 h. Yields refer to isolated yields. The ee value was determined by chiral HPLC analysis.

After this, we attempted to synthesize 1,4-dihydropyidazines. As summarized in Scheme 3, enones with different electron-withdrawing and -donating substituents at *ortho*, *meta*, and *para* positions on the aromatic ring were found to be tolerant of the reaction, affording a 76–99% yield and 92–94% ee (**6a**–**6i**). Interestingly, bridged-ring compound **6f** was synthesized through the following oxa-Michael addition to the iminium intermediate in 90% yield with 91% ee. Extending the length of the alkyl chain in the

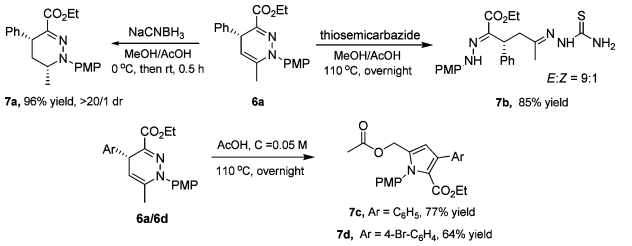
Scheme 3. Asymmetric Enantioselective Reaction of *N*-Monosubstituted Hydrazones To Synthesize 1,4-Dihydropyridazines[a]



[a] Reaction conditions: 0.20 mmol of **3a**, 0.30 mmol of **4a**, catalyst **2c** (20 mol %), and *o*-F-PhCO$_2$H (40 mol %) were stirred in CPME (C = 0.5 M) at rt for 72 h. [b] 0.60 mmol of **3**, 0.20 mmol of **4a**. [c] 50 °C for 72 h. [d] CPME/DCM = 1/1 (C = 0.5 M). [e] **2c** (30 mol %) and *o*-F-PhCO$_2$H (60 mol %), with additional 15 μL of H$_2$O. Yields refer to isolated yields. The ee value was determined by chiral HPLC analysis. PMP = *o*-CH$_3$O–C$_6$H$_4$.

α′ position of ketone lowered the reactivity, and 88% ee was obtained (**6j**). The reaction proceeded satisfactorily in all cases of alkyl enones with various chain lengths, furnishing adducts **6k**–**6m** in good yields and 90–95% ee. In further exploration, different types of hydrazones were tested. The ethyl ester group was changed into methyl and isopropyl ester, with 92% and 85% ee obtained respectively (**6n** and **6o**). When a weaker electron-withdrawing moiety (benzyl and Weinreb amide) was introduced to the substrate, the reactivity decreased. After a slight modification of the reaction parameters, including increasing the catalyst dosage and adding a small amount of deionized water, the yield and enantioselectivity of products **6p** and **6q** reached a satisfactory level. We then investigated the effect of the electronic properties of the *N*-aryl group. Electron-donating, neutral, and electron-withdrawing aromatic substituted hydrazones afforded the adducts in moderate to good yields with good enantioselectivities (**6r** to **6u**). The reaction hardly proceeded when *N*-alkyl substituted hydrazone was employed (**6v**). We are committed to exploring the nature of *N*-monosubstituted hydrazones in asymmetric organocatalytic reactions in the future.

Scheme 4. Transformations of the Formal Diaza–Ene Reaction Products



Finally, we tried to demonstrate the synthetic transformations of these products (Scheme 4). 1,4-Dihydropyridazine **6a** was successfully converted to 1,4,5,6-tetrahydropyridazine **7a** with >20/1 dr by reduction with NaCNBH$_3$ at 0 °C in the presence of AcOH. **6a** was hydrolyzed to form a carbonyl group *in situ* and immediately transformed into thiosemicarbazide related hydrazone **7b** by refluxing in MeOH/AcOH overnight. **7b** was obtained in 85% yield via single-crystal X-ray analysis, and the result revealed the configuration to be *R* (for details see SI). Multisubstituted pyrroles **7c** and **7d** were successfully synthesized in good yield (for X-ray analysis details see SI) utilizing carbonyl-hydrazone compounds as starting materials. Besides, gram-scale (0.9–2.15 g) synthesis of products **5a**, **5b**, and **6a** were realized in high yields and 91–96% enantioselectivities (see SI).

In summary, we have disclosed the first example of a highly enantioselective and scalable formal diaza–ene reaction between *N*-monosubstituted hydrazones and enones with broad substrate variables catalyzed by a primary-second diamine salt, affording enantioenriched products with excellent results (up to 98% yield and 99% ee). The catalytic process provides a highly practical synthetic method for bicycle 1,4,5,6-tetrahydropyridazines, 1,4-dihydropyidazines, which would be interesting in the search for diaza-heterocyclic compounds for novel therapeutic agents.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra, HPLC chromatograms of the products, and cif files for compounds CCDC 934931 (**5b**), CCDC 934930 (**6a**), CCDC 917404 (**7b**), CCDC 931694 (**7c**). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.