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

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Abstract

A versatile reaction cascade triggered by Rh(II)-catalyzed diazo decomposition followed by a vinylogous N-H insertion/Lewis acid catalyzed Mannich addition that produces highly substituted 1,2,3,6-tetrahydropyridazines in up to 97% ee with high yield and diastereocontrol has been developed.

Keywords

Asymmetric Catalysis; Tetrahydropyridazines; Enantioselective; Vinylogous N-H Insertion; Cycloaddition; Rhodium

Although rare, formal [3 + 3]-cycloaddition reactions are known to occur through sequential reactions of an activated substrate with the nucleophilic site of a dipole 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 centre (**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 an asymmetric vinylogous C-H functionalization of several vinyldiazoacetates have recently been reported.[8] We now report a highly selective catalytic process involving enoldiazoacetates in combination with aldehyde-derived hydrazones that occur with high enantioselectivity and catalyst-controlled diastereoselectivity.

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-

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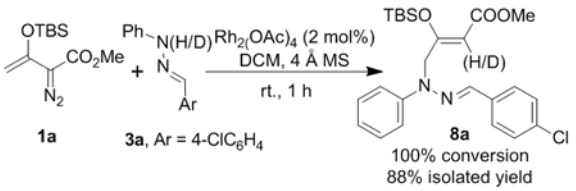
chlorobenzaldehyde (**3a**) with a catalytic amount of dirhodium tetraacetate at room temperature in dichloromethane. Complete conversion occurred within one hour but, instead of forming a tetrahydropyridazines, the product from vinylogous N-H insertion (**8a**) was formed exclusively as the terminal product (Eq 1). 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 was indeed a vinylogous N-H insertion was established by performing the reaction with deuterium-labeled **3a** (exchange of the N-H proton) from which deuterium was found to reside exclusively on the vinyl carbon alpha to the carboxylate ester.[10] Instead of undergoing a 1,2-proton transfer, as envisioned in Scheme 1, the hydrogen on nitrogen replaced the dirhodium catalyst on the original carbene carbon. Recognizing the advantages of this methodology, we investigated this transformation for enantiocontrol in the vinylogous N-H insertion reaction and, since **8** is suitable for intramolecular iminium ion ring closure,[11] Lewis acid catalysis was probed for subsequent diastereoselective cyclization to tetrahydropyridazines.



(1)

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) 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 the Rh_2(*R*-PTTL)$_4$ (entry 4), Hashimoto's phthalimide-amino acid-based chiral dirhodium carboxylate catalysts[12] showed higher reactivity and enantioselectivity compared to Davies' Rh_2(S-DOSP)$_4$ catalyst[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 the methyl ester **1b** resulted in an improvement in enantioselectivity (entry 8 vs entry 3). Using Rh_2(*R*-PTA)$_4$ with reaction solvents at temperatures down to −40 °C provided additional improvements in the control of enantioselectivity, optimally giving **8c** in up to 82% ee with high yield in toluene (entries 9–15). However, the highest yield and selectivity occurred with the Rh_2(*R*-PTL)$_4$ catalyst (R1 = ^{t}Bu) which effected 100% conversion within 2 h to **8c** which was isolated in 82% yield with 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. Thermal conditions (100 °C in toluene for 3 h) did not provide any evidence of ring-closing, and **8** was recovered intact. Various achiral Lewis acids were examined for cyclization of **8c**,[15] and 5 mol% of $Sc(OTf)_3$ was found to 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 efforts to influence diastereocontrol by changing the size of OTBS attachment various organosilyl protective groups were used on the reactant enoldiazoacetates.[16] 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). With the TIPS derivative **1e**, however, **10a** was formed with 96% ee under same conditions (entry 3), although 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 reaction medium diastereoselectivity improved to 82:12 (entry 9). Surprisingly, the reaction performed in dichloromethane at 50 °C in a closed container reversed diastereoselectivity while retaining high enantioselectivity (entry 6). The major *cis*-diastereoisomer was confirmed by single-crystal X-ray diffraction analysis.[17]

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 stereocontrol (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 sterically 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 up to 97%.

Enoldiazoacetate **1** with R = Me at the vinylogous position is optimum for enantioselective vinoylogous reactions with hydrazones. However, when enoldiazoacetates with larger substituents at the vinylogous position (R = Et, Ph, Bn) were applied, enantioselectivity decreased with R = Et (Scheme 2) and vinylogous N-H insertion was effectively inhibited when R = Ph or Bn. Davies has 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 of Scheme 2 suggests that steric effects are primarily responsible for the reactivity and selectivity that is observed for reactions with hydrazones.

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** (Scheme 3) with high diastereocontrol. 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 applied broadly are being pursued.

Experimental Section

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*-PTL)$_4$ (2.0 mol%) in toluene (0.5 mL), was added enoldiazoacetate **1e** (0.12 mmol) in toluene (0.5 mL) over 1 h period via a syringe pump at the indicated temperature (either −40 or −20 °C). The reaction mixture was stirred for

another hour under these conditions, then passed through a short flash column of silica gel (ϕ0.5 cm X 10 cm) and, after removal of the solvent under reduced pressure, acetonitrile (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 adding $Sc(OTf)_3$ (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** in moderate to high yield with high to excellent enantioselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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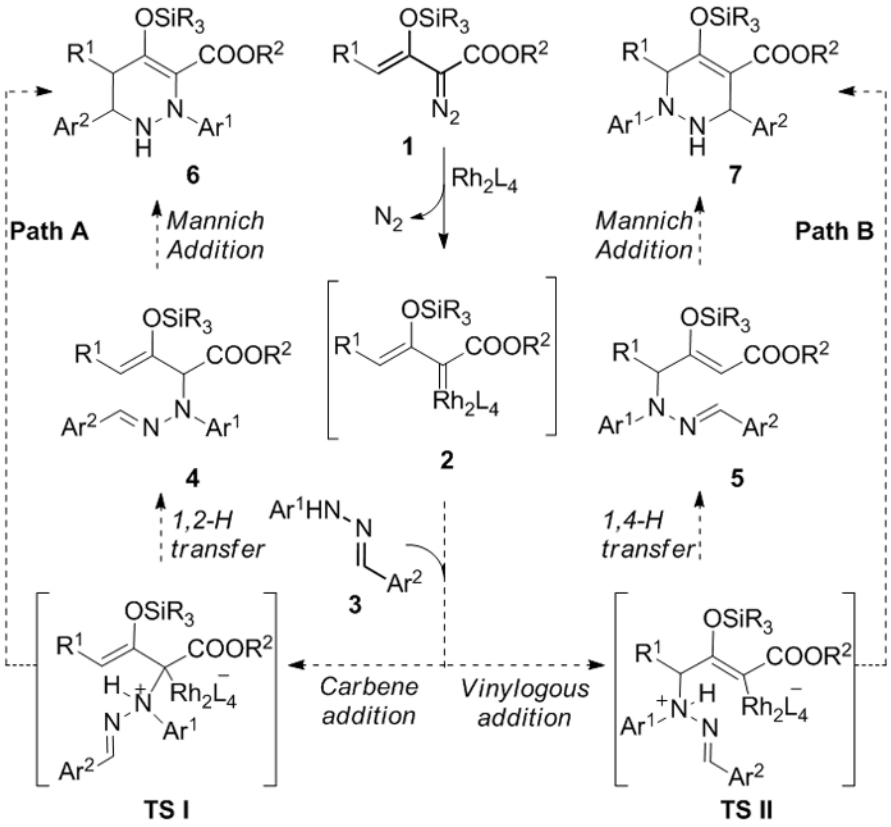
References

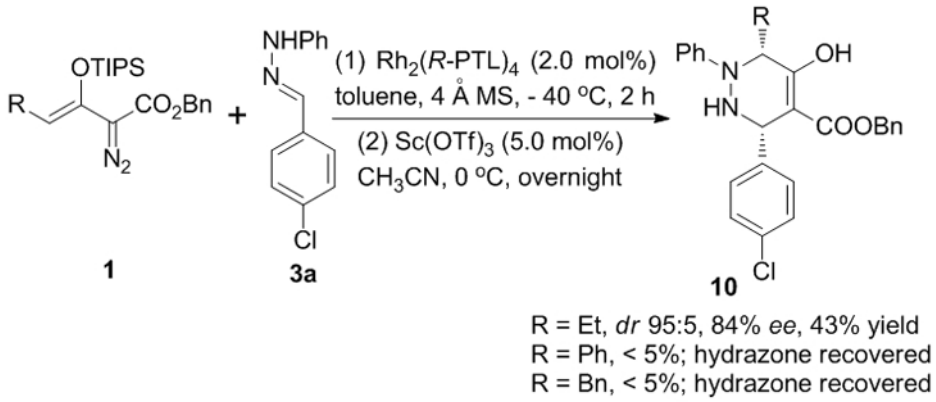
1. For reviews of formal [3 + 3]-cycloaddition reactions, see: Hsung RP, Wei LL, Sklenicka HM, Shen HC, McLaughlin MJ, Zehnder LO. Org Biomol Chem. 2005; 3:1349. [PubMed: 15827625] Buchanan GS, Feltenberger JB, Hsung RP. Curr Org Synth. 2010; 7:363. [PubMed: 20936076] For enantioselective organocatalytic formal [3+3]-cycloadditions see: Sklenicka HM, Hsung RP, McLaughlin MJ, Wie LL, Gerasyuto AI, Brennessel WB. J Am Chem Soc. 2002; 124:10435. [PubMed: 12197745] Hong BC, Wu MF, Tseng HC, Liao JH. Org Lett. 2006; 8:2217. [PubMed: 16706490] Chan A, Scheidt KA. J Am Chem Soc. 2007; 129:5334. [PubMed: 17407298]
2. a) Liu F, Qian D, Li L, Zhao X, Zhang J. Angew Chem. 2010; 122:6819.Angew Chem Int Ed. 2010; 49:6669.b) Shintani R, Hayashi T. J Am Chem Soc. 2006; 128:6330. [PubMed: 16683793]
3. Wang X, Xu X, Zavalij PY, Doyle MP. J Am Chem Soc. 2011; 133:16402. [PubMed: 21932856]
4. a) Shapiro ND, Shi Y, Toste FD. J Am Chem Soc. 2009; 131:11654. [PubMed: 19645449] b) Perreault C, Goudreau SR, Ee Zimmer L, Charette AB. Org Lett. 2008; 10:689. [PubMed: 18257580] c) Chan A, Scheidt KA. J Am Chem Soc. 2007; 129:5334. [PubMed: 17407298]
5. a) Hayashi Y, Gotoh H, Masui R, Ishikawa H. Angew Chem. 2008; 120:4076.Angew Chem Int Ed. 2008; 47:4012.b) Kanao K, Miyake Y, Nishibayashi Y. Organometal. 2010; 29:2126.c) Al-Harrasi A, Reiβig H-U. Angew Chem. 2005; 117:6383.Angew Chem Int Ed. 2005; 44:6227.d) Helms M, Schade W, Pulz R, Watanabe T, Al-Harrasi A, Fisera L, Hlobilová I, Zahn G, Reiβig HU. Eur J Org Chem. 2005:1003.e) Grover HK, Lebold TP, Kerr MA. Org Lett. 2011; 13:220. [PubMed: 21162555] f) Gerasyuto AI, Hsung RP, Sydorenko N, Slafer B. J Org Chem. 2005; 70:4248. [PubMed: 15903297]
6. With the exception of [3 + 3]-cycloaddition reactions, syntheses of 1,2,3,6-tetrahydropyridazine are rare: Xu S, Chen R, Qin Z, Wu G, He Z. Org Lett. 2012; 14:996. [PubMed: 22304572] Na R, Jing C, Xu Q, Jiang H, Wu X, Shi J, Zhong J, Wang M, Benitez D, Tkatchouk E, Goddard WA, Guo H, Kwon O. J Am Chem Soc. 2011; 133:13337. [PubMed: 21812448] Shen L, Sun L, Ye S. J Am Chem Soc. 2011; 133:15894. [PubMed: 21902208] Zhang Q, Yang L, Tong X. J Am Chem Soc. 2010; 132:2550. [PubMed: 20131904] Oelke AJ, France DJ, Hofmann T, Wuitschik G, Ley SV. Angew Chem. 2010; 122:6275.Angew Chem Int Ed. 2010; 49:6139.Nair V, Mathew SC, Biju AT, Suresh E. Angew Chem. 2007; 119:2116.Angew Chem Int Ed. 2007; 46:2070.Jensen HH, Lyngbye L, Jensen A, Bols M. Chem Eur J. 2002; 8:1218. [PubMed: 11891910]
7. Enantioselective heteroatom-carbene insertion reactions: Zhu SF, Xu B, Wang GP, Zhou QL. J Am Chem Soc. 2012; 134:346. [PubMed: 22118472] Liu B, Zhu SF, Zhang W, Chen C, Zhou QL. J Am Chem Soc. 2007; 129:5834. [PubMed: 17428059] Moody CJ. Angew Chem. 2007; 119:9308.Angew Chem Int Ed. 2007; 46:9148.Xu B, Zhu S, Xie X, Shen J, Zhou Q. Angew Chem.

2011; 123:11685;.Angew Chem Int Ed. 2011; 50:11483.Lee EC, Fu GC. J Am Chem Soc. 2007; 129:12066. [PubMed: 17877350]

8. Non-asymmetric vinylogous O-H insertion: Hansen JH, Davies HML. Chem Sci. 2011; 2:457.Davies HML, Yokota Y. Tetrahedron Lett. 2000; 41:4851.Sevryugina Y, Weaver B, Hansen J, Thompson J, Davies HML, Petrukhina MA. Organometallics. 2008; 27:1750.Asymmetric vinylogous C-H functionalization: Lian, Yajing; Davies, Huw ML. Org Lett. 2012; 14:1934. [PubMed: 22452332]
9. CCDC 881732 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 Supporting Information.
11. Selected examples of Mannich addition with silicon enolates Akiyama T, Itoh J, Yokota K, Fuchibe K. Angew Chem. 2004; 116:1592.Angew Chem Int Ed. 2004; 43:1566.Sugiura M, Kobayashi S. Angew Chem. 2005; 117:5306.Angew Chem Int Ed. 2005; 44:5176.Taylor MS, Jacobsen EN. Angew Chem. 2006; 118:1550.Angew Chem Int Ed. 2006; 45:1520.Marques MMB. Angew Chem. 2006; 118:356.Angew Chem Int Ed. 2006; 45:348.
12. a) Hashimoto S, Watanabe N, Sato T, Shiro M, Ikegami S. Tetrahedron lett. 1993; 34:5109.b) Tsutsui H, Abe T, Nakamura S, Anada M, Hashimoto S. Chem Pharm Bull. 2005; 53:1366. [PubMed: 16205006] c) Kitagaki S, Anada M, Kataoka O, Matsuno K, Umeda C, Watanabe N, Hashimoto S. J Am Chem Soc. 1999; 121:1417.
13. a) Wu J, Becerril J, Lian Y, Davies HML, Porco JA Jr, Panek JS. Angew Chem. 2011; 123:6060.Angew Chem Int Ed. 2011; 50:5938.b) Reddy RP, Lee GH, Davies HML. Org Lett. 2006; 8:3437. [PubMed: 16869629] c) Davies HML, Bruzinski PR, Lake DH, Kong N, Fall MJ. J Am Chem Soc. 1996; 118:6897.d) Lian Y, Hardcastle KI, Davies HML. Angew Chem. 2011; 123:9542.Angew Chem Int Ed. 2011; 50:9370.
14. Doyle, MP.; McKervey, MA.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. Wiley; New York, NY: 1998.
15. 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** was determined by ^{1}H NMR spectroscopy: **1b** = 90:10, **1c** = 89:11, **1d** = 96:4, **1c** = 82:18. See Supporting Information for details. Davies HML, Peng ZQ, Houser JH. Tetrahedron Lett. 1994; 35:8939.Ueda Y, Roberge G, Vinet V. Can J Chem. 1984; 62:2936.Davies HML, Ahmed G, Churchill MR. J Am Chem Soc. 1996; 118:10774.Kundu K, Doyle MP. Tetrahedron: Asymmetry. 2006; 17:574.Xu X, Zavalij PY, Hu W, Doyle MP. Angew Chem. 2011; 123:11348.Angew Chem Int Ed. 2011; 50:11152.
17. CCDC 881733 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): Watkins WJ, Ray AS, Chong LS. Curr Opin Drug Discovery Dev. 2010; 13:441.Manlove A, Groziak MP. Gordon G, John J. Prog Heterocycl Chem. 21Elsevier LtdOxford UK2009; :375–414.Ruebsam F, et al. Bioorg Med Chem Lett. 2008; 18:3616. [PubMed: 18487044] Stefania F, Stefano A, Maria LB, Laura DL, Frauke C, Rosaria G. J Heterocycl Chem. 2009; 46:1420.

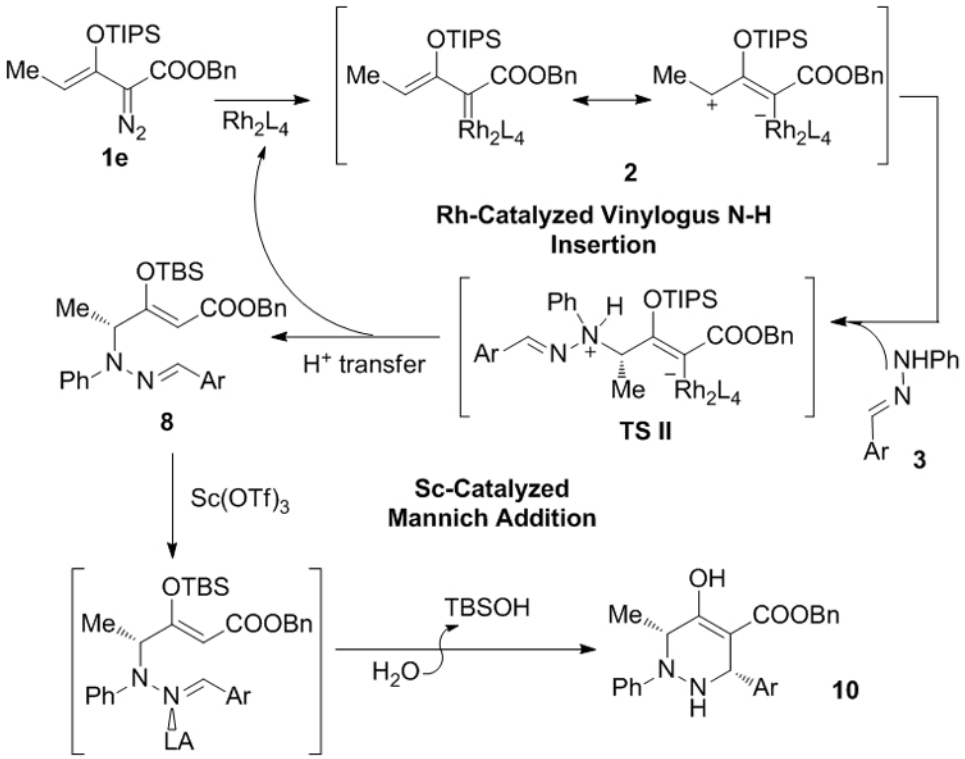


Scheme 1.
Competitive pathways for [3 + 3]-cycloaddition reactions of arylhydrazones.



Scheme 2.

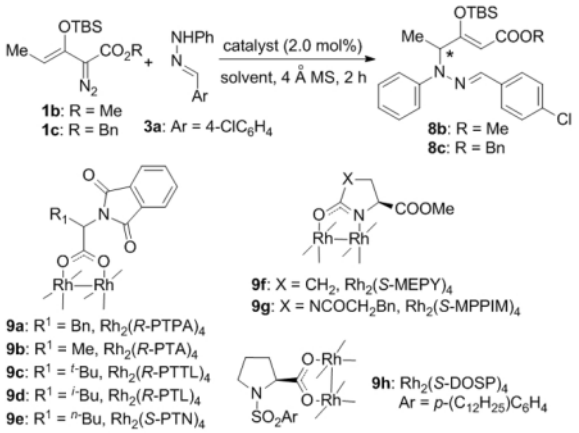
Effect on enantioselective cascade sequences with enoldiazoacetates having bulky substituents at the vinylogous position.



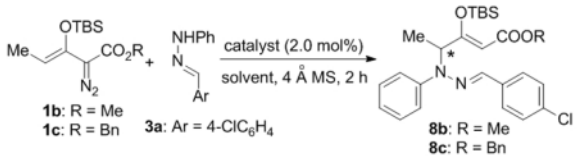
Scheme 3.
Tandem catalysis of the [3 + 3]-cycloaddition reaction from vinylogous N-H insertion/ Mannich addition.

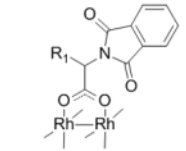
Table 1

Optimization for the enantioselective vinylogous N-H insertion of a phenylhydrazone.[a]



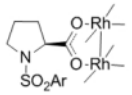
Entry	1	Catalyst (9)	*T* (°C)	Solvent	yield (%)[b]	ee (%)[c]
1	**1b**	Rh_2(*S*-PTPA)$_4$ (**9a**)	25	DCM	78	38
2	**1b**	Rh_2(*R*-PTA)$_4$ (**9b**)	25	DCM	71	45
3	**1b**	Rh_2(*R*-PTA)$_4$ (**9b**)	0	DCM	68	51
4	**1b**	Rh_2(*S*-PTTL)$_4$ (**9c**)	25	DCM	<5	-
5	**1b**	Rh_2(*S*-MEPY)$_4$ (**9f**)	25	DCM	<5	-
6	**1b**	Rh_2(*S*-MPPIM)$_4$ (**9g**)	25	DCM	<5	-
7	**1b**	Rh_2(*S*-DOSP)$_4$ (**9h**)	0	DCM	65	−35
8	**1c**	Rh_2(*R*-PTA)$_4$ (**9b**)	0	DCM	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





9a: R^1 = Bn, Rh_2(*R*-PTPA)$_4$
9b: R^1 = Me, Rh_2(*R*-PTA)$_4$
9c: R^1 = ^{t}Bu, Rh_2(*R*-PTTL)$_4$
9d: R^1 = ^{i}Bu, Rh_2(*R*-PTL)$_4$
9e: R^1 = ^{n}Bu, Rh_2(*S*-PTN)$_4$

9f: X = CH_2, Rh_2(*S*-MEPY)$_4$
9g: X = $NCOCH_2Bn$, Rh_2(*S*-MPPIM)$_4$



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

Entry	1	Catalyst (9)	*T* (°C)	Solvent	yield (%)[b]	ee (%)[c]
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

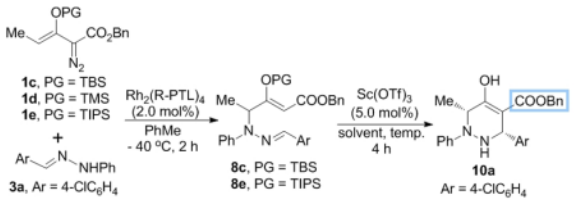
[a] Reactions were carried out over 2 h on a 0.10 mmol scale: **1** (0.12 mmol), **3a** (0.10 mmol), 4 Å MS (50 mg), in 1.0 mL solvent with 2.0 mol% catalyst at the stated temperature.

[b] Isolated yield. Except for entries 4–6, reactions proceeded to 100% completion.

[c] Determined by HPLC analysis with chiral columns.

Table 2

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



Entry	1	Solvent	T (°C)	*dr* (10a)[b] *cis:trans*	conversion 8→10 (%)[c]	*ee* (%)[d] *cis/trans*-10a
1	**1c**	DCM	25	72:28	>95	92/-
2	**1d**	DCM	25	70:30	>95	<5
3	**1e**	DCM	25	76:24	>95	96/-
4[e]	**1e**	Toluene	25	60:40	65	95.5/-
5	**1e**	DCM	0	76:24	>95	95.5/-
6	**1e**	DCM	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 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. Then the reaction solution was passed through a short flash column chromatography (*Φ*0.5 cm X 10 mm), solvent was evaporated, and the solvent for the Mannich addition was added with 5.0 mol% $Sc(OTf)_3$ 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**.

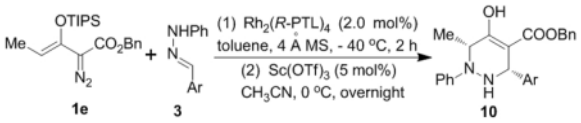
[d] Determined by HPLC analysis using chiral columns, see Supporting Information.

[e] The reaction mixture from the first step was used for the second step without removal of solvent.

[f] The reaction was run overnight at 0 °C.

Table 3

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



Entry	Ar (3)	10	*dr*[b]	yield (%)[c]	*ee* (%)[d] *cis*/*trans*
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)[g]	89/-
13[e,f]	9-anthryl (**3m**)	**10m**	>95:5	29 (60)[g]	97/-

[a] See experimental section.

[b] Determined from the ^{1}H NMR spectra of the reaction mixtures.

[c] Isolated yield of **10** (*cis* + *trans*) based on limiting reagent **3**.

[d] Determined by HPLC analyses with chiral columns.

[e] The second step was performed at room temperature.

[f] The first step was performed at −20 °C.

[g] The number in parenthesis is the yield of the hydrozed product from vinylogous N-H insertion.