

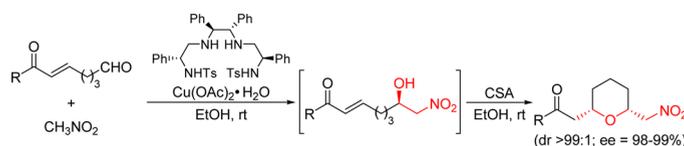
Highly Stereoselective Synthesis of 2,6-*cis*-Substituted Tetrahydropyrans Using a One-Pot Sequential Catalysis

Qipu Dai,[†] Nirmal K. Rana, and John Cong-Gui Zhao**Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas 78249-0698, United States*

cong.zhao@utsa.edu

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ABSTRACT



A catalytic highly diastereo- and enantioselective synthesis of 2,6-*cis*-substituted tetrahydropyrans was realized using a one-pot sequential catalysis involving Henry and oxa-Michael reactions. The nitroaldol products obtained in a highly enantioselective copper(II)-catalyzed Henry reaction between nitromethane and 7-oxo-hept-5-enals were subsequently treated with a catalytic amount of camphorsulfonic acid (CSA) to give the desired tetrahydropyran derivatives in excellent yields, diastereoselectivities (*dr* > 99:1), and enantioselectivities (*ee* = 98–99%). The reaction can also be used for the high stereoselective synthesis of a *cis*-2,6-disubstituted morpholine.

One-pot sequential catalysis, also referred to as tandem catalysis,¹ is a very efficient method for assembling complex molecular structures from relatively simple starting materials since this synthetic strategy involves a modular combination of several catalytic reactions into one synthetic operation with minimum workup or change in reaction conditions. Because this method can significantly improve the synthetic efficiency, recently there has been a lot of

attention in developing novel one-pot sequential catalytic methods.^{1,2}

Tetrahydropyran is an important structural motif that may be found in many natural products that often show diverse and potent biological activities.³ Due to their importance in organic synthesis, many synthetic strategies have been developed in order to obtain these derivatives in highly diastereo- and/or enantioselectivities.^{4,5} Among these reported methods, catalytic intramolecular oxa-Michael⁵

[†] Current address: Department of Chemistry, University of Alabama at Birmingham.

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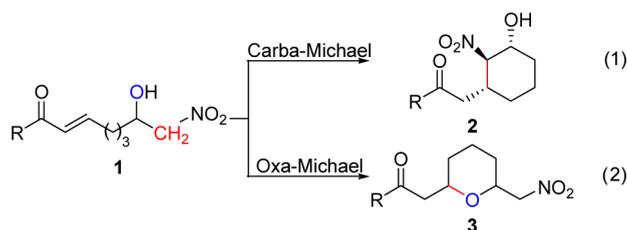
(5) For reviews, see: (a) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228. (b) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41*, 988–999.

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reactions have been shown to be a highly efficient approach for obtaining tetrahydropyran derivatives.^{6,7} For example, both *cis*- and *trans*-2,6-disubstituted tetrahydropyran derivatives, which are among the most abundant motifs in natural products, have been synthesized this way.^{6,7}

Scheme 1. Henry Product **1** May Be Used As an Ambident Nucleophile in Intramolecular Michael Reactions



Using a one-pot sequential catalysis, we recently developed a highly stereoselective synthesis of trisubstituted cyclohexane derivatives **2** from nitromethane and 7-oxohept-5-enals involving the Henry product **1** as the intermediate (Scheme 1).^{2b} A base-catalyzed intramolecular carba-Michael reaction leads to the formation of the cyclohexane derivatives **2** (Scheme 1, eq 1).^{2b,8} During this study, we envisioned that compound **1** may be used as an ambident nucleophile in catalysis: An intramolecular oxa-Michael reaction using the hydroxy group in compound **1** as a nucleophile should lead to the formation of 2,6-disubstituted tetrahydropyrans **3** (Scheme 1, eq 2). Developing stereoselective synthesis of pyran derivatives has been our ongoing research interest,⁹ and therefore, we sought methods to conduct a stereoselective oxa-Michael reaction on compound **1**. Herein we wish to report a highly diastereo- and enantioselective synthesis of *cis*-2,6-disubstituted tetrahydropyrans using a one-pot sequential catalysis.

Using the racemic Henry product **1a** (R = Ph) (Scheme 1) as the model substrate, we first attempted the oxa-Michael using different base catalysts; however, all

these catalysts led to the formation of the carba-Michael product **2** only.^{2b,8} No formation of the desired oxa-Michael product was observed probably because in compound **1a** the C–H bond is more acidic than the O–H bond. Most recently Fuwa and co-workers have reported that camphorsulfonic acid (CSA) (Figure 1) is a highly *syn*-selective catalyst for oxa-Michael reactions of 7-oxohept-5-enol derivatives.⁷ We then evaluated CSA as a catalyst for cyclizing compound **1a**. Indeed, with CSA as the catalyst, the intramolecular oxa-Michael reaction gave the expected 2,6-disubstituted **3a** (R = Ph) (Scheme 1) as a single diastereomer in a high yield. The relative stereochemistry of this product was determined to be *cis* by NOE experiments, which is also in agreement with the reported *syn*-selectivity.⁷ Unfortunately, **3a** was obtained as a racemic product using this protocol (data not shown). Nonetheless, according to the reported mechanism,⁷ if an optically enriched **1a** is used as the substrate, then product **3a** should be obtained in optically enriched form. Thus, we screened several catalysts to obtain compound **1a** in high optical purity from enal **6a** and nitromethane. Again many basic catalysts reported for Henry reactions failed to produce **1a** as the reactions went further to form compound **2** directly (data not shown). Gratifyingly, both Ooi's precatalyst **4** (Figure 1) in the presence of *t*-BuOK¹⁰ and Cu(OAc)₂ in the presence of Wan's ligands (**5** and *ent*-**5**) (Figure 1)¹¹ gave **1a** in good yields under their respective optimized conditions.^{10,11} The (*S*)-enantiomer of compound **1a** was obtained in 55% ee with **4**/*t*-BuOK (Scheme 2, eq 3). In contrast, with Wan's catalytic system, both the (*R*)- and (*S*)-enantiomers were obtained in a high ee value of 98% using the enantiomeric ligands **5** and *ent*-**5**, respectively (Scheme 2, eqs 4 and 5). With the optically enriched **1a** in hand, the CSA-catalyzed oxa-Michael reaction was conducted again, and product **3a** was obtained as a single diastereomer in 90% yield with complete retention of the optical purity (Scheme 2, eq 6). The enantiomer of **3a** may be similarly obtained by using (*S*)-**1a** as the starting material.

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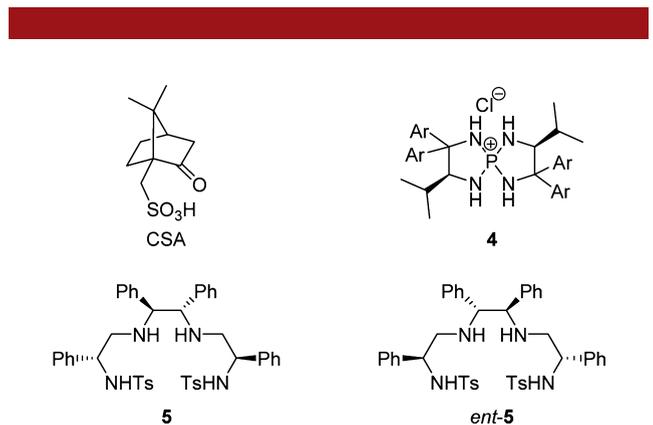
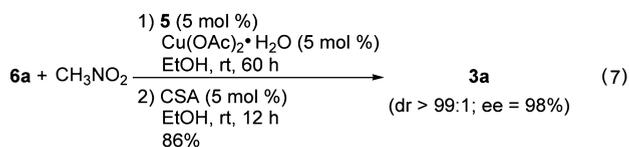
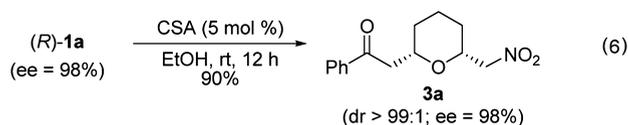
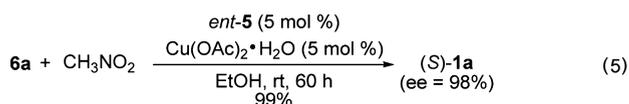
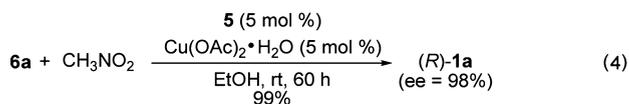
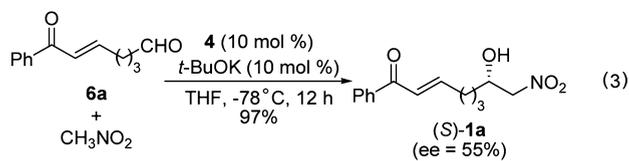


Figure 1. Structure of the catalyst and ligands used in this study (Ar = *p*-CF₃C₆H₄-).

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Scheme 2. Synthesis of the Oxa-Michael Product Using Stepwise and Sequential Catalyses

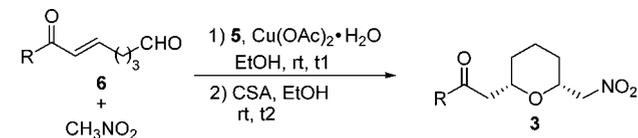


Although the synthesis of the tetrahydropyran **3a** may be achieved in excellent results using the above stepwise protocol, we thought a one-pot sequential catalysis using enal **6a** and nitromethane directly would be more convenient and efficient. Thus, enal **6a** and nitromethane were first treated with $\text{Cu}(\text{OAc})_2/\mathbf{5}$ for 60 h at rt and then with CSA for 12 h under their respective optimized conditions, and **3a** was obtained as a single diastereomer in 86% yield and 98% ee (Scheme 2, eq 7). These results are comparable with those of the stepwise protocol.

The scope of this one-pot sequential catalysis was then investigated with different enal derivatives **6**, and the results are summarized in Table 1. As the data in Table 1 show, all 7-aryl-substituted 7-oxo-hept-5-enals gave the desired tetrahydropyran products **3** in similarly high yields and excellent dr and ee values (Table 1, entries 1–11). The electronic nature of the substituent and its position on the phenyl ring have almost no influence at all on the reactivity, diastereoselectivity, or enantioselectivity of this reaction. Similarly, 7-alkyl-substituted 7-oxo-hept-5-enals also gave the desired tetrahydropyrans in excellent yields, dr, and enantioselectivities (Table 1, entries 12–14). It should be pointed out that the high dr and high ee value achieved in this reaction are of different origins: The high ee values of oxa-Michael product **3** originated in the first step of this reaction

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Table 1. Synthesis of 2,6-*cis*-Disubstituted Tetrahydropyrans Using a One-Pot Sequential Catalysis^a



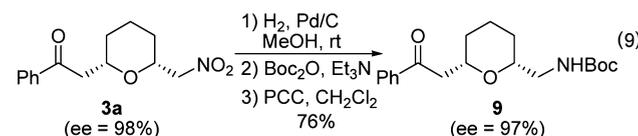
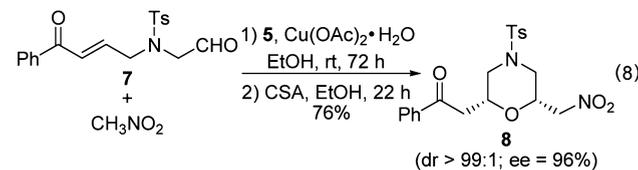
entry	R	time (h)		6/3	yield (%) ^b	dr ^c	ee (%) ^d
		t ₁	t ₂				
1	C ₆ H ₅	60	12	a	86	>99:1	98
2	4-F-C ₆ H ₄	48	6	b	89	>99:1	98
3	4-Cl-C ₆ H ₄	48	6	c	84	>99:1	99
4	4-Br-C ₆ H ₄	48	6	d	89	>99:1	98
5	4-CNC ₆ H ₄	48	6	e	90	>99:1	98
6	4-NO ₂ -C ₆ H ₄	48	6	f	94	>99:1	98
7	4-Me-C ₆ H ₄	48	6	g	94	>99:1	98
8	4-MeOC ₆ H ₄	48	6	h	96	>99:1	99
9	2-Cl-C ₆ H ₄	48	6	i	91	>99:1	98
10	3-Cl-C ₆ H ₄	48	6	j	94	>99:1	98
11	3-Br-C ₆ H ₄	48	6	k	91	>99:1	98
12	Me	60	12	l	90	>99:1	98
13	<i>t</i> -Bu	60	12	m	95	>99:1	98
14	<i>c</i> -C ₃ H ₅	48	6	n	93	>99:1	98

^aThe Henry reaction was carried out with enal **6** (0.10 mmol) and nitromethane (0.10 mL) in EtOH (0.4 mL) at room temperature with copper(II) acetate monohydrate (0.0050 mmol, 5.0 mol %) and ligand **5** (0.0050 mmol, 5.0 mol %) as the catalyst for the indicated reaction time (monitored by TLC). Once the Henry reaction was complete, CSA (0.010 mmol, 10.0 mol %) was added to reaction mixture and the reaction was continued for the indicated times (monitored by TLC) to give the desired oxa-Michael product **3**. ^bYield of isolated product **3**. ^cDetermined by ¹HNMR analysis of the crude oxa-Michael reaction product. ^dDetermined by HPLC analysis using chiral HPLC columns.

via Wan's catalytic system while the high diastereoselectivities were achieved in the second step via the CSA-catalysis.

Using a nitrogen-containing substrate **7**, the above reaction may also be used for the synthesis of the optically enriched *cis*-2,6-disubstituted morpholine derivative **8** in high diastereoselectivity (dr > 99:1) and ee value (ee = 96%) (Scheme 3, eq 8).

Scheme 3. Some Further Applications of the One-Pot Sequential Catalysis



As a potential application of this one-pot sequential Henry-oxa-Michael reaction, product **3a** was reduced by hydrogenation. It was found that both the nitro and keto groups in **3a** were reduced to give a diastereomeric mixture. The mixture was then in situ protected with Boc anhydride and oxidized with PCC to give compound **9** in 76% overall yield with complete retention of the stereochemistry of the starting material (Scheme 3, eq 9).

In summary, we have shown that the nitroaldol products of 7-oxo-hept-5-enals and nitromethane may be used as good substrates in the intramolecular oxa-Michael reaction. Through combining a highly enantioselective copper(II)-catalyzed Henry reaction between 7-oxo-hept-5-enals and nitromethane with the camphorsulfonic acid catalyzed highly diastereoselective intramolecular oxa-Michael reaction, the corresponding tetrahydrofuran derivatives were obtained in excellent yields, diastereoselectivities ($dr > 99:1$),

and enantioselectivities ($ee = 98-99\%$) in a one-pot sequential catalysis. Using an appropriate substrate, the reaction may also be used for the stereoselective synthesis of a *cis*-2,6-disubstituted morpholine.

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Supporting Information Available. General experimental procedure, characterization data of all new compounds, and copies of ^1H and ^{13}C NMR spectra and HPLC chromatograms of the oxa-Michael products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.