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Control of Five Contiguous Stereogenic Centers in an Organocatalytic Kinetic Resolution via Michael/Acetalization Sequence: Synthesis of Fully Substituted Tetrahydropyranols

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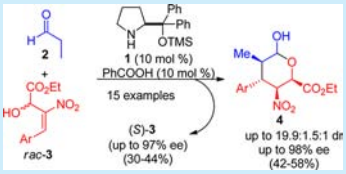
Supporting Information

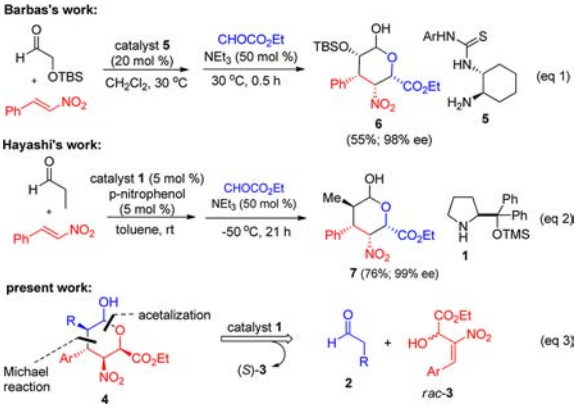
ABSTRACT: An organocatalytic kinetic resolution of racemic secondary nitroallylic alcohols via Michael/acetalization sequence to give fully substituted tetrahydropyranols is described. The process affords the products with high to excellent stereoselectivities (up to 19.9:1.5:1 dr and 98% ee). The highly enantioenriched, less reactive (*S*)-nitroallylic alcohols **3** were isolated with good to high chemical yields (30−44%). The synthetic application of the resolved substrate is shown toward the synthesis of enantioenriched (+)-(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid.



The synthesis of diverse chiral tetrahydropyran (THP) skeletons has attained considerable interest because of their abundance in natural products and bioactive molecules.[1] Various strategies have been developed for synthesizing the vital six-membered oxygenated ring.[2] Because of the diverse substituents and rich array of stereomeric THP derivatives, new methodologies are still in great demand. During the past decade, we have witnessed significant progress in asymmetric reactions mediated by small organic molecules.[3] Numerous organocatalytic methods have been developed for the synthesis of specific chiral THP molecules through amino[4] and/or hydrogen bonding catalysis.[5] A complementary desymmetrization of *meso* THPs has been published that involves a Lewis base catalysis.[6]

Previously, Barbas and co-workers reported the synthesis of chiral tetrahydropyranol **6** by using (*tert*-butyldimethylsilyloxy)-acetaldehyde, *β*-nitrostyrene, and ethyl glyoxylate under chiral primary amine derived thiourea **5** through the Michael/Henry/acetalization reaction sequence (Scheme 1, eq 1).[7a] Contemporarily, Hayashi and co-workers have successfully utilized Jørgensen−Hayashi's diphenylprolinol silyl ether catalyst **1** in a base-promoted three-component reaction to provide tetrahydropyranol **7** via a similar reaction sequence (Scheme 1, eq 2).[7b] The dense functionalities of nitroallylic alcohols **3** are readily available from the Baylis−Hillman reaction.[8] We envisioned using racemic nitroallylic alcohol **3** to achieve tetrahydropyranol **4** via a two-component organocatalytic kinetic resolution (KR) process. Kinetic resolution is a conventional approach that incorporates a chiral catalyst to prepare optically enriched materials from its racemate. Classical KR of secondary alcohols is generally performed through an acylation that involves no reactive chemistry at the stereogenic center(s). In this regard, numerous reports are available for the KR of various secondary alcohols via selective *O*-acylation.[9] The KR process that accompanies the creation of new stereogenic centers in products may provide functionalized products for further transformation. Although the process is synthetically attractive, stereodifferentiating a racemate in an organocatalytic reaction remains a frustrating challenge.[10,11] In continuation of our efforts toward asymmetric organocatalysis and KR,[12] we report an organocatalytic KR of secondary nitroallylic alcohols **3** via Michael/acetalization sequence to produce tetrahydropyranol **4** with an L-idose configuration along with the recovery of the enantioenriched, nitroallylic alcohols (*S*)-**3** (Scheme 1, eq 3). Although organocatalytic KR has emerged as a new avenue in asymmetric catalysis, to the best of our knowledge, the use of the organocatalytic KR method to afford the products with five continuous chiral centers is rare.

Scheme 1. Synthesis of Stereoisomers of Substituted Tetrahydropyranols



An initial investigation was conducted using (±)-[ethyl 2-hydroxy-3-nitro-4-phenylbut-3(*E*)-enoate] **3a** and propionaldehyde **2a** to identify the optimal reaction conditions. After scrutinizing various organocatalysts, solvents, and additives, we found that diphenylprolinol trimethylsilyl ether **1** (10 mol %) in combination with benzoic acid additive in dichloroethane

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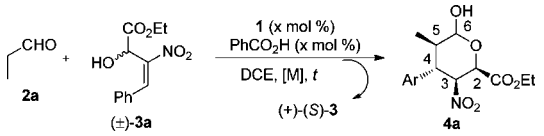
Table 1. Optimization of the Reaction Conditions[a]



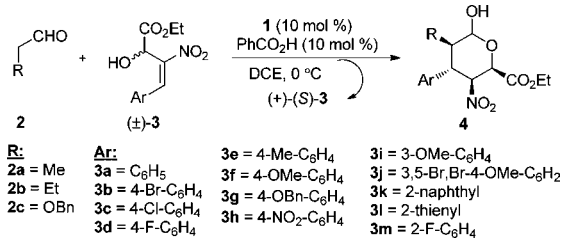
			t/ °C			4a			(S)-3a	
entry	x	[M]		t/h	conv[b]	yield (%)[c]	dr[b]	ee (%)[d]	yield (%)[c]	ee (%)[d]
1	20	0.5	23	2	54	44	7.8:1	98	41	81
2	10	0.5	23	8	55	40	7.0:1	97	46	75
3	20	1.0	0	2	56	44	7.2:1	98	44	75
4	20	0.5	0	3	54	36	8.0:1	98	46	85
5	10	1.0	0	9	55	41	6.5:1	96	45	81
6	10	0.5	0	19	54	45	5.7:1	96	40	92
7	10	1.0	-10	42	54	34	8.8:1	99	46	77
8	20	1.0	-10	13	57	42	7.6:1	98	43	90

[a]The reaction was carried out by taking **2a** (0.2 mmol) and **3a** (0.2 mmol) in the presence of catalyst **1** (*x* mol %) and benzoic acid (*x* mol %) in DCE at given temperature. [b]Determined by crude NMR using $CHPh_3$ as an internal standard. [c]Isolated yield. [d]Enantiomeric excess of the major dr (*α*-anomer) and was determined by chiral HPLC.

(DCE) at 0 °C afforded the desired product **4a** with encouraging results (Table 1, entry 5).[13] The less reactive substrate (*S*)-**3a** was recovered with 81% ee after 55% conversion. The reaction was further optimized by varying the catalyst loading (10−20 mol %) and concentration (0.5−1.0 M) at either ambient temperature or 0 °C (Table 1, entries 1−6). In general, the chemical yields and the ee of the product **4a** were found to be high to excellent, whereas the ee of the unreacted substrate (*S*)-**3a** varied slightly when the reaction was performed at 0 °C (Table 1, entries 1−6). In the best scenario, the product **4a** was obtained at 45% yield with 96% ee and 5.7:1.0 dr, leaving the nitroallylic alcohol (*S*)-**3a** at a 40% yield (92% ee) (Table 1, entry 6). Lowering the reaction temperarure to −10 °C failed to improve the stereochemical outcomes (Table 1, entries 7−8). Although the same catalyst **1** was used, an examination of the chemical structure of the product indicated that the major diastereomer **4a** ($J_{4,5}$ = 12.4 Hz, $J_{3,4}$ = 10.2 Hz) was isolated with an *L*-idose configuration which is different from the configurations of **7** that was previously reported.[7b] These results also differed from the configurations of **6** which arise in a chiral thiourea (**5**)/base catalyzed three-component reaction.[7a] Hence, the current methodology provides a complementary, alternative strategy to the synthesis of stereoisomers of fully substituted tetrahydropyranols.

The optimized conditions were applied to various secondary nitroallylic alcohols (**3b−m**) containing electron-releasing and -withdrawing groups by using propionaldehyde as a nucleophile. The substrates **3b−g** gave terahydropyranols **4b−g** in high chemical yields with enantioselectivities up to 98% ee, leaving the nitroallylic alcohols (**3b−g**) with up to 96% ee (Table 2, entries 1−6). The enantioselectivity of both product **4h** and recovered substrate **3h** dropped to 85% and 88% ee, respectively, when aryl contained the electron-withdrawing 4-nitro group (Table 2, entry 7). In addition, the reaction tolerated an aryl group having different substituents: 3-OMe (**3i**), trisubstituted phenyl (**3j**), 2-naphthyl (**3k**), and 2-thienyl (**3l**). The enantioselectivity of both products (**4i−l**) and recovered substrates (**3i−l**) were found to be high to excellent (up to 98% ee, Table 2, entries 8−11). Also, the KR process is compatible when 2-fluoro substituent substrate **3m** was used to give product **4m** with 94% ee and the recovered **3m** was obtained with 91% ee (Table 2, entry 12). Remarkably, when the nucleophile was changed to *n*-butyraldehyde **2b**, the

Table 2. Substrate Scope[a]



					4			(S)-3	
entry	R	3	t/h	conv[b]		yield (%)[c]	dr[b]	ee (%)[d]	yield (%)[c]	ee (%)[a]
1	Me	**3b**	14	65	**4b**	58	8.7:1:1.2	93	33	96
2	Me	**3c**	10	67	**4c**	54	9.2:1:1.2	91	33	94
3	Me	**3d**	13	63	**4d**	47	9.7:1	96	37	89
4	Me	**3e**	15	65	**4e**	43	6.5:1	94	34	94
5	Me	**3f**	15	64	**4f**	47	5.2:1	97	35	90
6	Me	**3g**	15	62	**4g**	48	6.2:1	98	36	89
7	Me	**3h**	11	64	**4h**	38	12.3:1:2	85	30	88
8	Me	**3i**	14	62	**4i**	44	7.7:1	97	35	84
9	Me	**3j**	10	66	**4j**	53	13.5:1:0.8	91	34	95
10	Me	**3k**	12	65	**4k**	42	9.5:1:1.3	94	35	97
11	Me	**3l**	14	68	**4l**	49	9.5:1	95	31	85
12[e]	Me	**3m**	16	62	**4m**	54	6.2:1.9:1	94	38	91
13[f]	Et	**3a**	4.5d	56	**4n**	46	19.9:1.5:1	74	44	74
14[f]	OBn	**3a**	9	64	**4o**	45	n.d.	94	36	91

[a]The reaction was carried out by taking **2** (0.2 mmol) and **3** (0.2 mmol) in the presence of catalyst **1** (10 mol %) and benzoic acid (10 mol %) in DCE (0.5 M) at 0 °C. [b]Determined by crude NMR using CH_2Br_2 or $CHPh_3$ as an internal standard. [c]Isolated yield. [d]Enantiomeric excess of the major dr (*α*-anomer) and was determined by chiral HPLC. [e]Reaction was carried out at 16 °C. Aldehyde **2** (0.4 mmol) was used. n.d.: not determined.

reactivity of the substrate **3a** and the enantioselectvity of both the product **4n** and the recovered substrate **3a** were dramatically decreased (Table 2, entry 13). However, the benzyloxy acetaldehyde **2c** reacted smoothly with substrate **3a** and furnished the product **4o** with 94% ee and substrate (*S*)-**3a** was recovered with 91% ee (Table 2, entry 14).

The C5−C6 *anti* stereochemistry in the major anomer **4b** (*α*-anomer) was assigned based on the coupling constant (J_{1-2} = 7.6 Hz). The absolute configuration of the product **4b** was found to be (2*R*,3*S*,4*S*,5*R*) by single crystal X-ray structural analysis of its lactone **8** obtained after the PCC oxidation.[14] The absolute stereochemistry of the recovered less reactive nitroallylic alcohol **3b** was found to be (*S*)-configuration based on a single crystal X-ray analysis.[15]

In a plausible reaction mechanism, the organocatalyst **1** forms the *anti* enamine **9** with aldehyde under acid catalysis. The Michael donor **9** reacts selectively to the kinetically more reactive intramolecularly hydrogen bonded (*R*)-**3** enantiomer from the *si* face as depicted in the favored transition state model **10A** (Figure 1). The resulting anion species pick up a proton from the less hindered bottom face. Hydrolysis of the resulting iminium ion regenerate the catalyst **1** and the produced intermediate **11** cyclized to give hemiacetal product **4**.

Since the products **4** and substrates **3** contain electron withdrawing ester and nitro groups, an epimerization might occur as in previous examples. Because this possibility could not be ignored, we have conducted control experiments to examine the phenomena of epimerization during and after the reaction. To check the epimerization during the reaction, we have performed the reaction in toluene by using optically enriched substrate (*R*)-**3b** (96% ee) and observed the product **4b** was

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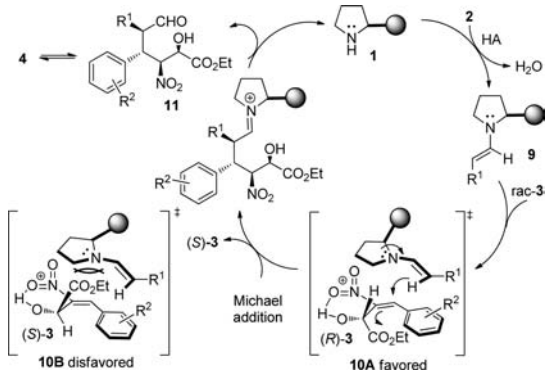
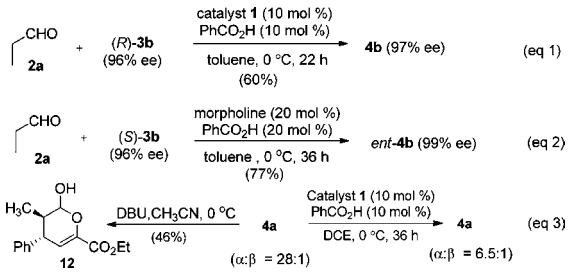


Figure 1. Proposed mechanism for the KR process.

isolated in a 97% ee (60% yield) along with unreacted substrate (*R*)-**3b** (15% yield, 96% ee). Notably, no other diastereomer was observed other than its β-anomer in this reaction, which indicates that no epimerization occurred during the reaction, either in the substrate (*R*)-**3b** or in the product **4b** (Scheme 2, eq 1). We were

Scheme 2. Examination of the Epimerization and Further Studies of the Tetrahydropyranol 4a and 4b

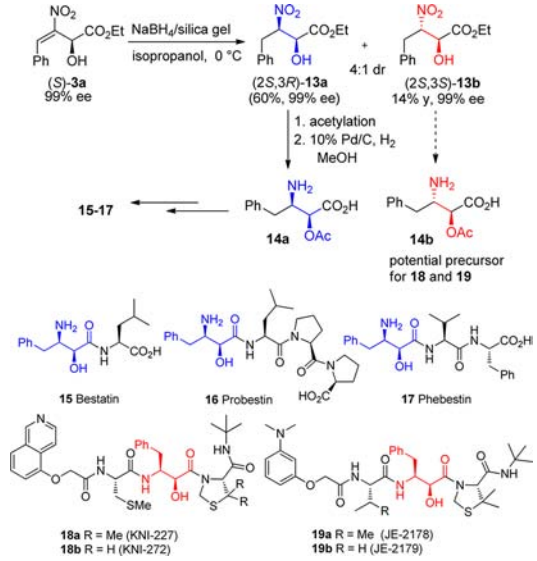


curious to study the scope of the inherited chirality of the substrate when inducing the stereocenters in product **4** in the absence of an external chiral environment. We then examined the diastereoselective synthesis by using an optically pure substrate (*S*)-**3b** (96% ee) and morpholine (20 mol %). To our delight, the chiral center present in the optically pure nitroallylic alcohol (*S*)-**3b** alone has the potential to induce the rest of the four chiral centers (Scheme 2, eq 2). The newly formed chiral centers are diastereomerically induced with the corresponding *ent*-**4b** was isolated with 77% chemical yield and 99% ee.

In order to check the extent of the epimerization in product **4a** after its formation, the isolated product **4a** was further examined. The crude ^{1}H NMR analysis reveals there was no epimerization in **4a** under the optimized conditions for 36 h (Scheme 2, eq 3). However, an equilibration between the anomers was observed under acid catalyzed optimized conditions. When product **4a** was treated with DBU, the nitrous acid was eliminated, and dihydropyranol **12** was isolated.[7b]

We have attempted for diastereoselective reduction of the recovered nitroallylic alcohols (*S*)-**3a** to β-nitro-α-hydroxy esters **13a**, which is a precursor for the synthesis of (+)-(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutyric acid (AHPA).[16] The four-carbon unit amino alcohol **14a** is a key intermediate for numerous biologically active skeletons such as bestatin,[17−19] probestin,[20] and phebestin.[21] After examining several reducing systems, we realized that $NaBH_4$/2-propanol/silica gel[22] reducing system gave the nitroaldol product **13** in 4:1 (*syn*:*anti*) selectivity, and the two separable products were isolated with 60% and 14% yields, respectively, with excellent enantioselectivities (Scheme 3). The relative *syn* stereochemistry on C3−C2 was assigned based on the coupling constant ($J_{2,3}$ = 3.9 Hz) and

Scheme 3. Synthetic Application of the Resolved Enantioenriched, Nitroallylic Alcohols (*S*)-3a and the Chemical Structures of HIV-I Protease Inhibitors



^{1}H−^{1}H COSY NMR analysis.[18] The other *anti*-selective nitro aldol product **13b** could be a potential precursor for the intermediate (2*S*,3*S*)-AHPA, which appears in several aminopeptidase and HIV-I protease inhibitors KNI-227, KNI-272 and JE-2178, and JE-2179.[23] The current methodology has the potentiality of providing the remaining two AHPA derivatives by choosing an appropriate *ent*-(**1**) catalyst.

In conclusion, we have described a unique organocatalytic KR method to synthesize fully substituted tetrahydropyranols via Michael/acetalization sequence reaction.[15,24] Treatment of simple aldehydes with various racemic secondary nitroallylic alcohols can achieve products with high to excellent levels of stereoselectivities (up to 19.9:1.5:1 dr and 98% ee) catalyzed by (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether catalyst **1**. This protocol complements previous examples for the synthesis of stereoisomeric tetrahydropyranols. The less reactive (*S*)-nitroallylic alcohols **3** were isolated with high optical purity (up to 97% ee). The study demonstrates the synthesis of 3-amino-2-hydroxy-4-phenylbutyric acids (AHPAs) which are crucial intermediates for aminopeptidase and HIV-I protease inhibitors. Further study on organocatalytic reactions is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and the characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Detailed X-ray crystallographic data for the starting nitroallylic alcohol (*S*)-**3b** [CCDC 1018847; space group: *P*21, Flack parameter: 0.009(6)] are available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. See also: Roy, S.; Chen, K.-F.; Gurubrahamam, R.; Chen, K. *J. Org. Chem.* **2014**, *79*, 8955.

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