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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Catalytic Asymmetric Cascade Vinylogous Mukaiyama 1,6-Michael/Michael Addition of 2-Silyloxyfurans with Azoalkenes: Direct Approach to Fused Butyrolactones

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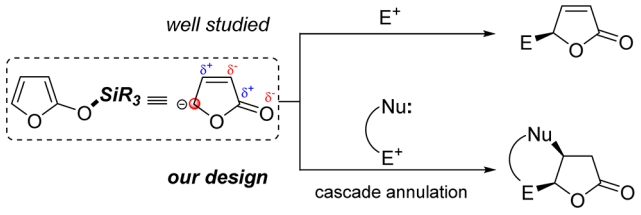
Supporting Information

ABSTRACT: An unprecedented cascade vinylogous Mukaiyama 1,6-MA/MA of 2-silyloxyfurans and azoalkenes was realized with a Cu(II)/^{t}Bu-Box complex. An array of fused butyrolactones containing multiple stereocenters was generally obtained in good yield (up to 90% yield) with exclusive diastereoselectivity (>20:1 dr) and excellent enantioselectivity (up to 99% ee). Carbon isotope effects measured by ^{13}C NMR revealed a stepwise mechanism for this annulation process.

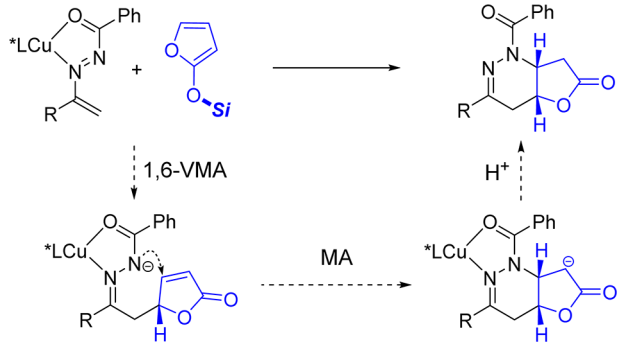
Development of a practical methodology for the construction of enantioenriched γ-butyrolactones and γ-butenolides represents an important research topic in organic synthesis because of their prevalence as the core structures in a number of biologically interesting natural and synthetic compounds.[1] In this context, elaboration of 2-silyloxyfurans[2] as the readily accessible nucleophilic synthons of the γ-anion of 2(5*H*)-furanone by means of vinylogous Mukaiyama−aldol,[3] Mukaiyama−Michael,[4] and Mukaiyama−Mannich-type additions[5] has been, thus far, the well-established method for electrophilic attack at the C5 position. Considering that an electron-deficient unsaturated lactone moiety in butenolide is a potential Michael acceptor easily trapped by a built-in nucleophile group, we envision that 2-silyloxyfurans could be utilized as dipole-type synthons in the cascade reaction by sequentially reacting as a nucleophile and an electrophile, giving rise to fused butyrolactone (Scheme 1). This cascade approach involves the nucleophilicity on C5 of the 2-silyloxyfuran and the electrophilicity of C4 of the formed butenolide. Surprisingly, however, this kind of asymmetric cascade annulation with 2-silyloxyfurans has received much less attention despite numerous examples of butyrolactone stereogenicity found in natural alkaloids and biologically active compounds.

Scheme 1. Nucleophilicity and Electrophilicity of 2-Silyloxyfurans



Recently, we have developed an asymmetric inverse-electron-demand azo-Diels−Alder (IEDDA) reaction of azoalkenes and indoles catalyzed by a Cu(I)/^{t}Bu-Phosferrox complex.[6] Meanwhile, azoalkene was a well-known key intermediate in the cascade annulation process for the synthesis of N-containing heterocycles.[7] We envisaged that the combination of 2-silyloxyfurans and azoalkenes could constitute an unprecedented formal [4 + 2] cycloaddition through a cascade protocol. As shown in Scheme 2, the initial vinylogous Mukaiyama 1,6-

Scheme 2. Proposed Cascade Annulation of Vinylogous Mukaiyama 1,6-Michael/Michael Addition of Azoalkene with 2-Silyloxyfuran



Michael addition of 2-silyloxyfuran to the in situ formed metalloazoalkene affords an butenolide intermediate. Subsequently, the negative charged N would attack the electron-deficient unsaturated lactone via Michael addition followed by protonation to afford the fused butyrolactones. In this communication, we describe an unprecedented Cu(II)/bisoxazoline-catalyzed cascade vinylogous Mukaiyama 1,6-Michael addition/Michael addition of 2-silyloxyfurans and azoalkenes with excellent diastereo/enantioselectivity control, providing a straightforward access to a variety of enantioenriched butyrolactones fused by a tetrahydropyridazine moiety, which is also often a structural element of biologically active compounds.[8] To our knowledge, this is the first example of utilizing 2-silyloxyfurans as a sequential nucleophile and electrophile in an asymmetric cascade

Received: June 23, 2015
Published: July 27, 2015

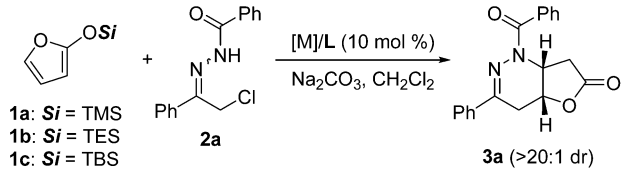
DOI: 10.1021/jacs.5b06509
J. Am. Chem. Soc. 2015, 137, 10124−10127

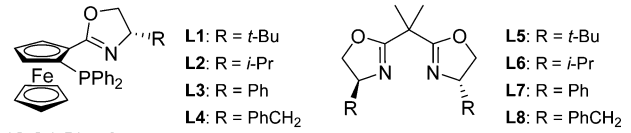
annulation process, which contributes to the synthetic chemistry of furan-based dienoxysilanes.

In view of Zanardi's research[9] on vinylogous Mukaiyama–Michael addition between 2-silyloxyfurans with azoalkene promoted by Lewis acid or without catalyst, we believed that the basic condition would not only facilitate forming the azoalkenes from α-halohydrazine but also enhance the feasibility of the designed annulation. We started our survey with 2-silyoxyfuran **1a** and α-chloro-*N*-benzoyl hydrazone **2a** as the azoalkene surrogate. When using Cs_2CO_3 as the base, the reaction finished smoothly in less than 20 h without other promoter, and the fused butyrolactone **3a** bearing two contiguous tertiary stereogenic centers was isolated as a single isomer with excellent diastereoselectivity (>20:1 dr), albeit in moderate yield (Table 1, entry 1). Hence, the main challenge to address to develop an asymmetric variant of this cascade process is to suppress the uncatalyzed background reaction; that is, the chiral catalyst must accelerate the asymmetric reaction faster than the racemic annulation. As the optimized catalyst for the asymmetric IEDDA reaction[6] and cross-1,3-dipolar [3 + 3] cycloaddition reaction[10] in our previous research, the Cu(I)/(S,S_P)-*t*Bu-Phosferrox complex was preferentially chosen as the chiral catalyst. However, difficulties were encountered, and only moderate enantioselectivity (64% ee) was achieved with unsatisfactory yields (50%) (entry 2). Cu(II) gave better results than Cu(I) in terms of enantioselectivity and reactivity (entry 3). It is well-known that in a vinylogous Mukaiyama-type reaction protic additive often dramatically affects the stereoselectivities or enhances the yields.[11] Among the tested protic additives, hexafluoroisopropanol (HFIPA) was revealed as the best one, and the yield was improved to 85% while the enantioselectivity remained at an unacceptable level (entry 5). Other Phosferrox-type ligands were also tested, delivering reduced enantioselectivities (entries 7–9). (*S*,*S*)-*t*Bu-Box **L5** was identified as the best chiral ligand in terms of chemical yield and enantioselectivity, leading to the fused **3a** in 82% yield with 90% ee (entry 10). Reducing the reaction temperature to 0 °C led to full conversion with good yield and 95% ee (entry 14). Variation of the silyl group has little influence on this transformation, and both enantioselectivity and efficiency remain untouched (entries 15 and 16).

Under the optimized conditions, the substrate scope and the generality of the current method with respect to *N*-benzoyl hydrazone were next investigated. As tabulated in Table 2, an array of α-chloro- or α-bromo-*N*-benzoyl hydrazones was

Table 1. Optimization of the Reaction Condition[a]

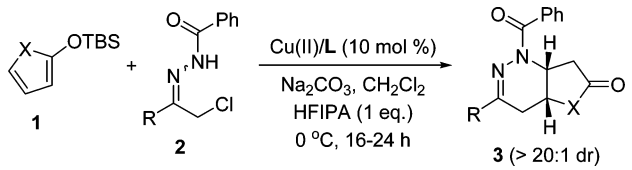


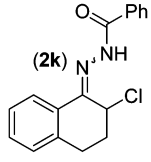
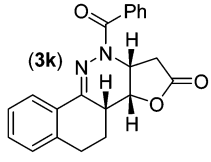


entry	1	[M]	ligand	additive[c]	*T* (°C)	time (h)	yield[d] (%)	ee[e] (%)
1[b]	**1a**	-	-	-	rt	20	45	-
2	**1a**	$CuBF_4$	**L1**	-	rt	10	50	64
3	**1a**	$Cu(OTf)_2$	**L1**	-	rt	10	55	75
4	**1a**	$Cu(OTf)_2$	**L1**	IPA	rt	10	69	75
5	**1a**	$Cu(OTf)_2$	**L1**	HFIPA	rt	10	85	75
6	**1a**	$Cu(OTf)_2$	**L1**	H_2O	rt	10	71	73
7	**1a**	$Cu(OTf)_2$	**L2**	HFIPA	rt	10	78	10
8	**1a**	$Cu(OTf)_2$	**L3**	HFIPA	rt	10	82	15
9	**1a**	$Cu(OTf)_2$	**L4**	HFIPA	rt	10	75	17
10	**1a**	$Cu(OTf)_2$	**L5**	HFIPA	rt	10	82	90
11	**1a**	$Cu(OTf)_2$	**L6**	HFIPA	rt	10	85	47
12	**1a**	$Cu(OTf)_2$	**L7**	HFIPA	rt	10	81	56
13	**1a**	$Cu(OTf)_2$	**L8**	HFIPA	rt	10	77	33
14	**1a**	$Cu(OTf)_2$	**L5**	HFIPA	0	15	87	95
15	**1b**	$Cu(OTf)_2$	**L5**	HFIPA	0	15	83	95
16	**1c**	$Cu(OTf)_2$	**L5**	HFIPA	0	15	85	97

[a]All reactions were carried out with 0.30 mmol of **1** and 0.40 mmol of **2a** in 2.0 mL of solvent. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Carried out without catalyst, and Cs_2CO_3 was used as base. [c]With 1 equiv of protic additive. [d]Isolated yield. [e]Determined by HPLC analysis, and >20:1 dr was determined by the crude ^{1}H NMR.

Table 2. Substrate Scope of Cu(II)-Catalyzed Cascade 1,6-VMA/MA Reaction of Heterocyclic Silyloxydienes 1 with Hydrazones 2[a]



entry	X	R	3	yield (%)[b]	ee (%)[c]
1	O (**1c**)	Ph (**2a**)	**3a**	85	97
2	O (**1c**)	*p*-Br-C_6H_4 (**2b**)	**3b**	86	94
3	O (**1c**)	*p*-Cl-C_6H_4 (**2c**)	**3c**	88	94
4	O (**1c**)	*m*-Cl-C_6H_4 (**2d**)	**3d**	81	91
5[d]	O (**1c**)	*o*-F-C_6H_4 (**2e**)	**3e**	86	93
6	O (**1c**)	*p*-Me-C_6H_4 (**2f**)	**3f**	80	96
7[d]	O (**1c**)	*p*-MeO-C_6H_4 (**2g**)	**3g**	87	94
8	O (**1c**)	*m*-Me-C_6H_4 (**2h**)	**3h**	78	92
9[d]	O (**1c**)	2-Naphthyl (**2i**)	**3i**	88	94
10	O (**1c**)	PhCH=CH (**2j**)	**3j**	83	71
11[e]				90	99
12	NBoc (**1d**)	Ph (**2a**)	**3l**	90	92
13	NBoc (**1d**)	*p*-Br-C_6H_4 (**2b**)	**3m**	87	95
14[d]	NBoc (**1d**)	*o*-F-C_6H_4 (**2e**)	**3n**	82	97
15	NBoc (**1d**)	*p*-Me-C_6H_4 (**2f**)	**3o**	80	98

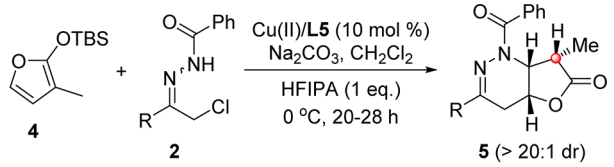
[a]All reactions were carried out with 0.30 mmol of **1** and 0.40 mmol of **2** in 2.0 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by HPLC analysis, and >20:1 dr was determined by the crude ^{1}H NMR. [d]α-Bromo-*N*-benzoyl hydrazone was used. [e]Relative configuration of **3k** was determined by NOESY (see SI).

DOI: 10.1021/jacs.5b06509
J. Am. Chem. Soc. 2015, 137, 10124–10127

examined as the azoalkene precursors, and it was revealed that with electron-neutral groups (Table 2, entry 1), electron-deficient groups (entries 2−5), or electron-rich groups (entries 6−8) on the phenyl ring of hydrazones the fused butyrolactones (**3a**−**3h**) were obtained in good yields (78−88%) and excellent stereoselectivities (>20:1 dr, 91−97% ee). The substitution pattern of the phenyl ring had a negligible effect on the reactivity and enantioselectivity, and *para*-, *meta*-, or *ortho*-substituted hydrazones were all tolerated in this annulation. Fused aromatic 2-naphthyl-substituted hydrazone **2i** was also proven to be a viable substrate, leading to the corresponding adduct in good yield with 94% ee (entry 9). The substrate scope of this annulation was successfully extended to alkenyl-substituted hydrazone **2j**, and the desired adduct **3j** was isolated in good yield with moderate enantioselectivity (entry 10). Alkyl-substituted hydrazone was not a viable substrate, affording the cycloadduct as a racemate probably due to the overwhelmingly disadvantageous background reaction. The strong electron-donating effect of the alkyl group on the azoalkene might lead to a decrease in activity in the annulation reaction. Remarkably, cyclic hydrazone **2k** was proven to be a suitable substrate, delivering the polycyclic adduct **3k** with three contiguous tertiary stereogenic centers in good yields with exclusive diastereoselectivity and excellent enantioselectivity (entry 11). To further expand the synthetic utility of this cascade 1,6-VMA/MA annulation, pyrrole-based dienoxysilane (**1d**) was also evaluated, and the fused butyrolactams **3l**−**3o** were obtained in a satisfactory yield and excellent stereoselectivity control (>20:1 dr, 92−98% ee) (entries 11−14). The absolute configuration of cycloadduct **3c** was determined as (4a*R*,7a*R*) by X-ray diffraction analysis (see Supporting Information (SI) for details).

Having succeeded in the cascade 1,6-VMA/MA annulation of 2-silyloxyfuran (TBSOF) with azoalkenes, we then investigated several substituted furans under the optimized reaction conditions. As tabulated in Table 3, 3-methyl-substituted

Table 3. Substrate Scope of Cu(II)-Catalyzed Cascade 1,6-VMA/MA Reaction of 3-Methyl-Substituted Silyloxyfuran 4 with Hydrazones 2[a]

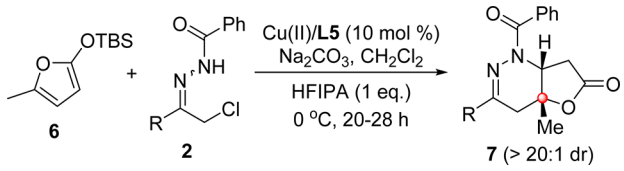


entry	R	5	yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	**5a**	82	97
2	*p*-Cl-C_6H_4 (**2c**)	**5b**	75	96
3[d]	*p*-CF_3-C_6H_4 (**2k**)	**5c**	83	97
4	*p*-Me-C_6H_4 (**2f**)	**5d**	78	93
5	*m*-Me-C_6H_4 (**2h**)	**5e**	75	93

[a]All reactions were carried out with 0.30 mmol of **4** and 0.40 mmol of **2** in 2.0 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by HPLC analysis, and >20:1 dr was determined by the crude ^{1}H NMR. [d]Relative configuration of **5c** was determined by NOESY (see SI).

TBSOF **4** proved to be a viable substrate for this annulation process, affording the desired cycloadduct **5** containing three contiguous tertiary stereogenic centers in good yield with high diastereoselectivity (>20:1 dr) and excellent enantioselectivity (Table 3, entries 1−5). Although 4-methyl-substituted TBSOF was not tolerated in this transformation, probably due to the disfavored steric hindrance, 5-methyl-substituted TBSOF **6** worked well in this tandem annulation, leading to the fused butyrolactones **7** containing adjacent tertiary and quaternary stereogenic centers, which highlighted the generality of this current protocol (Table 4, entries 1−5).

Table 4. Substrate Scope of Cu(II)-Catalyzed Cascade 1,6-VMA/MA Reaction of 5-Methyl-Substituted Silyloxyfuran 6 with Hydrazones 2[a]

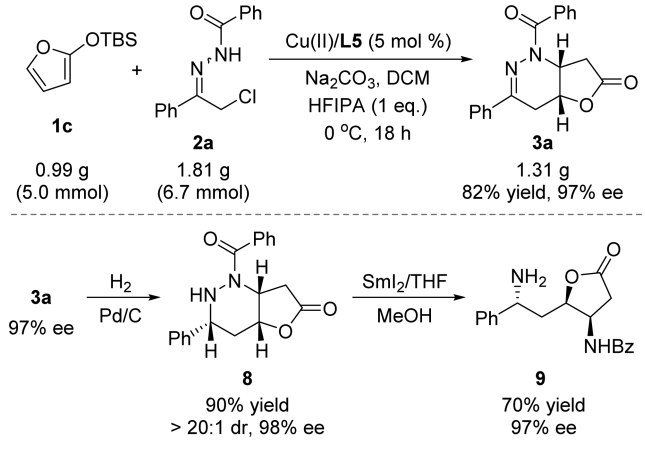


entry	R	7	yield[b] (%)	ee[c] (%)
1[d]	Ph (**2a**)	**7a**	81	97
2	*p*-Br-C_6H_4 (**2b**)	**7b**	86	95
3	*p*-Cl-C_6H_4 (**2c**)	**7c**	84	96
4	*p*-Me-C_6H_4 (**2f**)	**7d**	80	94
5	*m*-Me-C_6H_4 (**2h**)	**7e**	76	96

[a]All reactions were carried out with 0.30 mmol of **6** and 0.40 mmol of **2** in 2.0 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by HPLC analysis, and >20:1 dr was determined by the crude ^{1}H NMR. [d]Relative configuration of **7c** was determined by NOESY (see SI).

To probe the potential scalability of this methodology, we performed this Cu(II)-catalyzed asymmetric cascade 1,6-VMA/MA annulation on a gram scale with 5 mol % catalyst loading. The reaction proceeded smoothly, affording **3a** in 82% yield and 97% ee (Scheme 3). Hydrogenation of **3a** with a catalytic amount

Scheme 3. Scale-Up of Cu(II)-Catalyed Asymmetric Cascade 1,6-VMA/MA Reaction and Synthetic Elaboration of Cycloadduct 3a



of Pd/C led to the reduction of the C=N bond in a highly diastereoselective manner (the relative configuration was determined by NOESY; see SI for details), affording the hexahydropyridazine **8** in good yield, which could be readily converted to a biologically important 1,4-diamine derivative[12] **9** via SmI_2-mediated cleavage of the N−N bond.[13]

To shed some light on the reaction mechanism, that is, the annulation through a stepwise cascade vinylogous Mukaiyama 1,6-Michael/Michael addition or a concerted [4 + 2] annulation pathway followed by sequential desilylation, the investigation of

DOI: 10.1021/jacs.5b06509
J. Am. Chem. Soc. 2015, 137, 10124−10127

carbon isotope effects for the current reaction between TBSOF and azoalkene was performed using Singleton's ^{13}C NMR method at natural abundance.[14] As shown in Figure 1, only a

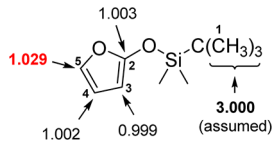


Figure 1. Carbon isotope effects (R/R_0) calculated for TBSOF **1c**. The three methyl carbons of the ^{t}Bu group (in bold) was taken as the internal standard. For more details, see the SI.

noticeable carbon isotope effect was detected on the carbon at the 5-position ($^{13}C_{recovered}/^{13}C_{virgin}$ = 1.029, average of three runs), revealing that the first vinylogous Mukaiyama 1,6-Michael addition is the rate-determining step and that this annulation proceeds through a stepwise pathway.

In conclusion, we have successfully developed an unprecedented Cu(II)-catalyzed asymmetric cascade vinylogous Mukaiyama 1,6-Michael/Michael addition of 2-silyloxyfurans with in situ formed azoalkenes. The key feature of the current methodology is that furan-based dienoxysilanes could be utilized as efficient dipole-type synthons. This cascade annulation process provides a straightforward approach to a variety of biologically important and structurally complicated fused butyrolactones in good yield with high regioselectivity and excellent stereoselectivity. The studies of carbon isotope effects measured by ^{13}C NMR indicated a stepwise mechanism for this annulation. Further efforts are currently underway to understand the origin of stereoselectivity control and application of this methodology in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06509.

Experimental procedures and compound characterization data (PDF)

X-ray data for compound **3c** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by 973 Program (2011CB808600), NSFC (21172176, 21372180), Hubei NSF (ZRZ0273), and the Fundamental Research Funds for the Central Universities. The authors thank all referees for their helpful comments and suggestions.

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DOI: 10.1021/jacs.5b06509
J. Am. Chem. Soc. 2015, 137, 10124−10127