Published in final edited form as:

Org Biomol Chem. 2013 December 7; 11(45): . doi:10.1039/c3ob41815d.

Catalytic, Enantioselective 1,3-Dipolar Cycloadditions of Nitrile Imines with Methyleneindolinones

Anthony L. Gerten^a, Michael C. Slade^b, Kelsie M. Pugh^a, and Levi M. Stanley^a

Levi M. Stanley: lstanley@iastate.edu

^aDepartment of Chemistry, Iowa State University, Ames, Iowa 50011, United States.

Abstract

Catalytic, enantioselective 1,3-dipolar cycloadditions of nitrile imines with methyleneindolinones are reported. The spiro[pyrazolin[3,3'-oxindole] products are formed in good yields (up to 98%) and high enantioselectivity (up to 99% ee).

1,3-Dipolar cycloadditions of nitrile imines with alkenes represent an attractive strategy to generate pyrazolines. Reactions of nitrile imines with a wide variety of olefinic dipolarophiles have been developed to provide an array of compounds containing a pyrazoline motif.^{1,2} Despite efforts to develop the utility of nitrile imine cycloadditions, controlling the enantioselectivity of nitrile imine cycloadditions remains difficult to achieve. The high reactivity of nitrile imines renders catalytic, enantioselective cycloadditions of this class of dipole challenging due to the high rates of uncatalyzed background cycloaddition. To date, only a select few examples of catalytic, enantioselective cycloadditions of nitrile imines have been reported. Sibi et al. showed that 1,3-dipolar cycloadditions of nitrile imines with α,β -unsaturated oxazolidinone and pyrazolidinone imides occur in high yields with high enantioselectivity in the presence of chiral, non-racemic magnesium catalysts.³ However, the scope of dipolarophiles in enantioselective nitrile imine cycloadditions remains narrow.

The prevalence of pyrazoline motifs in bioactive compounds⁴ and the growing importance of spirocyclic oxindole derivatives^{5,6} led our group and others to investigate synthetic approaches to spiro[pyrazolin-3,3'-oxindoles]. During the course of our studies, Roth et al.⁷ and Feng et al.⁸ reported the first cycloadditions of nitrile imines with methyleneindolinones to generate spiro[pyrazolin-3,3'-oxindoles]. Roth and co-workers reported the first racemic synthesis of spiro[pyrazolin-3,3'-oxindoles] by uncatalyzed cycloadditions of nitrile imines with methyleneindolinones.⁷ Shortly thereafter, Feng and co-workers reported the first catalytic, enantioselective cycloadditions of nitrile imines generated from hydrazoneoyl chlorides with methyleneindolinones (Scheme 1a).⁸ These cycloadditions occur with high enantioselectivity (up to 99% ee) provided the β -substituent of the methyleneindolinone substrate is a bulky alkyl (*tert*-butyl) group or an *ortho*-substituted aryl group. Cycloadditions of nitrile imines with methyleneindolinones substituted with smaller β -alkyl (e.g. *iso*-propyl) groups or β -aryl (e.g. Ph, 4-Cl-C₆H₄) groups lacking *ortho*-substitution occur with lower enantioselectivity.

This journal is © The Royal Society of Chemistry 2012

Correspondence to: Levi M. Stanley, lstanley@iastate.edu.

^bCurrent Address: Department of Chemistry, University of Evansville, Evansville, Indiana 47722, United States.

[†]Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data for new compounds, and crystallographic data (CIF) for compound **3g**. See DOI: 10.1039/c000000x/

Herein, we report catalytic, enantioselective cycloadditions of nitrile imines generated from hydrazonoyl bromides with a variety of methyleneindolinones (Scheme 1b). The nitrile imine cycloadditions occur in the presence of a catalyst generated *in situ* from $\text{Mg}(\text{NTf}_2)_2$ and an aminoindanol-derived bisoxazoline ligand **L2**. The spiro[pyrazolin-3,3'-oxindole] products are formed in good to high yields with high enantioselectivities. Furthermore, the nitrile imine cycloadditions that occur with high enantioselectivity encompass methyleneindolinones containing β -aryl groups lacking substitution at the *ortho* position. This methodology expands the breadth of spiro[pyrazolin-3,3'-oxindoles] that can be accessed in highly enantioselective fashion and is complementary to the methodology reported by Feng.

Our initial studies focused on reactions of the nitrile imine generated from hydrazonoyl bromide **2a** with methyleneindolinones **1a–e**. Table 1 summarizes the effect of Lewis acid identity, Lewis acid loading, temperature, and substitution at the oxindole nitrogen on these reactions. We chose to begin our investigation by conducting cycloadditions catalyzed by 30 mol % loading of a complex prepared *in situ* from $\text{Mg}(\text{NTf}_2)_2$ and bisoxazoline ligand **L2**. The cycloaddition of the nitrile imine generated at room temperature from **2a** with **1a** ($R = \text{Ph}$) formed spirocycle **3a** in high yield but with poor enantioselectivity. While lowering the temperature of the cycloaddition from room temperature to -78°C did not significantly impact the yield of **3a**, this modification led to a dramatic increase in enantioselectivity (entries 1–3). The cycloaddition of the nitrile imine generated from **2a** with **1a** formed **3a** in 88% and 90% ee when the reaction was conducted at -78°C (entry 3). Reducing the catalyst loading from 30 mol % to 10 mol % did not have a significant impact on the enantioselectivity of the cycloaddition (entries 3–5). In fact, the reaction performed with 10 mol % catalyst occurred in slightly higher yield (98%) and enantioselectivity (92% ee) than the reactions performed with 20 and 30 mol % catalyst. The reaction conducted in the presence of 5 mol % catalyst formed **3a** in high yield, but the enantioselectivity was marginally lower (89% ee, entry 6).

The identity of the $\text{Mg}(\text{II})$ salt and the oxindole nitrogen substituent proved important to the yields and/or selectivities of the cycloaddition reactions (entries 5, 7–11). Cycloadditions catalyzed by complexes of $\text{Mg}(\text{ClO}_4)_2$ or MgI_2 and **L2** occurred with low enantioselectivity relative to the cycloaddition catalyzed by a complex of $\text{Mg}(\text{NTf}_2)_2$ and **L2** (compare entries 7 and 8 with entry 5). Cycloadditions of *N*-acetyl and *N*-Boc arylidene methyleneindolinones **1b** and **1d** with the nitrile imine generated from **2a** formed spiro[pyrazolin-3,3'-oxindoles] **3b** and **3d** in 94% and 98% ee, but the yields were substantially lower than the corresponding reaction with **1a** (entries 9 and 11). In contrast, the reaction of *N*-pivaloyl methyleneindolinone **1c** generated spiro[pyrazolin-3,3'-oxindole] **3c** in high yield, but the enantioselectivity was poor (40% ee, entry 10).

The scope of the Mg -catalyzed cycloaddition of the nitrile imine generated from **2a** with a variety of methyleneindolinones is summarized in Table 2. The reactions of an electron-rich methyleneindolinone and halogenated methyleneindolinones generated products **3e–g** in moderate to good yields with high enantioselectivities (entries 1–3). The absolute configuration of spiro[pyrazolin-3,3'-oxindole] **3h** was determined to be (3*S*,4'*S*) by X-ray crystallographic analysis (Figure 1). In contrast, the reaction of an electron-deficient dipolarophile **1h** furnished the corresponding cycloadduct **3h** with modest enantioselectivity (entry 4). The reaction of a *meta*-substituted methyleneindolinone **1i** formed spiro[pyrazolin-3,3'-oxindole] **3i** in high yield with high enantioselectivity (entry 5).

The reaction of a highly electron-rich dipolarophile proved more challenging. The reaction of methyleneindolinone **1j** occurred with 61% ee in the presence of 10 mol % catalyst (Table 2, entry 6). The observed decrease in enantioselectivity likely results from product

inhibition instead of poor facial selection, as product **3j** was formed with 91% ee in the presence of 100 mol % catalyst (entry 7).

Reactions of methyleneindolinones containing an *ortho*-substituted aryl group were sensitive to the size of the *ortho* substituent. The reaction of *ortho*-fluorinated dipolarophile **1k** formed cycloadduct **3k** in high yield with high enantioselectivity (entry 8), but the reactivity of *ortho*-brominated dipolarophile **1l** was poor and the corresponding product **3l** was generated as a racemic mixture (entry 9).

Although aryl groups with large *ortho*-substituents are not well tolerated by the current catalyst, bulky β -alkyl substituents are well tolerated. The reaction of (*E*)-methyleneindolinone **1m** (R = *t*-Bu) furnished cycloadduct **3m** in 70% yield and 99% ee (Table 2, entry 10). However, the enantioselectivity of the cycloaddition is sensitive to the geometry of the alkene unit. The reaction of (*Z*)-methyleneindolinone **1n** (R = *t*-Bu) furnished the diastereomeric cycloadduct **3n** with only 66% ee (eq 1).

(1)

The scope of the Mg-catalyzed cycloaddition of **1a** with a selection of nitrile imines is summarized in Table 3. As illustrated in Table 1, entry 5, the nitrile imine generated from benzaldehyde-derived hydrazonoyl bromide **2a** furnished cycloadduct **3a** in high yield with excellent enantioselectivity. The reaction of a nitrile imine bearing an electron-deficient aryl group (Ar¹ = 4-CF₃C₆H₄) at the C-terminus of the dipole also generated the corresponding spiro[pyrazolin-3,3'-oxindole] **3o** in high yield with high enantioselectivity (Table 3, entry 1). The reaction of a nitrile imine containing a 3-bromophenyl group at the C-terminus furnished cycloadduct **3p** in 72% yield with 84% ee (entry 2). The reaction also appears sensitive to the size of the substituent at the 2-position of the C-terminal aryl ring: whereas reaction with a smaller fluoro substituent afforded product **3q** in 90% yield and 90% ee (entry 3), the reaction to afford product **3r** with a larger bromo substituent only proceeded in 81% yield with 62% ee (entry 4).

Nitrile imines with electron-deficient aryl groups at the *N*-terminus of the dipole were also well tolerated. Reactions of nitrile imines substituted with *N*-terminal 4-fluorophenyl and 4-trifluoromethylphenyl groups formed the corresponding cycloadducts **3s** and **3t** in 83% and 87% yields with 91% and 90% ee, respectively (entries 5 and 6).

The scope of cycloadditions with methyleneindolinone **1a** encompasses a range of sterically and electronically distinct nitrile imines. However, the hydrazonoyl bromide precursors to nitrile imines with electron-rich aryl groups at either the C- or *N*-terminus were too unstable in our hands to generate reproducible results. In addition, attempts to utilize hydrazonoyl chlorides as nitrile imine precursors resulted in either low reactivity or poor enantioselectivity.

In summary, we have developed a method for 1,3-dipolar cycloadditions of nitrile imines to form spiro[pyrazolin-3,3'-oxindole] in high yields with high enantioselectivity. This process is complementary to extant methods, allowing for the formation of spiro[pyrazolin-3,3'-oxindole] from that could not previously be accessed in highly enantioenriched form. Specifically, spiro[pyrazolin-3,3'-oxindole] cycloadducts are formed with high enantioselectivity from methyleneindolinones lacking an *ortho*-substituted aryl group at β -position of the dipolarophile. Studies to develop asymmetric cycloadditions of nitrile imines with additional classes of dipolarophiles are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Iowa State University and the ISU Institute for Physical Research for financial support of this work. We thank Dr. Arkady Ellern and the Molecular Structure Laboratory (Iowa State University) for X-ray diffraction data collection and structure determination. We thank Professor Emeritus Richard Larock (Iowa State University) for instrumentation and chemicals. M.C.S. thanks the HHMI program for improving STEM education at Iowa State University for funding as a Postdoctoral Science Teaching Fellow (HHMI grant P.I.: C. Ogilvie). L.S. thanks the NIH for a Pathways to Independence Award (GM95697).

Notes and references

1. a) Huisgen R. *Angew. Chem. Int. Ed.* 1963; 2:565. b) Huisgen R. *Angew. Chem. Int. Ed.* 1963; 2:633. c) Bianchi, G.; Gandolfi, R. 1,3-Dipolar Cycloaddition Chemistry. Padwa, A., editor. New York: Wiley; 1984. p. 470-477.
2. For selected examples, see: Chandanshive JZ, González PB, Tiznado W, Bonini BF, Caballero J, Femoni C, Franchini MC. *Tetrahedron*. 2012; 68:3319. Yildirim M, Dürüst Y. *Tetrahedron*. 2011; 67:3209. Wang Y, Song W, Hu WJ, Lin Q. *Angew. Chem. Int. Ed.* 2009; 48:5330. Wang Y, Rivera Vera CI, Lin Q. *Org. Lett.* 2007; 9:4155. [PubMed: 17867694] Manyem S, Sibi MP, Lushington GH, Neuenswander B, Schoenen F, Aube J. J. *Comb. Chem.* 2007; 9:20. [PubMed: 17206829] Conti P, Pinto A, Tamborini L, Rizzo V, De Micheli C. *Tetrahedron*. 2007; 63:5554. Molteni G. *Heterocycles*. 2005; 65:2513. Broggin G, DeMarchi I, Martinelli M, Paladino G, Pilati T, Terraneo T. *Synthesis*. 2005; 13:2246. Barluenga J, Fernández-Marí F, González R, Aguilar E, Revelli GA, Viado AL, Fañanás FJ, Olano B. *Eur. J. Org. Chem.* 2000:1773.
3. a) Sibi MP, Stanley LM, Jasperse CP. *J. Am. Chem. Soc.* 2005; 127:8276. [PubMed: 15941248] b) Sibi MP, Stanley LM, Soeta T. *Adv. Synth. Catal.* 2006; 348:2371.
4. For reviews, see: Lévai A. J. *Heterocycl. Chem.* 2002; 39:1. Kumar S, Bawa S, Drah S, Kumar R, Gupta H. *Recent Pat. Anti-Infect. Drug Discovery*. 2009; 4:154. Rahman MA, Siddiqui A. *Int. J. Pharm. Sciences Drug Res.* 2010; 2:165.
5. For recent reviews on the spirocyclic oxindoles, see: Ball-Jones NR, Badillo JJ, Franz AK. *Org. Biomol. Chem.* 2012; 10:5165. [PubMed: 22581310] Trost BM, Brennan MK. *Synthesis*. 2009:3003.
6. For selected examples of catalytic, enantioselective synthesis of spirocyclic oxindoles by [3+2] cycloadditions with methyleneindolinones, see: Trost BM, Cramer N, Silverman SM. *J. Am. Chem. Soc.* 2007; 129:12396. [PubMed: 17880222] Chen X-H, Wei Q, Luo S-W, Xiao H, Gong L-Z. *J. Am. Chem. Soc.* 2009; 131:13819. [PubMed: 19736987] Antonchick AP, Gerding-Reimers C, Catarinella M, Schürmann M, Preut H, Ziegler S, Rauh D, Waldmann H. *Nat. Chem.* 2010; 2:735. [PubMed: 20729892] Tan B, Candeias NR, Barbas CF III. *J. Am. Chem. Soc.* 2011; 133:4672. [PubMed: 21395245] Deng H-P, Wei Y, Shi M. *Org. Lett.* 2011; 13:3348. [PubMed: 21650190] Zhong F, Han X, Wang Y, Lu Y. *Angew. Chem. Int. Ed.* 2011; 50:7837. Awata A, Arai T. *Chem. Eur. J.* 2012; 18:8278. [PubMed: 22689536] Guo C, Song J, Gong L-Z. *Org. Lett.* 2013; 15:2676. [PubMed: 23679128] Hong L, Kai M, Wu C, Sun W, Zhu G, Li G, Yao X, Wang R. *Chem. Commun.* 2013; 49:6713.
7. Singh A, Loomer AL, Roth GP. *Org. Lett.* 2012; 14:5266. [PubMed: 23050551]

8. Wang G, Liu X, Huang T, Kuang Y, Lin L, Feng X. *Org. Lett.* 2013; 15:76. [PubMed: 23228061]

Figure 1.
Absolute stereochemistry and structure of **3g** based on X-ray diffraction data.

R = Ph (77% ee), 4-Cl-C₆H₄ (63% ee),
 2-Br-C₆H₄ (84% ee), *t*-Bu (96% ee)

Ar = 4-Br-C₆H₄
 R = Ph (92% ee), 4-Cl-C₆H₄ (99% ee),
 2-Br-C₆H₄ (0% ee), *t*-Bu (99% ee)

Scheme 1.
 Catalytic, Enantioselective Cycloadditions of Nitrile Imines with Methyleneindolinones.

Table 1

Identification of Catalyst Precursors and Reaction Conditions^a

entry	R (1)	MgX ₂ (mol %)	Temp (°C)	3	Yield (%) ^b	ee (%) ^c
1	Ph (1a)	Mg(NTf ₂) ₂ (30)	rt	3a	82	29
2	Ph (1a)	Mg(NTf ₂) ₂ (30)	-20	3a	88	55
3	Ph (1a)	Mg(NTf ₂) ₂ (30)	-78	3a	88	90
4	Ph (1a)	Mg(NTf ₂) ₂ (20)	-78	3a	91	91
5	Ph (1a)	Mg(NTf ₂) ₂ (10)	-78	3a	98	92
6	Ph (1a)	Mg(NTf ₂) ₂ (5)	-78	3a	96	89
7	Ph (1a)	Mg(ClO ₄) ₂ (10)	-78	3a	98	44
8	Ph (1a)	MgI ₂ (10)	-78	3a	95	64
9	Me (1b)	Mg(NTf ₂) ₂ (10)	-78	3b	76	94
10	<i>i</i> -Bu (1c)	Mg(NTf ₂) ₂ (10)	-78	3c	97	40
11	<i>O</i> -Bu (1d)	Mg(NTf ₂) ₂ (10)	-78	3d	37	98

^aReactions conditions: **1** (0.20 mmol), **2a** (0.24 mmol), **L2** (0.022–0.066 mmol), MgX₂ (0.020–0.060 mmol), Et₃N (0.30 mmol), 4Å MS (100 mg), CH₂Cl₂ (2 mL).^bIsolated yield of **3** with >95:5 diastereomeric and regioisomeric ratios.^cDetermined by chiral HPLC.

Table 2

Scope of Nitrile Imine Cycloadditions with Various Methyleneindolinones^a

entry	1	R	3	Yield (%) ^b	ee (%) ^c
1	1e	4-MeO-C ₆ H ₄	3e	81	99
2	1f	4-Cl-C ₆ H ₄	3f	86	99
3	1g	4-Br-C ₆ H ₄	3g	63 ^d	94
4	1h	4-CF ₃ -C ₆ H ₄	3h	81	80
5	1i	3-MeO-C ₆ H ₄	3i	90 ^e	94
6	1j	3,4,5-(MeO) ₃ -C ₆ H ₂	3j	91	61
7 ^f	1i	3,4,5-(MeO) ₃ -C ₆ H ₂	3j	88	91
8	1k	2-F-C ₆ H ₄	3k	84	92
9	1l	2-Br-C ₆ H ₄	3l	43	0
10	1m	(<i>E</i>)- <i>tert</i> -butyl	3m	70	99

^aFor detailed reaction conditions, see the Supporting Information.

^bIsolated yield of **3** with >95:5 diastereomeric and regioisomeric ratios.

^cDetermined by chiral HPLC.

^dIsolated yield of **3g** as a 10:1 mixture of diastereomers and an 11:1 mixture of regioisomers.

^eIsolated yield of **1i** as a 9:1 mixture of diastereomers.

^fThe reaction was conducted in the presence of 100 mol % of the Mg catalyst.

Table

Scope of 1,3-Dipolar Cycloadditions of Methyleneindolinone **1a** with Nitrile Imines^a

entry	2	Ar¹	Ar²	3	Yield (%)^b	ee (%)^c
1	2b	4-CF ₃ -C ₆ H ₄	4-Br-C ₆ H ₄	3o	86	94
2	2c	3-Br-C ₆ H ₄	4-Br-C ₆ H ₄	3p	72	84
3	2d	2-F-C ₆ H ₄	4-Br-C ₆ H ₄	3q	90	90
4	2e	2-Br-C ₆ H ₄	4-Br-C ₆ H ₄	3r	81	62
5	2f	Ph	4-F-C ₆ H ₄	3s	83	91
6	2g	Ph	4-CF ₃ -C ₆ H ₄	3t	87	90

^aFor detailed reaction conditions, see the Supporting Information.

^bIsolated yield of **3** with >95:5 diastereomeric and regioisomeric ratios.

^cDetermined by chiral HPLC.