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

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Abstract

The metal-ligand complexes of $\text{Cu}(\text{OTf})_2$ 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-1-ol with aldehydes.⁸ This methodology appeared attractive due to 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 $\text{Cu}(\text{OTf})_2$ -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 benzyloxy acetaldehyde (**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, 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

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

of **3a**) and ClO_4^- (0% yield of **3a**) showed poor results. The $\text{Cu}(\text{OTf})_2$ -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 $\text{Cu}(\text{dppe})(\text{OTf})_2$ in dichloroethane at 65 °C resulted in 37% yield after 24 h (entry 6). The $\text{Cu}(\text{OTf})_2$ -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 $\text{Cu}(\text{OTf})_2$ in CH_2Cl_2 at 25 °C for 24 h provided no product formation. The reaction with $\text{Cu}(\text{BINAP})(\text{OTf})_2$ in CH_2Cl_2 at 25 °C afforded 80% yield of **3a** and **3b** (entry 10). The corresponding reaction with $\text{Pt}(\text{BINAP})(\text{OTf})_2$ required 100 °C to provide **3a** and **3b** in 55% yield (entry 11). We then examined $\text{Cu}(\text{OTf})_2$ and a number of bisphosphine complexes (entries 12–18). Among them, metal-ligand complexes of $\text{Cu}(\text{OTf})_2$ -with *cis*-1,2-bis(diphenylphosphino)ethylene (**L1**) or $\text{Cu}(\text{OTf})_2$ -1,2-bis(biphenylphosphino)benzene (**L2**) provided the best results at 40 °C (entries 17, 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 0.1M solution of CH_2Cl_2 , provided best results. The $\text{Cu}(\text{II})$ -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.

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, 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.

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 ^1H -NMR NOESY experiments (Figure 1). The observed NOESY between $\text{H}_a\text{--H}_d$, $\text{H}_b\text{--H}_c$, $\text{H}_c\text{--H}_f$, and $\text{H}_d\text{--H}_e$ for compound **7a** is consistent with the assigned *trans*-stereochemistry. Similarly, the observed NOESY between $\text{H}_b\text{--H}_c$, $\text{H}_c\text{--H}_d$, $\text{H}_c\text{--H}_f$, and $\text{H}_d\text{--H}_f$ 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 CH₂Cl₂ (−20 °C, 14 days). Subsequent single crystal X-ray crystallographic analysis (Figure 2) further supported the assignment of the *trans*-stereochemistry.^{11,12}

We have also carried out olefin migration and Prins cyclization using enantioenriched alcohol **29**, which was prepared by Corey-Bakshi-Shibata reduction¹³ 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 indicates that the present cyclization pathway does not involve a [3,3]-sigmatropic rearrangement.

The stereochemical outcome of the olefin migration and Prins cyclization reactions which lead to *trans*-2,3-disubstituted tetrahydropyran derivatives can be rationalized based upon the Zimmerman-Traxler¹⁵ 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 good yields and excellent *trans*-diastereoselectivity. The combination of Cu(OTf)₂ and bisphosphine 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

white = hydrogen, black = carbon, red = oxygen,
and blue = nitrogen.

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

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

Scheme 1.
Catalytic diastereoselective synthesis of substituted tetrahydropyrans.

Scheme 2.
Synthesis of optically active tetrahydropyran.

Table 1

Survey of metals and ligands for the formation of substituted tetrahydropyrans.

entry	catalyst (10 mol %)	solvent	temp / time (°C) / (h)	yield (%)
1	Pd(OTf) ₂	PhMe	111 (12)	29
2	Ni(OTf) ₂ •6H ₂ O	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(<i>t</i> -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			L1	67 (81)	>20:1
2	2 R = Bn	3 R = Bn	L2	57 (60)	>20:1
3	6 R = Ts	7 R = Ts	L1	67 (82)	16:1
4			L2	67 (88)	13:1
5	8 R = H		L1	92 (97)	>20:1
6	10 R = NO ₂	9 R = H	L2	52 (78)	>20:1
7		11 R = NO ₂	L1	80 (92)	>20:1
8			L2	62 (84)	>20:1
9		12	L1	59 (95)	16:1 ^[d]
10		13	L2	50 (90)	24:1 ^[d]
11		14	L1	84 (99)	>20:1 ^[d]
12		15	L2	82 (96)	>20:1 ^[d]
13		16	L1	59 (66)	>20:1
14		17	L2	53 (75)	>20:1
15		18 n = 1	L1	62 (76)	>20:1
16	20 n = 2	19 n = 1	L2	61 (61)	>20:1
17		21 n = 2	L1	69 (78)	>20:1
18			L2	68 (71)	>20:1
19		22 n = 0	L1	59 (95)	>20:1
20		23 n = 0	L2	59 (68)	>20:1
21	24 n = 1	24 n = 1	L1	59 (61)	>20:1
22		25 n = 1	L2	62 (68)	>20:1
23		26	L1	38 (39)	>20:1
		27			

[a] Conditions: **1** (1.25 equiv), aldehyde (1 equiv), Cu(OTf)₂ (0.15 equiv), ligand (0.15 equiv), 0.1 M in CH₂Cl₂, 40 °C, 12–40 h.

[b] Values shown in parentheses are brsm.

[c] Determined by NMR.

[d] GC-MS analysis.