Cascade Catalysis

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Synthesis of Tetrahydropyridazines by a Metal–Carbene-Directed Enantioselective Vinylogous N–H Insertion/Lewis Acid-Catalyzed Diastereoselective Mannich Addition**

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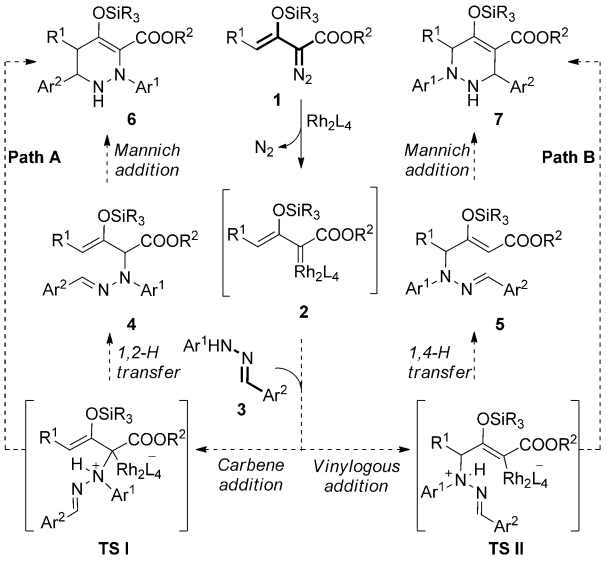
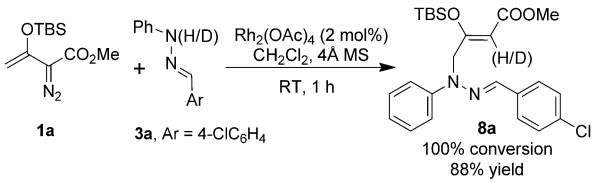
Although rare, formal [3+3]-cycloaddition reactions are known to occur through sequential reactions of an activated substrate, first with the nucleophilic site of a dipole and then with its electrophilic site to form the cycloaddition product.[1] Systems that follow this pathway include reactions of catalytically-generated substrates with nitrones[2,3] and azomethine imines;[2b,4] enantiocontrol, examples of which have only recently been published, occurs through the intervention of a chiral catalyst.[5] We envisioned that readily accessible hydrazones could be employed in place of azomethine imines to form tetrahydropyridazines[6] with enoldiazoacetates **1** (Scheme 1). Nucleophilic addition of hydrazone **3** to metal carbene intermediate **2** could occur either at the metal carbene center (**2**→**TS I**) or at the vinylogous position (**2**→**TS II**) to give **6** or **7**, respectively, after 1,2-hydrogen transfer between the two nitrogen atoms and Mannich addition (Path A and Path B). The 1,2-hydrogen transfer is formally a N–H insertion reaction but, in contrast to the direct process (**TS I**→**4**),[7] the 1,4-hydrogen transfer (**TS II**→**5**) from nitrogen to carbon is a vinylogous variant for which there has been no previous example of stereocontrol, although non-asymmetric vinylogous O–H insertion reactions and the asymmetric vinylogous C–H functionalization of several vinyldiazoacetates have recently been reported.[8] Herein, we report a highly selective catalytic process involving enoldiazoacetates in combination with aldehyde-derived hydrazones that occurs with high enantioselectivity and catalyst-controlled diastereoselectivity.



Scheme 1. Competitive pathways for [3+3]-cycloaddition reactions of arylhydrazones.

To determine the feasibility of the formal [3+3]-cycloaddition with hydrazones we treated 3-(*tert*-butyldimethylsiloxy)-2-diazo-3-butenoate **1a** and the phenylhydrazone of 4-chlorobenzaldehyde (**3a**) with a catalytic amount of dirhodium tetraacetate at room temperature in dichloromethane. Complete conversion occurred within one hour, but, instead of forming tetrahydropyridazines, the product from vinylogous N–H insertion (**8a**) was formed exclusively as the terminal product (Scheme 2). The *Z* geometry of the newly formed trisubstituted C=C bond in **8a** was confirmed by single crystal X-ray diffraction.[9] That the reaction process



Scheme 2. Test reaction for a formal [3+3]-cycloaddition with hydrazones. Yield shown is of isolated product. MS = molecular sieves, TBS = *tert*-butyldimethylsilyl, OAc = acetate.

was indeed a vinylogous N–H insertion was established by performing the reaction with deuterium-labeled **3a** (N–H proton exchange) from which deuterium was found to reside exclusively on the vinylic carbon atom alpha to the carboxylate ester.[10] Instead of undergoing the 1,2-proton transfer envisioned in Scheme 1, the hydrogen on nitrogen replaced the dirhodium catalyst at the original metal carbene center. Recognizing the advantages of this method, we investigated this transformation for enantiocontrol in the vinylogous N–H insertion reaction and, as **8** is suitable for intramolecular iminium ion ring closure,[11] Lewis acid catalysis was probed

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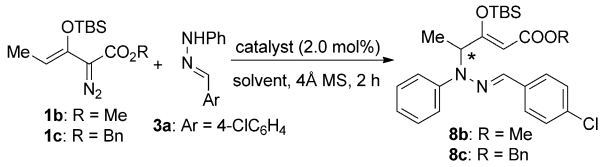
for subsequent diastereoselective cyclization to tetrahydropyridazines.

To address enantiocontrol in the vinylogous N–H insertion reaction, 3-(*tert*-butyldimethylsiloxy)-2-diazo-3-pentenoates **1b** (R^1 = Me, R^2 = Me) and **1c** (R^1 = Me, R^2 = Bn; Bn = benzyl) were treated with hydrazone **3a** in the presence of various chiral dirhodium catalysts, and the results from this investigation are summarized in Table 1. Except for [Rh_2{(*S*)-pttl}$_4$] (entry 4; see Table 1 for ligand structures), the phthalimide/amino acid-based chiral dirhodium carboxylate catalysts reported by Hashimoto et al.[12] showed higher reactivity and enantioselectivity than the [Rh_2{(*S*)-dosp}$_4$] catalyst reported by Davies et al.[13] (entries 1 and 2 vs. entry 7), and dirhodium carboxamidate catalysts[14] were ineffective (entries 5 and 6). Adopting benzyl enoldiazoacetate **1c** instead of methyl ester **1b** resulted in an improvement in enantioselectivity (entry 8 vs. entry 3). Using [Rh_2{(*R*)-pta}$_4$] at temperatures down to −40 °C provided additional improvements in the control of enantioselectivity, giving **8c** in up to 82 % *ee* with high yield in toluene (entries 9–15). However, the highest yield and selectivity were obtained with [Rh_2{(*R*)-ptl}$_4$] (R^1 = *i*Bu), which effected 100 % conversion within 2 h to give **8c**, which was isolated in 82 % yield and 92 % *ee* (entry 16). The *Z* geometry of the newly formed C=C bond in **8** was further confirmed by a 1D-nOe study.[9]

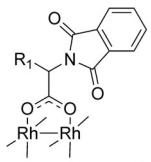
Having established the optimized conditions for the vinylogous N–H insertion, we investigated the potential of **8** to undergo Mannich addition to complete the tetrahydropyridazine synthesis. Heating (100 °C in toluene for 3 h) did not provide any ring-closed product, and **8** was recovered intact. Various achiral Lewis acids were examined for the cyclization of **8c**,[15] and 5 mol % of $Sc(OTf)_3$ (OTf = trifluoromethanesulfonate) was found to be superior to other acid catalysts in smoothly promoting the formation of 1,2,3,6-tetrahydropyridazine **10a** and in maintaining the high enantiomeric excess of the reactant. However, product diastereoselectivity was moderate (Table 2, entry 1, *cis*/*trans* = 72:28). In our efforts to influence diastereocontrol by changing the size of the *tert*-butyldimethylsilyl (TBS) group, various organosilyl protecting groups were used on the enoldiazoacetate reactants.[16]

Table 1: Optimization for the enantioselective vinylogous N–H insertion of a phenylhydrazone.[a]

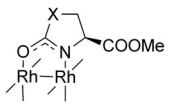


Entry	**1**	Catalyst (**9**)	*T* [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1	**1b**	[Rh_2{(*R*)-ptpa}$_4$] (**9a**)	25	CH_2Cl_2	78	38
2	**1b**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	25	CH_2Cl_2	71	45
3	**1b**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	0	CH_2Cl_2	68	51
4	**1b**	[Rh_2{(*S*)-pttl}$_4$] (**9c**)	25	CH_2Cl_2	< 5	–
5	**1b**	[Rh_2{(*S*)-mepy}$_4$] (**9f**)	25	CH_2Cl_2	< 5	–
6	**1b**	[Rh_2{(*S*)-mppim}$_4$] (**9g**)	25	CH_2Cl_2	< 5	–
7	**1b**	[Rh_2{(*S*)-dosp}$_4$] (**9h**)	0	CH_2Cl_2	65	−35
8	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	0	CH_2Cl_2	91	56
9	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	0	toluene	85	69
10	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−25	toluene	78	74
11	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−25	ClC_6H_5	72	69
12	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−25	FC_6H_5	75	68
13	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−25	$CF_3C_6H_5$	71	70
14	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−40	toluene	77	82
15	**1c**	[Rh_2{(*R*)-pta}$_4$] (**9b**)	−40	TBME	75	80
16	**1c**	[Rh_2{(*R*)-ptl}$_4$] (**9d**)	−40	toluene	82	92
17	**1c**	[Rh_2{(*S*)-ptn}$_4$] (**9e**)	−40	toluene	79	−83

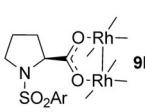
[a] Reactions were carried out over 2 h on a 0.10 mmol scale: **1** (0.12 mmol), **3a** (0.10 mmol), 4 Å MS (50 mg), in 1.0 mL solvent with 2.0 mol % catalyst at the stated temperature. [b] Yield of isolated product. Except for entries 4–6, reactions proceeded to 100 % completion. [c] Determined by HPLC analysis on a chiral stationary phase. TBME = *tert*-butyl methyl ether.



9a: [Rh_2{(*R*)-ptpa}$_4$], R^1 = Bn
9b: [Rh_2{(*R*)-pta}$_4$], R^1 = Me
9c: [Rh_2{(*S*)-pttl}$_4$], R^1 = *t*Bu
9d: [Rh_2{(*R*)-ptl}$_4$], R^1 = *i*Bu
9e: [Rh_2{(*S*)-ptn}$_4$], R^1 = *n*Bu

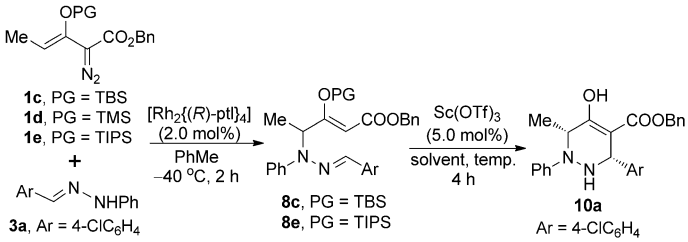


9f: [Rh_2{(*S*)-mepy}$_4$], X = CH_2
9g: [Rh_2{(*S*)-mppim}$_4$], X = $NCOCH_2Bn$



9h: [Rh_2{(*S*)-dosp}$_4$]
Ar = *p*-($C_{12}H_{25}$)C_6H_4

Table 2: Optimization of Lewis acid catalyzed Mannich addition for the synthesis of 1,2,3,6-tetrahydropyridazines.[a]



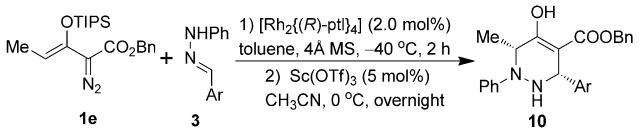
Entry	**1**	Solvent	*T* [°C]	d.r. (**10a**)[b] *cis*/*trans*	Conversion **8**→**10** [%][c]	*ee* (*cis*/*trans*) **10a** [%][d]
1	**1c**	CH_2Cl_2	25	72:28	> 95	92/–
2	**1d**	CH_2Cl_2	25	70:30	> 95	< 5
3	**1e**	CH_2Cl_2	25	76:24	> 95	96/–
4[e]	**1e**	toluene	25	60:40	65	95.5/–
5	**1e**	CH_2Cl_2	0	76:24	> 95	95.5/–
6	**1e**	CH_2Cl_2	50	23:77	> 95	–/93
7	**1e**	acetonitrile	25	80:20	> 95	96/93
8	**1e**	acetonitrile	50	50:50	> 95	95/93
9[f]	**1e**	acetonitrile	0	82:18	> 95	96/93

[a] Reactions were carried out on a 0.10 mol scale: **1** (0.12 mmol), **3a** (0.10 mmol), and 4 Å MS (50 mg) in 1.0 mL toluene with 2.0 mol % [Rh_2{(*R*)-ptl}$_4$] at −40 °C for 2 h. The reaction solution was then passed through a short flash chromatography column (dimensions: 0.5 cm × 10 mm), the solvent was evaporated, and the solvent for the Mannich addition was added along with $Sc(OTf)_3$ (5.0 mol %) at the indicated temperature. [b] Determined from the ^{1}H NMR spectra of the reaction mixtures. [c] Determined from the ^{1}H NMR spectra of the reaction mixtures based on limiting reagent **8**. [d] Determined by HPLC analysis on a chiral stationary phase; see the Supporting Information. [e] The reaction mixture from the first step was used for the second step without removal of the solvent. [f] The reaction was run overnight at 0 °C. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl, OTf = trifluoromethanesulfonate.

The labile TMS derivative **1d** underwent vinylogous N–H insertion, but gave the hydrolyzed product derived from **8** that, although proceeding to **10a**,[10] did so with complete racemization (entry 2). However, with the triisopropylsilyl (TIPS) derivative **1e**, **10a** was formed with 96% *ee* under same conditions (entry 3), although the diastereoselectivity was only modestly improved to 76:24. Further investigation of the conditions for optimization found that solvent plays an important role in the Mannich addition process; the reaction performed in toluene was much slower than that which was run in dichloromethane and occurred with much lower diastereoselectivity, but when acetonitrile was used as the reaction medium the diastereoselectivity improved to 82:12 (entry 9). The major *cis* diastereoisomer was confirmed by single-crystal X-ray diffraction analysis.[17] Surprisingly, the reaction performed in dichloromethane at 50°C in a closed container reversed the diastereoselectivity while retaining high enantioselectivity (entry 6).

The generality of this enantioselective cascade reaction was further investigated using these optimum conditions, and the results of this investigation are given in Table 3. Product yields were high, and 1,2,3,6-tetrahydropyridazines **10** were the sole isolated reaction products. The position of the chloro substituent on the aryl group did not affect the efficiency of the reaction, and these substrates underwent the two-step process with high stereoselectivity (entries 1–3). The electronic nature of the substituents had little influence on reactivity and selectivity (entries 4–10), except in cases where reactant solubility required that the vinylogous N–H insertion reaction be conducted at higher temperature (entries 5, 6, and 11–13). Reactions with bulky mesityl and anthranyl substrates (entries 12 and 13) gave mixtures of the corresponding tetrahydropyridazines **10l** or **10m** along with hydrolyzed racemic ketone from the vinylogous N–H insertion reaction.[10] However, these sterically hindered substrates produced only one tetrahydropyridazine diastereoisomer with enantiomeric excesses of up to 97%.

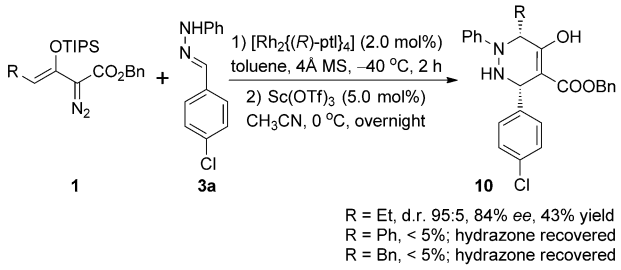
Table 3: Enantioselective cascade sequences synthesis of 1,2,3,6- tetrahydropyridazines from **1e** and hydrazones.[a]



Entry	Ar (**3**)	**10**	d.r.[b]	Yield [%][c]	*ee* (*cis*/*trans*) [%][d]
1	4-ClC_6H_4 (**3a**)	**10a**	82:18	77	96/93
2	3-ClC_6H_4 (**3b**)	**10b**	84:16	82	95/93
3[e]	2-ClC_6H_4 (**3c**)	**10c**	81:19	73	97/95
4	4-$MeOC_6H_4$ (**3d**)	**10d**	76:24	91	92/91
5[e,f]	4-$NO_2C_6H_4$ (**3e**)	**10e**	81:19	90	92/88
6[f]	4-BrC_6H_4 (**3f**)	**10f**	95:5	72	90/78
7	4-FC_6H_4 (**3g**)	**10g**	86:14	80	91/91
8	4-MeC_6H_4 (**3h**)	**10h**	83:17	85	90/93
9	2-furyl (**3i**)	**10i**	79:21	77	78/77
10	4-PhC_6H_4 (**3j**)	**10j**	>95:5	70	91/–
11[f]	2-$CF_3C_6H_4$ (**3k**)	**10k**	>95:5	67	87/–
12[f]	2,4,6-$Me_3C_6H_2$ (**3l**)	**10l**	>95:5	35 (57)	89/–
13[e,f]	9-anthryl (**3m**)	**10m**	>95:5	29 (60)	97/–

[a] See the Experimental Section. [b] Determined from the ^{1}H NMR spectra of the reaction mixtures. [c] Yield of isolated **10** (*cis*+*trans*) based on limiting reagent **3**. Numbers in parentheses are yields of hydrolyzed product from the vinylogous N–H insertion [d] Determined by HPLC analysis on a chiral stationary phase. [e] The second step was performed at room temperature. [f] The first step was performed at –20°C.

Enoldiazoacetate **1**, which has a methyl group in the vinylogous position, is optimum for enantioselective vinoylogous reactions with hydrazones. However, enoldiazoacetates with larger substituents in the vinylogous position (R = Et, Ph, Bn) were deleterious to the reaction. Enantioselectivity decreased when R = Et (Scheme 3), and vinylogous N–H insertion was effectively inhibited when R = Ph or Bn. Davies et al. have reported that vinylogous carbenoid reactions from O–H insertion reactions using dirhodium(II) catalysts are highly restricted, but can be overcome in selected cases with the use of more electron deficient silver(I), molybdenum, or diruthenium(I) catalysts.[8] The data in Scheme 3 suggests that steric effects are primarily responsible for the reactivity and selectivity that is observed for reactions with hydrazones.

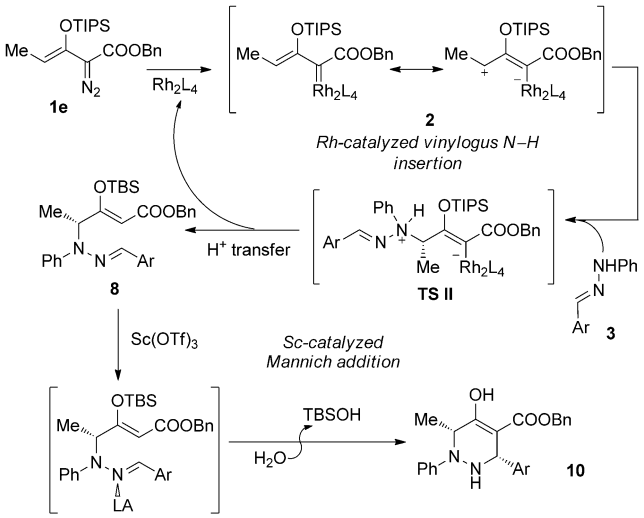


Scheme 3. Effect on enantioselective cascade sequences with enoldiazoacetates having bulky substituents at the vinylogous position.

In summary, we have developed a cascade transformation that enables the efficient preparation of highly substituted 1,2,3,6-tetrahydropyridazines[18] starting from enoldiazoacetates and hydrazones in good overall yields, high diastereoselectivities, and excellent enantioselectivities that are controlled by catalysts and conditions. The sequence of reactions is triggered by Rh^{II}-catalyzed dinitrogen extrusion followed by asymmetric vinylogous N–H insertion into hydrazones. Subsequent Lewis acid promoted Mannich addition of **8** smoothly produces 1,2,3,6-tetrahydropyridazines **10** with high diastereocontrol (Scheme 4). To the best of our knowledge, this is the first example of highly enantioselective vinylogous N–H insertion. Further expansion of vinylogous reactivity with enoldiazoacetates are being pursued.

Experimental Section

Enoldiazoacetate **1e** (0.12 mmol) in toluene (0.5 mL) was added over a 1 h period by a syringe pump at the indicated temperature (either –40 or –20°C) to an oven-dried flask containing a magnetic stirring bar, hydrazone **3** (0.1 mmol), 4 Å molecular sieves (50 mg), and $[Rh_2\{(R)\text{-ptl}\}_4]$ (2.0 mol%) in toluene (0.5 mL). The reaction mixture was stirred for another hour under these conditions, then passed through a short flash column of silica gel (dimensions: 0.5 cm × 10 cm) and, after removal of the solvent under reduced pressure, acetonitrile



Scheme 4. Tandem catalysis of the [3+3]-cycloaddition reaction from vinylogous N–H insertion/Mannich addition.

(2.0 mL) was added. This solution was transferred to a reaction tube containing a magnetic stirring bar, and the temperature of the solution was decreased to 0 °C (or to room temperature, as indicated), followed by the addition of $Sc(OTf)_3$ (5.0 mol %). The reaction mixture was stirred for another 4 h, and then subjected to ^1H NMR spectroscopic analysis after solvent removal to determine product diastereoselectivity. The crude reaction mixture was purified by column chromatography on silica gel (eluent hexanes/EtOAc = 100:0 to 90:10) to give the pure tetrahydropyridazines **10**.

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[1] For reviews of formal [3+3]-cycloaddition reactions, see: a) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, H. C. Shen, M. J. McLaughlin, L. O. Zehnder, *Org. Biomol. Chem.* **2005**, *3*, 1349; b) G. S. Buchanan, J. B. Feltenberger, R. P. Hsung, *Curr. Org. Synth.* **2010**, *7*, 363; for enantioselective organocatalytic formal [3+3]-cycloadditions, see: c) H. M. Sklenicka, R. P. Hsung, M. J. McLaughlin, L.-L. Wie, A. I. Gerasyuto, W. B. Brennessel, *J. Am. Chem. Soc.* **2002**, *124*, 10435; d) B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, *8*, 2217; e) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334.

[2] a) F. Liu, D. Qian, L. Li, X. Zhao, J. Zhang, *Angew. Chem.* **2010**, *122*, 6819; *Angew. Chem. Int. Ed.* **2010**, *49*, 6669; b) R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 6330.

[3] X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402.

[4] a) N. D. Shapiro, Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654; b) C. Perreault, S. R. Goudreau, L. E. Zimmer, A. B. Charette, *Org. Lett.* **2008**, *10*, 689.

[5] a) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012; b) K. Kanao, Y. Miyake, Y. Nishibayashi, *Organometallics* **2010**, *29*, 2126; c) A. Al-Harrasi, H.-U. Reißig, *Angew. Chem.* **2005**, *117*, 6383; *Angew. Chem. Int. Ed.* **2005**, *44*, 6227; d) M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fisera, I. Hlobilová, G. Zahn, H.-U. Reißig, *Eur. J. Org. Chem.* **2005**, 1003; e) H. K. Grover, T. P. Lebold, M. A. Kerr, *Org. Lett.* **2011**, *13*, 220; f) A. I. Gerasyuto, R. P. Hsung, N. Sydorenko, B. Slafer, *J. Org. Chem.* **2005**, *70*, 4248.

[6] With the exception of [3+3]-cycloaddition reactions, syntheses of 1,2,3,6-tetrahydropyridazine are rare; see: a) S. Xu, R. Chen, Z. Qin, G. Wu, Z. He, *Org. Lett.* **2012**, *14*, 996; b) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo, O. Kwon, *J. Am. Chem. Soc.* **2011**, *133*, 13337; c) L. Shen, L. Sun, S. Ye, *J. Am. Chem. Soc.* **2011**, *133*, 15894; d) Q. Zhang, L. Yang, X. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550; e) A. J. Oelke, D. J. France, T. Hofmann, G. Wuitschik, S. V. Ley, *Angew. Chem.* **2010**, *122*, 6275; *Angew. Chem. Int. Ed.* **2010**, *49*, 6139; f) V. Nair, S. C. Mathew, A. T. Biju, E. Suresh, *Angew. Chem.* **2007**, *119*, 2116; *Angew. Chem. Int. Ed.* **2007**, *46*, 2070; g) H. H. Jensen, L. Lyngbye, A. Jensen, M. Bols, *Chem. Eur. J.* **2002**, *8*, 1218.

[7] For enantioselective heteroatom-carbene insertion reactions, see: a) S.-F. Zhu, B. Xu, G.-P. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 346; b) B. Liu, S.-F. Zhu, W. Zhang, C. Chen, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 5834; c) C. J. Moody, *Angew. Chem.* **2007**, *119*, 9308; *Angew. Chem. Int. Ed.* **2007**, *46*, 9148; d) B. Xu, S. Zhu, X. Xie, J. Shen, Q. Zhou, *Angew. Chem.* **2011**, *123*, 11685; *Angew. Chem. Int. Ed.* **2011**, *50*, 11483; e) E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066.

[8] For non-asymmetric vinylogous O–H insertion, see: a) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457; b) H. M. L. Davies, Y. Yokota, *Tetrahedron Lett.* **2000**, *41*, 4851; c) Y. Sevryugina, B. Weaver, J. Hansen, J. Thompson, H. M. L. Davies, M. A. Petrukhina, *Organometallics* **2008**, *27*, 1750; for asymmetric vinylogous C–H functionalization, see: d) Y. Lian, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 1934.

[9] CCDC 881732 (**8a**) contains 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.

[10] See the Supporting Information.

[11] For selected examples of Mannich addition with silicon enolates, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) M. Sugiura, S. Kobayashi, *Angew. Chem.* **2005**, *117*, 5306; *Angew. Chem. Int. Ed.* **2005**, *44*, 5176; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348.

[12] a) S. Hashimoto, N. Watanabe, T. Sato, M. Shiro, S. Ikegami, *Tetrahedron lett.* **1993**, *34*, 5109; b) H. Tsutsui, T. Abe, S. Nakamura, M. Anada, S. Hashimoto, *Chem. Pharm. Bull.* **2005**, *53*, 1366; c) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417.

[13] a) J. Wu, J. Becerril, Y. Lian, H. M. L. Davies, J. A. Porco, Jr., J. S. Panek, *Angew. Chem.* **2011**, *123*, 6060; *Angew. Chem. Int. Ed.* **2011**, *50*, 5938; b) R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 3437; c) H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897; d) Y. Lian, K. I. Hardcastle, H. M. L. Davies, *Angew. Chem.* **2011**, *123*, 9542; *Angew. Chem. Int. Ed.* **2011**, *50*, 9370.

[14] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, NY, **1998**.

[15] The use of $In(OTf)_3$ or $Cu(OTf)_2$ gave similar results, but required longer reaction times.

[16] The *Z*/*E* ratios of **1b**–**1e** were determined by ^1H NMR spectroscopy: **1b** = 90:10, **1c** = 89:11, **1d** = 96:4, **1c** = 82:18. See the Supporting Information for details. a) H. M. L. Davies, Z.-Q. Peng, J. H. Houser, *Tetrahedron Lett.* **1994**, *35*, 8939; b) Y.

Ueda, G. Roberge, V. Vinet, *Can. J. Chem.* **1984**, *62*, 2936; c) H. M. L. Davies, G. Ahmed, M. R. Churchill, *J. Am. Chem. Soc.* **1996**, *118*, 10774; d) K. Kundu, M. P. Doyle, *Tetrahedron: Asymmetry* **2006**, *17*, 574; e) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *Angew. Chem.* **2011**, *123*, 11348; *Angew. Chem. Int. Ed.* **2011**, *50*, 11152.

[17] CCDC 881733 (**10a**) contains 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.

[18] 1,2,5,6-Tetrahydropyridazines are structural components of potent novel inhibitors of human immunodeficiency virus (HIV) and hepatitis C virus (HCV); see: a) W. J. Watkins, A. S. Ray, L. S. Chong, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 441; b) A. Manlove, M. P. Groziak in *Progress in Heterocyclic Chemistry*, *Vol 21* (Eds.: G. Gordon, J. John) Elsevier Ltd., Oxford, UK, **2009**, pp. 375–414; c) F. Ruebsam, et al., *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3616; d) F. Stefania, A. Stefano, L. B. Maria, D. L. Laura, C. Frauke, G. Rosaria, *J. Heterocycl. Chem.* **2009**, *46*, 1420.

