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Cu(II)-Catalyzed Olefin Migration and Prins Cyclization: Highly Diastereoselective Synthesis of Substituted Tetrahydropyrans

Arun K. Ghosh* and Daniel R. Nicponski

Departments of Chemistry and Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907, United States

akghosh@purdue.edu

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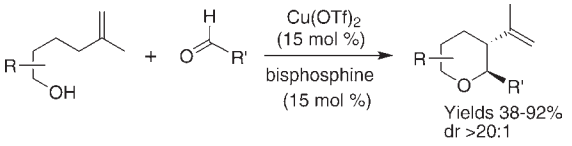
ABSTRACT



Metal−ligand complexes of $Cu(OTf)_2$ with an appropriate bisphosphine ligand have been shown to effectively catalyze the formation of substituted tetrahydropyrans via a sequential olefin migration and Prins-type cyclization. This methodology provides convenient access to a variety of functionalized tetrahydropyrans in excellent diastereoselectivities and good to excellent yields.

Substituted tetrahydropyran rings are important structural motifs in a variety of bioactive natural products.[1,2] These heterocycles are also frequently utilized in medicinal chemistry.[3] As a result, numerous new strategies for the synthesis of tetrahydropyran units have been developed and utilized in the synthesis of bioactive compounds.[4] Methods such as hetero-Diels−Alder reactions,[5a] Prins reactions,[5b] oxy-Michael reactions,[5c] Petasis−Ferrier rearrangement,[5d] and Maitland−Japp reactions[5e] have been widely used for the synthesis of highly functionalized tetrahydropyrans.[5,6] In our continuing studies to probe the active sites of various aspartic acid proteases with stereochemically defined, cyclic ether-derived ligands, we required a range of 2,3-disubstituted tetrahydropyran derivatives.[7] Hosomi and co-workers have reported access to these functionalized tetrahydropyrans by a platinum(II)-catalyzed condensation of 5-methyl-5-hexen-l-ol with aldehydes.[8] This methodology appeared attractive because of the ready availability of the starting alkenols and aldehydes. However, the reported platinum(II)-catalyzed condensation reaction required an elevated reaction temperature (100 °C).[8] In an effort to carry out this transformation under more ambient conditions, we have investigated a variety of ligand−metal complexes under mild conditions. Herein, we report a $Cu(OTf)_2$-bisphosphine catalyzed sequential olefin migration and Prins cyclization of alkenols with a variety of aldehydes to provide 2,3-disubstituted and 2,3,6-trisubstituted tetrahydropyrans in a highly diastereoselective manner.

As shown in Scheme 1, we initially surveyed the reaction of 5-methyl-5-hexen-1-ol (**1**) with benzyloxyacetaldehyde

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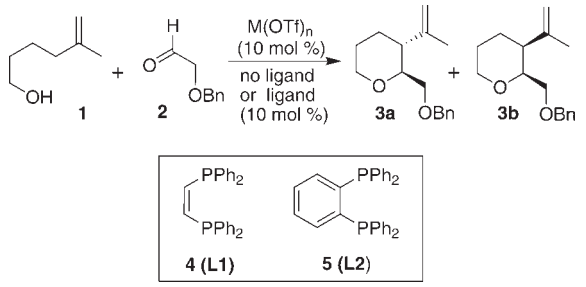
Scheme 1. Catalytic Diastereoselective Synthesis of Substituted Tetrahydropyrans



(**2**) in the presence of a number of metal−ligand complexes typically utilized in Prins-type cyclization reactions.[9] As can be seen in Table 1, various metal triflate-catalyzed reactions (10 mol %, entries 1−4, and 11) at 100 °C provided only moderate yields of diastereomeric mixtures (dr > 20:1) of products **3a** and **3b**. In addition to the triflate in entry 4, we studied counterion effects at 100 °C in PhMe for 24 h. Both BF_4^- (18% yield of **3a**) and ClO_4^- (0% yield of **3a**) showed poor results. The $Cu(OTf)_2$-catalyzed reaction in dichloroethane at 65 °C provided 26% yield of **3a** as the major product (entry 5). Interestingly, the addition of water or the attempted elimination of water ($CaCl_2$, $MgSO_4$, and 4 Å MS) resulted in the cessation of this reaction.[10] The reaction with $Cu(dppe)(OTf)_2$ in dichloroethane at 65 °C resulted in 37% yield after 24 h (entry 6). The $Cu(OTf)_2$-catalyzed reaction with ligand **L2** in CH_2Cl_2 at 25 °C provided a slight improvement in the yield (entry 8). Of particular note, the corresponding reaction with $Cu(OTf)_2$ in CH_2Cl_2 at 25 °C for 24 h provided no product formation. The reaction with $Cu(BINAP)(OTf)_2$ in CH_2Cl_2 at 25 °C afforded 80% yield of **3a** and **3b** (entry 10) The corresponding reaction with $Pt(BINAP)(OTf)_2$ required 100 °C to provide **3a** and **3b** in 55% yield (entry 11). We then examined $Cu(OTf)_2$ and a number of bisphosphine complexes (entries 12−18). Among them, metal−ligand complexes of $Cu(OTf)_2$−*cis*-1,2-bis(diphenylphosphino)ethylene (**L1**) or $Cu(OTf)_2$−1,2-bis(diphenylphosphino)benzene (**L2**) provided the best results at 40 °C (entries 17 and 18). Catalyst loading was found to be optimal at 15 mol %. Also, we found that 1.25 equiv of alkenol, 1 equiv of aldehyde in 0.1 M solution of CH_2Cl_2, provided best results. The Cu(II)-catalyzed reaction with 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl also provided good conversion and yield. However, this reaction did not exhibit any enantioselectivity with the atropisomerically chiral BINAP. We therefore decided to use achiral ligands **4** (**L1**) and **5** (**L2**) and planned to investigate the scope and utility of this catalytic system using a range of aldehydes.

Table 1. Survey of Metals and Ligands for the Formation of Substituted Tetrahydropyrans

entry	catalyst (10 mol %)	solvent	temp (°C) (time (h))	yield (%)
1	$Pd(OTf)_2$	PhMe	111 (12)	29
2	$Ni(OTf)_2 \cdot 6H_2O$	PhMe	100 (12)	24
3	$Ni(PPh_3)_2(OTf)_2$	PhMe	100 (12)	31
4	$Cu(OTf)_2$	PhMe	100 (15)	52
5	$Cu(OTf)_2$	DCE	65 (12)	26
6	$Cu(dppe)(OTf)_2$	DCE	65 (12)	37
7	Cu(**L1**)$(OTf)_2$	DCM	25 (120)	38
8	Cu(**L2**)$(OTf)_2$	DCM	25 (168)	52
9	Cu(t-BuBOX)$(OTf)_2$	DCM	25 (144)	0
10	$Cu(BINAP)(OTf)_2$	DCM	25 (12)	80
11	$Pt(BINAP)(OTf)_2$	PhMe	100 (5)	55
12	$Cu(MeCN)_2(OTf)_2$	DCM	25 (120)	58
13	$Cu(dppm)(OTf)_2$	DCM	25 (12)	15
14	$Cu(dppe)(OTf)_2$	DCM	25 (14)	43
15	$Cu(DIOP)(OTf)_2$	DCM	25 (72)	24
16	$Cu(TRIPhos)(OTf)_2$	DCM	25 (168)	33
17	Cu(**L1**)$(OTf)_2$	DCM	40 (40)	64
18	Cu(**L2**)$(OTf)_2$	DCM	40 (40)	51

Table 2. Substrate Scope and Product Structure of Substituted Tetrahydropyrans

entry	aldehyde	product[a]	ligand	yield[b]	dr[c]
1	RO	**2** R = Bn	**L1**	67 (81)	>20:1
2			**L2**	57 (60)	>20:1
3		**6** R = Ts	**L1**	67 (82)	16:1
4			**L2**	67 (88)	13:1
5	R	**8** R = H	**L1**	92 (97)	>20:1
6			**L2**	52 (78)	>20:1
7		**10** R = NO_2	**L1**	80 (92)	>20:1
8			**L2**	62 (84)	>20:1
9	**12**		**L1**	59 (95)	16:1[d]
10			**L2**	50 (90)	24:1[d]
11	S	**14**	**L1**	84 (99)	>20:1[d]
12			**L2**	82 (96)	>20:1[d]
13	Ph	**16**	**L1**	59 (66)	>20:1
14			**L2**	53 (75)	>20:1
15	Ph	**18** n = 1	**L1**	62 (76)	>20:1
16			**L2**	61 (61)	>20:1
17		**20** n = 2	**L1**	69 (78)	>20:1
18			**L2**	68 (71)	>20:1
19		**22** n = 0	**L1**	59 (95)	>20:1
20			**L2**	59 (68)	>20:1
21		**24** n = 1	**L1**	59 (61)	>20:1
22			**L2**	62 (68)	>20:1
23		**26**	**L1**	38 (39)	>20:1

[a] Conditions: **1** (1.25 equiv), aldehyde (1 equiv), $Cu(OTf)_2$ (0.15 equiv), ligand (0.15 equiv), 0.1 M in CH_2Cl_2, 40 °C, 12−40 h. [b] Values shown in parentheses are brsm. [c] Determined by NMR. [d] GC−MS analysis.

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As can be seen from Table 2, a wide range of functionality is tolerated in this reaction. In the case of reaction with benzyloxyacetaldehyde (**2**), good yield and excellent diastereoselectivity were observed (entries 1 and 2). The corresponding reaction with tosyloxyacetaldehyde (entries 3 and 4) also provided good yield; however, the observed diastereomeric ratio was 16:1 with **L1** and 13:1 with **L2**. Both benzaldehyde (**8**) and electron-poor 4-nitrobenzaldehyde (**10**) provided respective products **9** and **11** in good yield and excellent diastereoselectivity (entries 5–8). In the case of anthracene-9-carboxaldehyde (**12**), good yield and good diastereoselectivity were observed (entries 9 and 10). Thiophene-2-carboxaldehyde (**14**) is also a suitable substrate for this reaction, providing excellent yield and diastereoselectivity (entries 11 and 12). Conjugated aldehyde **16** (entries 13 and 14) or saturated arylalkyl aldehydes **18** and **20** (entries 15–18) also gave good results. Branched chain aliphatic aldehydes afforded good yields and excellent diastereoselectivity (entries 19–22). The reaction with *n*-butyraldehyde provided only moderate yield but excellent diastereoselectivity (entry 23). Attempted reaction with electron-rich *p*-anisaldehyde resulted in no appreciable cyclization product.

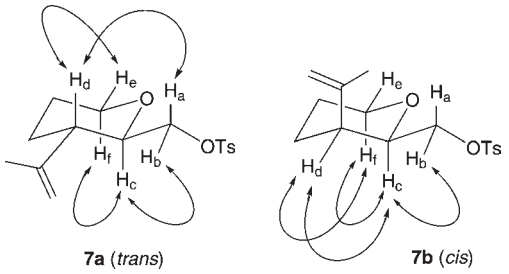

Figure 1. ^{1}H NOESY analysis of **7a** (*trans*-isomer) and **7b** (*cis*-isomer).

As shown, the *trans* isomer was the major product. Typically, only a single isomer was observed by NMR or GC–MS analysis. The reaction of 5-methyl-5-hexen-1-ol (**1**) with tosyloxyacetaldehyde (**6**) (entries 3 and 4) was found to provide chromatographically separable diastereoisomers **7a** (*trans*-major) and **7b** (*cis*-minor). The stereochemical assignment of these compounds was carried out by ^{1}H NMR NOESY experiments (Figure 1). The observed NOESY between H_a–H_d, H_b–H_c, H_c–H_f, and H_d–H_e for compound **7a** is consistent with the assigned *trans*-stereochemistry. Similarly, the observed NOESY between H_b–H_c, H_c–H_d, H_c–H_f, and H_d–H_f supported the assigned *cis*-stereochemistry for compound **7b**.

For determination of the X-ray crystal structure, the major product **3** (entry 1) was subjected to hydrogenation under a hydrogen atmosphere in the presence of 10% Pearlman's catalyst in ethanol. This resulted in the saturation of the double bond as well as the removal of the benzyl protecting group.

The resulting alcohol was treated with *p*-nitrobenzoyl chloride and triethylamine to provide nitrobenzoate derivative **28**. This was later recrystallized from hexanes and CH_2Cl_2 (−20 °C, 14 days). Subsequent single crystal X-ray crystallographic analysis (Figure 2) further supported the assignment of the *trans*-stereochemistry.[11,12]

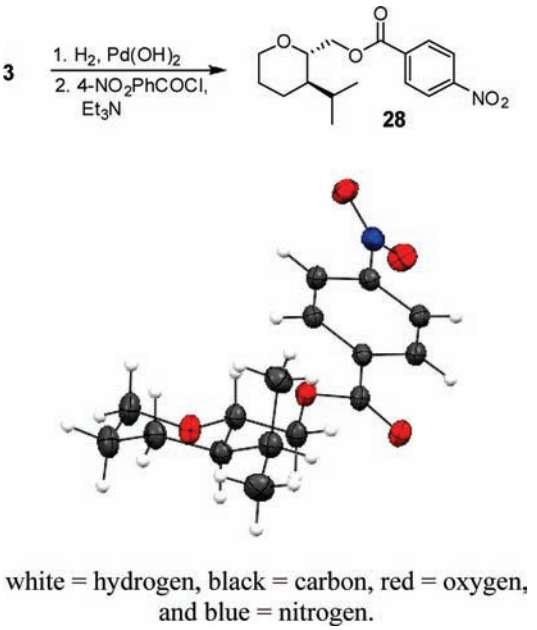

Figure 2. Synthesis and ORTEP drawing of **28**.

We have also carried out olefin migration and Prins cyclization using enantioenriched alcohol **29**, which was prepared by Corey–Bakshi–Shibata reduction[13] of the corresponding ketone. Alcohol **29** was obtained in 89% ee. As shown in Scheme 2, reaction of alcohol **29** with benzyloxyacetaldehyde **2** provided **30a** diastereoselectively (dr > 20:1). The *trans*-isomer **30a** was obtained in 89% ee which indicated that the cyclization resulted in no loss of optical activity. Rychnovski and co-workers have shown that the condensation of alcohols with aldehydes in attempted 6-(2,5)-Prins reactions undergoes partial or complete racemization via an oxonia-Cope processes.[14] This

(11) Single-crystal X-ray analysis was performed in-house. Dr. Phil Fanwick, X-Ray Crystallography Laboratory, Department of Chemistry, Purdue University, West Lafayette, IN, 47907.

(12) CCDC 830732 contains the supplementary crystallographic data for Compound **28**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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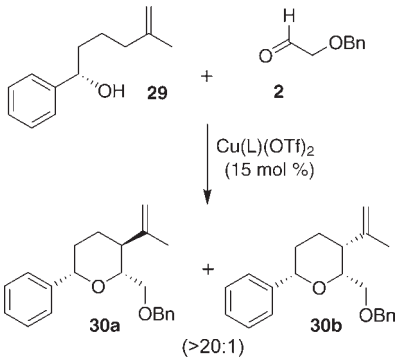
Scheme 2. Synthesis of Optically Active Tetrahydropyran



indicates that the present cyclization pathway does not involve a [3,3]-sigmatropic rearrangement.

The stereochemical outcome of the olefin migration and Prins cylization reactions which lead to *trans*-2,3-disubstituted tetrahydropyran derivatives can be rationalized based upon the Zimmerman–Traxler[15] transition-state models shown in Figure 3. The $Cu(OTf)_2$-based Lewis acid catalyzed reaction could lead to the formation of an oxycarbenium ion.[16] Subsequent olefin migration followed by cyclization may proceed through either favored transition state **32** or disfavored transition state **33**. The proton abstraction beta to the carbocation would give rise to *trans*-2,3- and *cis*-2,3-tetrahydropyrans **34** and **35**, respectively.[17,18] The transition state **32** is favored due to the lack of developing pseudo-1,3-diaxial interactions, as is seen in **33**. Consistent with the primary alkenol cyclizations, the secondary alkenol cyclization (**29**) also provided a 2,3,6-*trans*,*trans*-tetrahydropyran (**30a**) as the only detectable isomer.

In summary, we have developed a mild $Cu(OTf)_2$-bisphosphine-catalyzed reaction for the synthesis of substituted tetrahydropyran derivatives using 5-methyl-5-hexen-1-ol and an appropriate aldehyde. The reaction proceeded with an olefin migration followed by a Prins cyclization to provide a range of tetrahydropyran derivatives in

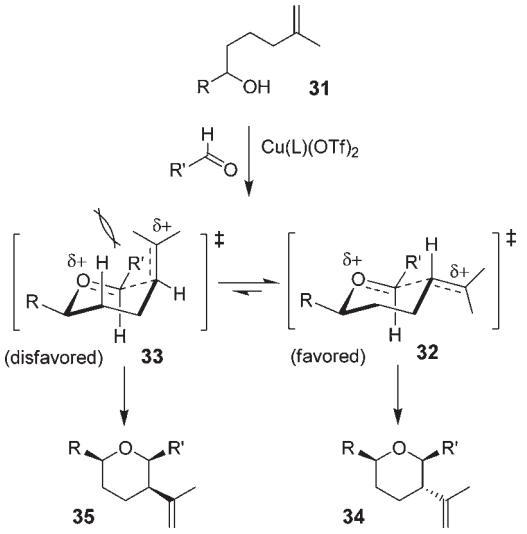


Figure 3. Stereochemical model for *trans*-selectivity.

good yields and excellent *trans*-diastereoselectivity. The combination of $Cu(OTf)_2$ and bisphophine ligands **4** and **5** has not been previously used in the synthesis of such substituted tetrahydropyran derivatives. Further application of these substituted tetrahydropyran derivatives are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.