Diastereoselective Synthesis of Substituted Tetrahydropyrans by Copper(II)–Bisphosphine-Catalyzed Olefin Migration and Prins Cyclization

Arun K. Ghosh,* Jorden Kass, Daniel R. Nicponski, Chad Keyes

Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, IN 47907, USA
Fax +1(765)4961612; E-mail: akghosh@purdue.edu

Received: 06.07.2012; Accepted after revision: 30.09.2012

Abstract: We developed a copper(II) triflate–bisphosphine complex catalyzed olefin migration and Prins cyclization which lead to the synthesis of substituted tetrahydropyran derivatives. The protocol is convenient and a variety of substituted tetrahydropyrans were obtained in good to excellent yields with excellent diastereoselectivities.

Key words: tetrahydropyrans, olefin migration, Prins cyclization, diastereoselective, metal-ligand catalyzed

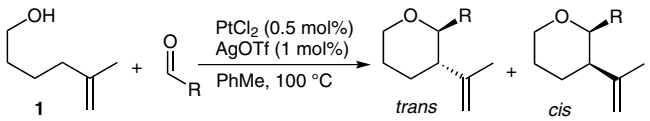
Substituted tetrahydropyran structural motifs are ubiquitous in numerous bioactive natural products.[1] The importance of this heterocycle is also well recognized in medicinal chemistry.[2] Compounds containing this ring system are widely utilized as pharmaceutical agents and molecular probes.[3] Recently, in the context of our nonpeptide ligand design and synthesis work, we have demonstrated that the tetrahydropyran ring oxygen can be used to mimic the carbonyl oxygen of a peptide bond.[4] Over the years, a lot of effort has been devoted to the synthesis of stereochemically defined and substituted tetrahydropyran derivatives.[5] Among these, hetero-Diels–Alder reactions,[6] Prins cyclizations,[7] oxy-Michael reactions,[8] Petasis–Ferrier rearrangements,[9] and Maitland–Japp reactions[10] are widely used for the synthesis of functionalized tetrahydropyrans containing multiple stereocenters. We recently reported a highly diastereoselective synthesis of di- and trisubstituted tetrahydropyrans via a tandem olefin migration and Prins cyclization process.[11] For example, the reaction of 5-methylhex-5-en-1-ol with a variety of aliphatic, electron-rich, and electron-poor aromatic aldehydes proceeded efficiently in the presence of a catalytic amount of copper(II) triflate–bisphosphine complex. This protocol is an improvement over previously reported platinum(II) triflate catalyzed cyclizations[12] in both lowering reaction temperature and broadening substrate scope.

In an earlier paper, Hosomi et al. utilized a combination of platinum(II) chloride (0.5 mol%) and silver(I) triflate (1 mol%) catalyst system at 100 °C with 5-methylhex-5-en-1-ol (**1**) and a number of aldehydes to affect cyclization resulting in 2,3-disubstituted tetrahydropyrans.[12] As shown in Table 1, reaction with benzaldehyde (**2**) gave *trans* product *trans*-**3** in 77% yield along with the *cis*-diastereomer *cis*-**3** and other unidentified products (entry 1).

SYNTHESIS 2012, 44, 3579–3589
Advanced online publication: 06.11.2012
DOI: 10.1055/s-0032-1317495; Art ID: SS-2012-Z0569-FA

Electron-poor aromatic aldehydes 4-fluorobenzaldehyde (**4**), 4-nitrobenzaldehyde (**6**), and 4-cyanobenzaldehyde (**8**) also resulted in good yields (75–85%) of the *trans* products *trans*-**5**, *trans*-**7**, and *trans*-**9**, respectively, along with some (7–17%) *cis* product (entries 2–4). However, reaction with electron-rich *p*-anisaldehyde (**10**) gave a complex mixture with <37% yield of the desired *trans* product *trans*-**11** (entry 5). Reaction with aliphatic aldehydes, octanal (**12**) and cyclohexanecarbaldehyde (**14**) gave slightly lower yields 65% and 59% in comparison to electron-poor aromatic aldehydes, but better diastereoselectivity with no detectable *cis* isomers (entries 6 and 7).

Table 1 Earlier Work by Hosomi et al.[12]



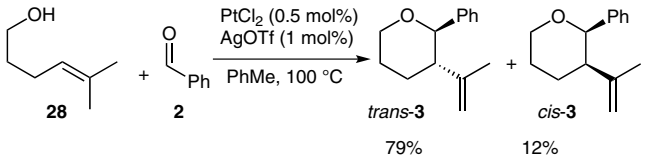
Entry	Aldehyde	R	Product	Yield (%)	dr
1	**2**	Ph	**3**	77	9:1
2	**4**	4-FC_6H_4	**5**	75	4.4:1
3	**6**	4-$O_2NC_6H_4$	**7**	77	11:1
4	**8**	4-NCC_6H_4	**9**	85	11:1
5	**10**	4-$MeOC_6H_4$	**11**	<37	–[a]
6	**12**	$(CH_2)_6Me$	**13**	65	>20:1
7	**14**	Cy	**15**	59	>20:1

[a] Not determined.

As shown in Table 2, synthesis of trisubstituted tetrahydropyrans was also explored with the platinum(II) chloride/silver(I) triflate catalyst system.[12] Reactions with 1-, 2-, and 3-methylalkenols **16**, **20**, and **24** gave 6-, 5-, and 4-methyltetrahydropyrans, respectively. Use of 6-methylhept-6-en-2-ol (**16**) under the standard reaction conditions gave **17**–**19** in excellent yields (>84%) and diastereoselectivities (>15:1 dr) (entries 1–3). Reactions with 2,5-dimethylhex-5-en-1-ol (**20**) under standard conditions lead to Prins cyclization giving **21**–**23** in excellent yields (>80%), but result in lower diastereoselectivities (from 99:1 to 4:1 dr, entries 4–6). However, reactions with 3,5-dimethylhex-5-en-1-ol (**24**) resulted in substituted tetrahydropyrans **25**–**27** with excellent diastereoselectivity

(19:1), but lower yields than the unsubstituted analogues (entries 7–9).

In an effort to probe the reaction mechanism, reactions of 5-methylhex-4-en-1-ol (**28**) and benzaldehyde (**2**) were used (Scheme 1). This reaction afforded major product *trans*-**3** in high yield (79%) and a small amount (12%) of the *cis*-**3** product. This result has provided some evidence that the reaction with either substrate likely involved similar intermediates or transition states.



Scheme 1 Earlier work by Hosomi et al.[12]

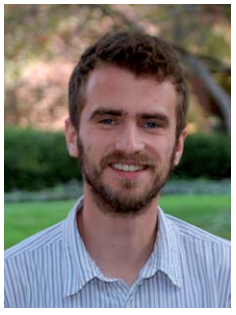
As shown in Table 3, similar reactions were reported previously by Loh et al. wherein 6-methylhept-5-en-2-ol (**29**)

Biographical Sketches

Arun K. Ghosh was born and raised in Calcutta, India. He received his B.S. in chemistry (1979) and M.S. in chemistry (1981) from the University of Calcutta and Indian Institute of Technology, Kanpur respectively. He received his Ph.D. in organic chemistry in 1985 at the University of Pittsburgh. He then pursued postdoctoral research with Professor E. J. Corey at Harvard University (1985–1988). He was a research fellow at Merck Research Laboratories and in 1994, he joined University of Illinois, Chicago as Assistant Professor, eventually becoming Professor of chemistry in 1998. In 2005, he moved to Purdue University, with a joint appointment in the Department of Chemistry and the Department of Medicinal Chemistry and Molecular Pharmacology. He became the Ian P. Rothwell Distinguished Professor in 2009. His research interests include diverse areas of organic, bioorganic, and medicinal chemistry with particular emphasis on organic synthesis and protein-structure-based drug design.

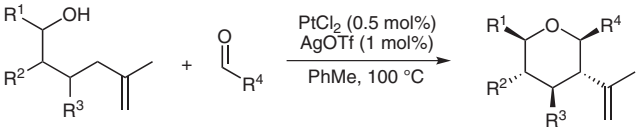
Jorden Kass was born in Toledo, Ohio (USA) in 1984. He received his B.S. in chemistry in 2006 from Eastern Kentucky University. He taught at Lehman College (spring 2007). In fall 2007, he began his graduate studies at Purdue University. Subsequently, he joined Professor Ghosh's research group for his thesis work. He was awarded the Fredrick N. Andrews Fellowship from 2007–2009 followed by a Purdue Research Foundation Fellowship at Purdue University (2009–2011). His thesis work has focused on the development of asymmetric multicomponent reactions and total synthesis. He plans to defend his thesis work in fall 2012.

Daniel R. Nicponski was born in 1984 in Medina, New York (USA). He received his B.S. in chemistry in 2006 from the University at Buffalo in Buffalo, New York. He is presently studying for his Ph.D. degree in organic chemistry at Purdue University. His research work has focused on the development of novel, asymmetric carbon–carbon bond forming reactions, and on the synthesis of reaction-tailored, phosphine-based ligands.



Chad Keyes was born in West Lafayette, Indiana (USA). He received his BS in chemistry from Ball State University. Chad was an intern during the summer of 2008 at Dow Agrosciences. Upon completion of his B.S., he moved to Purdue University in the spring of 2010 to further pursue his graduate studies in organic chemistry with Professor Arun Ghosh. He was awarded the Ross Fellowship in 2008 at Purdue University. Currently, his thesis work is focused on asymmetric catalysis and synthesis of natural products.

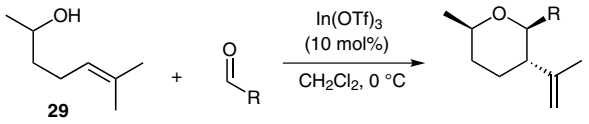
Table 2 Earlier Work by Hosomi et al. with Substituted Alkenols[12]



Entry	Alkenol	R^1	R^2	R^3	Aldehyde	R^4	Product	Yield (%)	dr
1	**16**	Me	H	H	**2**	Ph	**17**	85	19:1
2	**16**	Me	H	H	**8**	4-NCC_6H_4	**18**	90	16:1
3	**16**	Me	H	H	**12**	$(CH_2)_6Me$	**19**	84	24:1
4	**20**	H	Me	H	**2**	Ph	**21**	82	4:1
5	**20**	H	Me	H	**8**	4-NCC_6H_4	**22**	84	20:1
6	**20**	H	Me	H	**12**	$(CH_2)_6Me$	**23**	80	4:1
7	**24**	H	H	Me	**2**	Ph	**25**	56	20:1
8	**24**	H	H	Me	**8**	4-NCC_6H_4	**26**	68	20:1
9	**24**	H	H	Me	**12**	$(CH_2)_6Me$	**27**	65	19:1

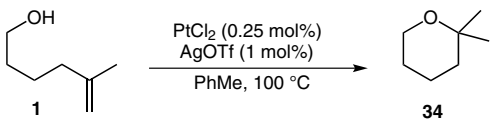
and an appropriate aldehyde in the presence of indium(III) triflate afforded substituted tetrahydropyrans.[13] It was proposed that the reaction proceeded through a (3,5) oxonium-ene-type cyclization. However, there is evidence that the reaction proceeds in a stepwise manner via an intermediate carbocation.[14]

Table 3 Earlier Work by Loh et al.[13]



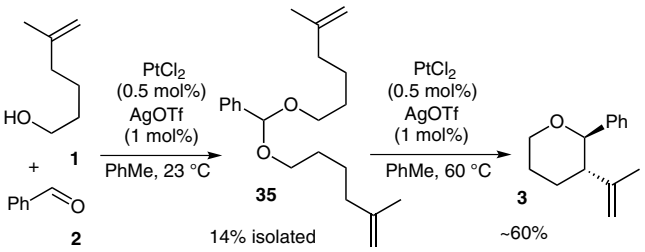
Entry	Aldehyde	R	Product	Yield (%)	dr
1	**2**	Ph	**17**	77	12:1
2	**8**	4-NCC_6H_4	**18**	86	13:1
3	**30**	(*E*)-CH=CHPh	**31**	89	9:1
4	**32**	$(CH_2)_7Me$	**33**	87	20:1

Further studies on the olefin isomerization from **1** and **28** without the presence of an aldehyde were carried out. As shown in Scheme 2, the reaction of 5-methylhex-5-en-1-ol (**1**) in the presence of platinum(II) chloride/silver(I) triflate catalytic system provided a cyclized product 2,2-dimethyltetrahydro-2*H*-pyran (**34**). It was found that **34** was often a byproduct of the reaction, lowering the yield of the desired tetrahydropyran. In fact, this reaction was previously reported as a synthetic method for the synthesis of tetrahydropyrans and tetrahydrofurans.[15]



Scheme 2 Side product found by Hosomi et al.[12]

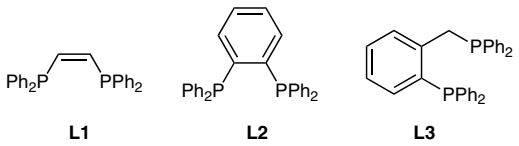
As shown in Scheme 3, reaction of 5-methylhex-5-en-1-ol (**1**) with benzaldehyde (**2**) utilizing the same platinum(II) chloride and silver(I) triflate catalyst at room temperature afforded acetal **35** exclusively albeit in low yield (14%). It was found that reaction of this acetal **35** under the typical reaction conditions with an elevated temperature gave the expected cyclized product **3**.



Scheme 3 Reaction involving an acetal[12]

While this reaction did proceed well for electron-poor aromatic or aliphatic aldehydes, improvement was needed both in reaction temperature and substrate scope. Also, platinum(II) was implicated in the olefin migration process. In light of this precedence, we planned to explore this transformation with relatively inexpensive metal–ligand complexes. Towards this objective, we examined a variety of Lewis acids and Lewis acid–ligand complexes to catalyze these reactions. For initial studies, we utilized 5-methylhex-5-en-1-ol (**1**) with benzyloxyacetaldehyde (**47**) and bisphosphine ligands shown in Figure 1. First, we examined various metal triflates typically used for Prins-type cyclizations[16] at 100 °C. This led to the identification of copper(II) triflate as the best ligand-free Lewis acid. However, copper(II) triflate by itself turned out to be

unsatisfactory at lower temperatures. Subsequently, we examined copper(II) triflate–bisphosphine complex catalyzed reactions and found that 1,2-bis(diphenylphosphino)ethylene (**L1**) and 1,2-bis(diphenylphosphino)benzene (**L2**) were effective ligands at 40 °C.[11a] Further exploration led to the development of 1-(diphenylphosphino)-2-[(diphenylphosphino)methyl]benzene (**L3**) which allowed the reaction to proceed at room temperature.[11b] Reactions with benzaldehyde (**2**) and electron-poor aromatic aldehydes gave good yields and excellent diastereoselectivity with ligands **L1** and **L2**, however electron-rich aromatic aldehydes resulted in much lower yields. This prompted us to explore the development of the phosphine ligand **L3** with a varied bite angle that also possesses a σ-donor ability through an electron-neutral triarylphosphine.[17]

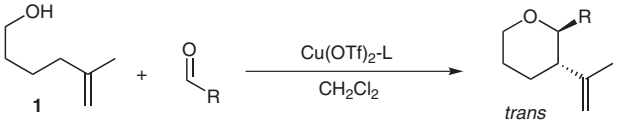


L1 L2 L3

Figure 1 Ligands found to be effective with copper(II) triflate

As shown in Table 4, the use of benzaldehyde (**2**) and 5-methylhex-5-en-1-ol (**1**) provided an excellent yield of *trans*-tetrahydropyran **3** (92% with **L1**) and high diastereoselectivity. While the copper(II) triflate–**L3**-catalyzed reaction with electron-poor 4-nitrobenzaldehyde (**6**) showed similar results as those with ligand **L2**, the reaction yield was significantly better with ligand **L1** (entries 3–5). As can be seen, the reaction of **1** with electron-rich *p*-anisaldehyde (**10**) in the presence of copper(II) triflate–**L3** complex proceeded at 23 °C to provide **11** in 69% yield with excellent diastereoselectivity (dr >20:1); the corresponding reactions with ligands **L1** and **L2** were less satisfactory and were very slow at room temperature. These reactions were all carried out at 40 °C for two hours (entries 6–8). Reaction of electron-rich *o*-anisaldehyde (**36**) with copper(II) triflate–**L3** complex provided tetrahydropyran **37** in 34% yield at 23 °C for 24 hours. The corresponding reaction with **L1** and **L2** provided lower yields of **37** (entries 9–11). Reaction of piperonal (**38**) using copper(II) triflate–**L3** complex provided tetrahydropyran **39** in 46% yield and the corresponding reaction using **L1** or **L2** ligands afforded **39** in lower yields (entries 12–14). The copper(II) triflate–**L3** catalyzed reaction with *trans*-cinnamaldehyde (**30**) proceeded with improved yield and excellent diastereoselectivitity, providing tetrahydropyran **40** in 74% yield and dr >20:1. In the case of anthracene-9-carbaldehyde (**41**), good yield and good diastereoselectivity were observed with **L1** and **L2**. Thiophene-2-carbaldehyde (**43**) is also a suitable substrate for this reaction, providing excellent yields and diastereoselectivities (entries 20, 21). The reaction with isovaleraldehyde (**45**) utilizing **L3** also provided improved yields over **L1** and **L2** with comparable diastereoselectivity (entries 22–24). Reactions of benzyloxyacetaldehyde (**47**) with **L1** and **L2** gave pyran **48** with good yield and excellent diastereoselectivity (>20:1). Similarly, while tosyloxyacetaldehyde **49** also afforded good yield of **50**, the diastereomeric ratio was reduced with **L1** (dr 16:1) and **L2** (dr 13:1, entries 25–28).

Table 4 Copper(II) Triflate–**L1**–**L3** Catalyzed Reactions with Aldehydes

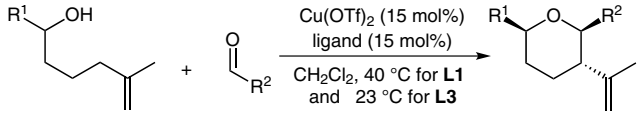


Entry	Aldehyde	R	Product	Ligand[a]	Yield (%)	dr
1	**2**	Ph	**3**	**L1**	92	>20:1
2				**L2**	52	>20:1
3	**6**	4-$O_2NC_6H_4$	**7**	**L1**	80	>20:1
4				**L2**	62	>20:1
5				**L3**	63	11:1
6	**10**	4-$MeOC_6H_4$	**11**	**L1**	42	>20:1
7				**L2**	20	>20:1
8				**L3**	69	>20:1
9	**36**	2-$MeOC_6H_4$	**37**	**L1**	22	>20:1
10				**L2**	27	>20:1
11				**L3**	34	>20:1
12	**38**	3,4-$(OCH_2O)C_6H_3$	**39**	**L1**	36	>20:1
13				**L2**	29	>20:1
14				**L3**	46	>20:1
15	**30**	(*E*)-CH=CHPh	**40**	**L1**	59	>20:1
16				**L2**	53	>20:1
17				**L3**	74	>20:1
18	**41**	9-anthryl	**42**	**L1**	59	16:1
19				**L2**	50	24:1
20	**43**	2-thienyl	**44**	**L1**	84	>20:1
21				**L2**	82	>20:1
22	**45**	*i*-Bu	**46**	**L1**	59	>20:1
23				**L2**	62	>20:1
24				**L3**	70	16:1
25	**47**	CH_2OBn	**48**	**L1**	67	>20:1
26				**L2**	57	>20:1
27	**49**	CH_2OTs	**50**	**L1**	67	16:1
28				**L2**	67	13:1

[a] Reaction temperature: 40 °C for **L1** and **L2**, 23 °C for **L3**.

We then examined reactions with 1-substituted 5-methylhex-5-en-1-ols. As shown in Table 5, substituted alkenols provided the expected 2,3,6-trisubstituted tetrahydropyrans, however product yields were lower. Reactions with *trans*-cinnamaldehyde (**30**) utilizing either copper(II) triflate–**L1** or copper(II) triflate–**L3** resulted in good yields and excellent diastereoselectivity. Reaction of methyl-substituted alkenol **16** with *trans*-cinnamaldehyde (**30**) catalyzed by copper(II) triflate–**L1** led to the desired tetrahydropyran **31** in 64% yield and excellent diastereose-

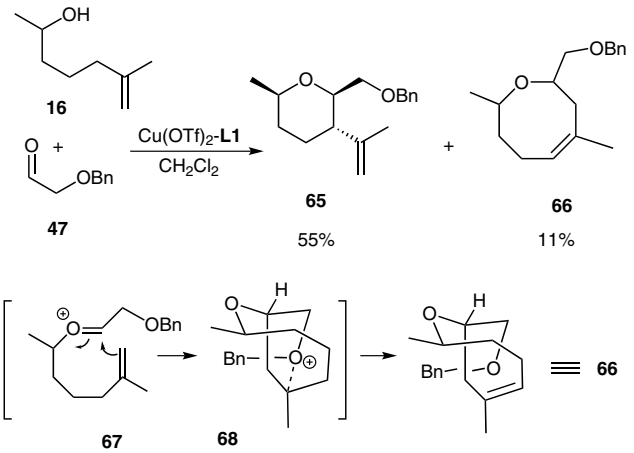
Table 5 Reactions with Substituted Alkenols



Entry	Alkenol	R^1	Aldehyde	R^2	Ligand	Product	Yield (%)	dr
1	**16**	Me	**30**	(*E*)-CH=CHPh	**L1**	**31**	64	19:1
2	**51**	*i*-Pr	**30**	(*E*)-CH=CHPh	**L3**	**52**	56	>20:1
3	**53**	*t*-Bu	**30**	(*E*)-CH=CHPh	**L1**	**54**	28	13:1
4	**53**	*t*-Bu	**30**	(*E*)-CH=CHPh	**L3**	**54**	48	>20:1
5	**55**	allyl	**30**	(*E*)-CH=CHPh	**L3**	**56**	34	18:1
6	**57**	Bn	**30**	(*E*)-CH=CHPh	**L3**	**58**	34	>20:1
7	**59**	Ph	**30**	(*E*)-CH=CHPh	**L3**	**60**	48	>20:1
8	**16**	Me	**10**	4-$MeOC_6H_4$	**L3**	**61**	56	>20:1
9	**51**	*i*-Pr	**10**	4-$MeOC_6H_4$	**L3**	**62**	59	>20:1
10	**55**	allyl	**10**	4-$MeOC_6H_4$	**L3**	**63**	46	>20:1
11	**57**	Bn	**10**	4-$MeOC_6H_4$	**L3**	**64**	61	>20:1

lectivity [19:1 dr (^{1}H NMR), entry 1]. The use of the bulkier isopropyl-substituted alkenol **51** catalyzed by copper(II) triflate–**L3** gave the desired trisubstituted tetrahydropyran **52** with good yield and excellent diastereoselectivity (entry 2). The copper(II) triflate–**L3** catalyzed reaction between *tert*-butyl-substituted alkenol **53** with *trans*-cinnamaldehyde (**30**) was a significant improvement over the similar copper(II) triflate–**L1** catalyzed system (48% vs 28% yield, entries 3 and 4). Phenyl-substituted alkenol **59** also reacted with *trans*-cinnamaldehyde (**30**) to give the tetrahydropyran **60** in moderate yield (entry 7). While both allyl **55** and benzyl **57** substitutions were tolerated, their reactions with *trans*-cinnamaldehyde (**30**) proceeded with slightly lower yields (entries 5, 6). Reaction of the methyl-substituted alkenol **16** with *p*-anisaldehyde (**10**) maintained the high yield and diastereoselectivity previously observed with an unsubstituted alkenol. Use of isopropyl-substituted alkenol **51** with *p*-anisaldehyde (**10**) catalyzed by copper(II) triflate–**L3** led to the desired product **62** in 59% yield with excellent diastereoselectivity (entry 9). Unlike with *trans*-cinnamaldehyde, reactions with allyl- **55** and benzyl-substituted alkenols **57** with *p*-anisaldehyde (**10**) maintained good yield and diastereoselectivity (entries 10, 11).

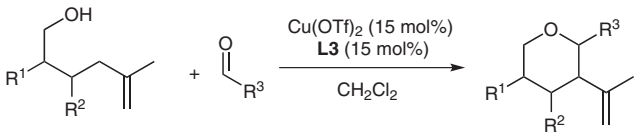
Reaction of methyl-substituted alkenol **16** with benzyloxyacetaldehyde (**47**) utilizing reaction conditions with either **L1** or **L3** ligand and copper(II) triflate led to a mixture of expected tetrahydropyran **65** along with a small amount of the eight-member cyclic ether **66** (3,4,7,8-tetrahydro-2*H*-oxocin) (Scheme 4). Presumably, this was formed by a direct nucleophilic attack by the olefin onto the oxocarbenium ion **67** leading to the oxygen-stabilized tertiary carbocation **68**, followed by elimination. The formation of eight-membered ring was observed as a minor product for reactions with benzyloxyacetaldehyde (**47**) or tosyloxyacetaldehyde (**49**) with all alkenol substrates shown in Table 5. Further studies on this interesting ring formation are currently being explored.



Scheme 4 Formation of an oxocin byproduct

As shown in Table 6, reactions with 2,5-dimethylhex-5-en-1-ol (**20**) and 3,5-dimethylhex-5-en-1-ol (**24**) with our standard conditions using copper(II) triflate and **L3** resulted in lower yields. The reaction of methyl alkenol **20** and *p*-anisaldehyde (**10**) provided the desired trisubstituted tetrahydropyran **69** in 49% yield, but with lower diastereoselectivity (methyl diastereomer 6:1). Similar results were obtained by Hosomi et al.[12] Similar results were also

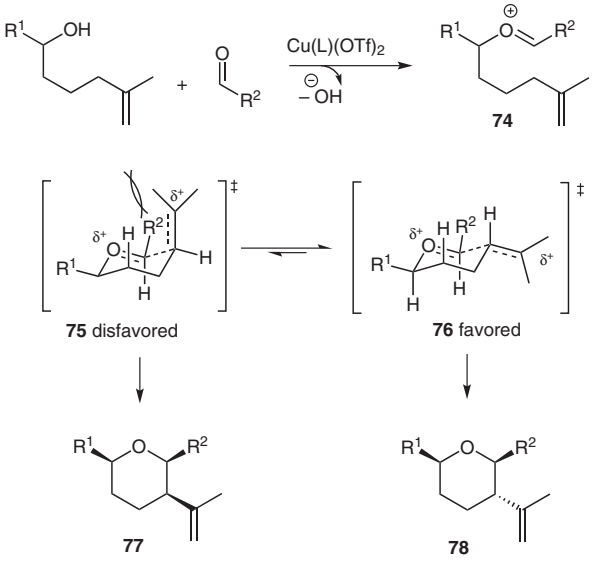
Table 6 Reactions with Dimethylhex-5-en-1-ols



Entry	Alkenol	R^1	R^2	Aldehyde	R^3	Product	Yield (%)	dr
1	**20**	Me	H	**10**	4-$MeOC_6H_4$	**69**	49	6:1
2	**20**	Me	H	**30**	(*E*)-CH=CHPh	**70**	43	4:1
3	**20**	Me	H	**6**	4-$O_2NC_6H_4$	**71**	29	6:1
4	**24**	H	Me	**10**	4-$MeOC_6H_4$	**72**	12	20:1
5	**24**	H	Me	**30**	(*E*)-CH=CHPh	**73**	13	20:1

observed when *trans*-cinnamaldehyde (**30**) was used to give tetrahydropyran **70**. Again, there was a drop in yield when methyl alkenol **20** was reacted with 4-nitrobenzaldehyde (**6**) as previously shown in Table 4. When 3,5-dimethylhex-5-en-1-ol (**24**) was used as the substrate, the drop in reaction yield was even more dramatic. Reaction with either *p*-anisaldehyde (**10**) or *trans*-cinnamaldehyde (**30**) resulted in formation of tetrahydropyrans **72** and **73**, respectively, in less than 20% yield. In all of these reactions, along with formation of the desired tetrahydropyrans, cyclization of the alkenol also resulted in substituted 2,2-dimethyltetrahydropyran as shown in Scheme 2. Unreacted aldehyde was also recovered. Reaction yield based on recovered aldehyde (limiting reagent) is typically >85%.

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–Traxler[18] transition-state models (Scheme 5). The copper(II) triflate based Lewis acid catalyzed reaction could lead to the formation of an oxocarbenium ion **74**.[19] Subsequent olefin migration followed by cyclization may proceed through either favored transition state **76** or disfavored transition state **75**. Proton abstraction β to the carbocation would give rise to *trans*-2,3- and *cis*-2,3-tetrahydropyrans **78** and **77**, respectively.[20,21] The transition state **76** is favored due to the lack of developing pseudo-1,3-diaxial interactions, as is seen in **75**. Consistent with the primary alkenol cyclizations, the secondary alkenol cyclization also provided a 2,3,6-*trans*,*trans*-tetrahydropyran **78** as the major isomer. Stereochemistry of the trisubstituted tetrahydropyran products shown in Table 6 can similarly be explained via the same Zimmerman–Traxler transition-state model. This also accounts for the lower diastereoselectivity in reactions with 2,5-dimethylhex-5-en-1-ol (**20**).

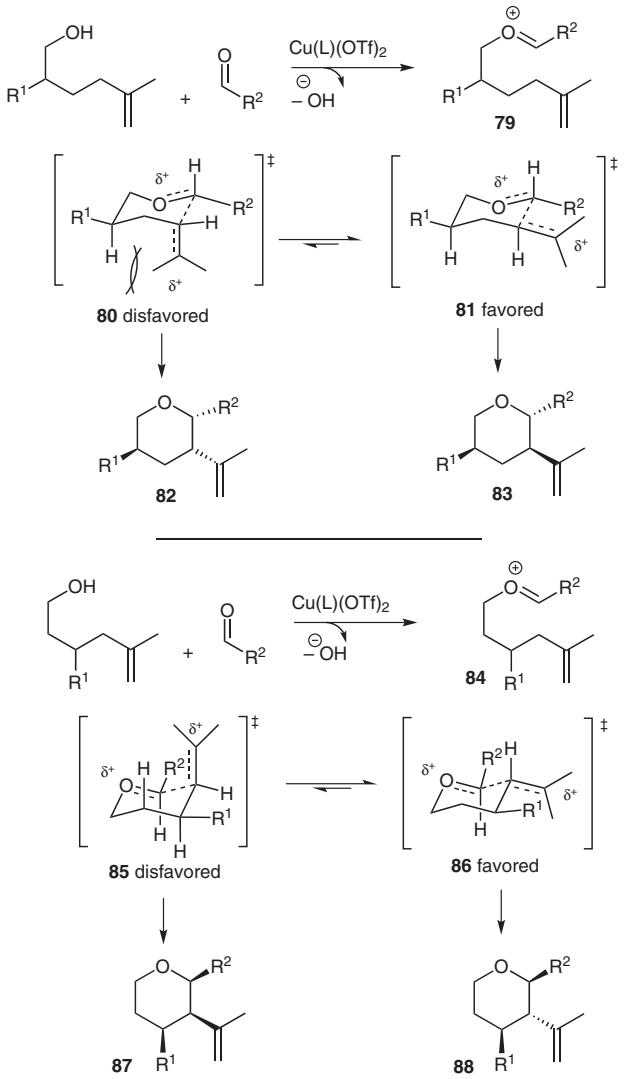


Scheme 5 Zimmerman–Traxler transition states

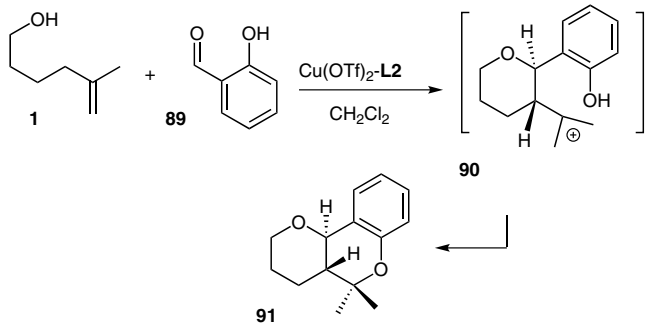
Interestingly, the addition of water or the attempted elimination of water ($CaCl_2$, $MgSO_4$, and 4 Å MS) resulted in the cessation of this reaction.[22] However, the reaction did proceed once a catalytic amount of triflic acid was added. Thus, it appears that a protic acid is possibly required for the olefin rearrangement step.[23]

Stereochemical models for reactions of 2,5-dimethylhex-5-en-1-ol (**20**) and 3,5-dimethylhex-5-en-1-ol (**24**) with various aldehydes are shown in Scheme 6. As can be seen, for reactions with 2,5-dimethylhex-5-en-1-ol (**20**), the major product **83** would form through transition state **81**, which shows all equatorial substituents. The minor diastereomer **82** would form through transition state **80**, which shows unfavorable 1,3-diaxial interaction between substituents. Similarly, for reactions with 3,5-dimethylhex-5-en-1-ol (**24**), transition state **86** would be favored over **85**, providing product **88** as the major diastereomer.

In an effort to further gain insight, reaction of 5-methylhex-5-en-1-ol (**1**) with salicylaldehyde was explored. As shown in Scheme 7, under standard conditions utilizing the copper(II) triflate–**L2** at 40 °C gave bicyclic product **91** in 55% yield as a single diastereomer (by ^1H NMR). Presumably, the product **91** resulted from the nucleophilic attack of salicylaldehyde phenol to the tertiary carbocation intermediate formed by olefin migration. The forma-



Scheme 6 Stereochemical models for alkenols **20** and **24**



Scheme 7 Reaction of alkenol **1** with salicylaldehyde

tion of tricyclic product **91** was previously observed by Inoue and co-workers.[24]

As shown, the *trans*-isomer was the major product and often the only isomer observable by NMR analysis. The reaction of 5-methylhex-5-en-1-ol (**1**) with tosyloxyacetaldehyde (**49**) was found to provide chromatographically separable diastereomers **50a** (*trans*-major) and **50b** (*cis*-minor). The stereochemical assignment of these compounds was carried out by ^{1}H NMR NOESY experiments (Figure 2). The observed NOESY between H_a–H_d, H_b–H_c, H_c–H_f, and H_d–H_e for compound **50a** 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 **50b**.

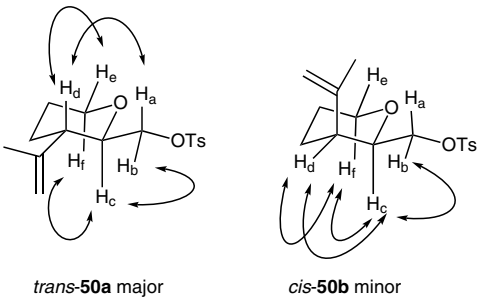
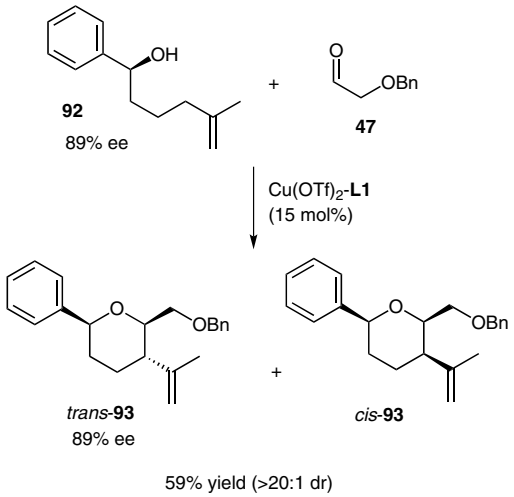


Figure 2 NOE of tetrahydropyran **50**

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 process.[25] To examine whether our catalytic system can undergo such stereoisomerization or not, we have carried out olefin migration and Prins cyclization using enantioenriched alcohol **92**. This was prepared by Corey–Bakshi–Shibata reduction[26] of the corresponding ketone in 89% ee. As shown in Scheme 8, reaction of alcohol **92** with benzyloxyacetaldehyde (**47**) provided **93**, with good diastereoselectively (dr >20:1) and 59% yield. The *trans*-isomer **93** was obtained in 89% ee, which indicated that the cyclization resulted in no loss of optical activity.[11a] This indicates that the present cyclization pathway does not involve a [3,3]-sigmatropic rearrangement.



Scheme 8 Experiment with optically enriched alkenol

In conclusion, we have developed a mild copper(II) triflate–bisphosphine-catalyzed reaction involving an appropriate alkenol and an aldehyde to provide a variety of substituted tetrahydropyrans. Both electron-rich and electron-deficient aromatic aldehydes were tolerated under our reaction conditions. The reaction proceeded via a tandem olefin migration and Prins cyclization to provide tetrahydropyran derivatives in good to excellent yields and excellent *trans* diastereoselectivity. This copper(II) triflate and bisphosphine ligand combination has not been previously employed in such synthesis of substituted tetrahydropyrans. Mechanistic explorations and further applications are in progress in our laboratory.

Chemicals and reagents were purchased from commercial suppliers and used without further purification. **L3** was prepared as reported.[11b] Anhydrous CH_2Cl_2 was distilled from CaH_2. All other solvents were reagent grade. All moisture-sensitive reactions were carried out in oven-dried glassware under argon. All new compounds were isolated as colorless oils except **71**. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance ARX-400, a Bruker DRX-500, or a Bruker Avance III-800 spectrometer. Chemical shifts are given in ppm and are referenced against the diluting solvent. For chloroform-*d*: ^{13}C triplet = 77.00 and ^{1}H singlet = 7.26 ppm. For methanol-d_4: ^{13}C septuplet = 49.05 and ^{1}H quintuplet = 3.31 ppm.

(2*S,3*S**,6*R**)-3-Isopropenyl-6-methyl-2-[(*E*)-styryl]tetrahydro-2*H*-pyran (31); Typical Procedure Using Ligands L1 and L2**

To a suspension of $Cu(OTf)_2$ (33 mg, 0.092 mmol, 15 mol%) in CH_2Cl_2 (4 mL) was added bis(diphenylphosphino)ethylene (**L1**; 36 mg, 0.092 mmol, 15 mol%) under an argon atmosphere. This was stirred at r.t. for 1 h to form completely the **L1**–$Cu(OTf)_2$ complex. To this was added a soln of 6-methylhept-6-en-2-ol (**16**; 98 mg, 0.766 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 77 μL, 0.613 mmol, 1 equiv) in CH_2Cl_2 (4 mL) via cannula. The flask was fitted with a reflux condenser and heated to 40 °C for 2 h. Upon cooling the reaction was diluted with CH_2Cl_2 (10 mL) and washed with aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (10% EtOAc–hexanes) to provide tetrahydropyran **31** (95 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 2 H), 7.35–7.30 (m, 2 H), 7.27–7.21 (m, 1 H), 6.64 (d, *J* = 15.9 Hz, 1 H), 6.21 (dd, *J* = 16.0, 6.7 Hz, 1 H), 4.80 (s, 2 H), 3.96 (ddd, *J* = 10.0, 6.7, 1.2 Hz, 1 H), 3.62 (ddd, *J* = 11.4, 6.3, 2.0 Hz, 1 H), 2.11 (ddd, *J* = 11.8, 10.1, 3.8 Hz, 1 H), 1.95–1.81 (m, 1 H), 1.79–1.65 (m, 5 H), 1.50–1.36 (m, 1 H), 1.29 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.29, 137.14, 131.24, 129.07, 128.35, 127.33, 126.54, 112.13, 80.94, 77.25, 77.00, 76.93, 76.75, 73.67, 49.71, 33.37, 29.98, 22.05, 20.88.

MS (EI): *m*/*z* = 131, 227, 242 [M^+].

MS (CI): *m*/*z* = 133, 138, 225, 243 [M + H].

(2*S,3*R**,5*R**)-3-Isopropenyl-2-(4-methoxyphenyl)-5-methyltetrahydro-2*H*-pyran (69); Typical Procedure for Ligand L3**

To a suspension of $Cu(OTf)_2$ (34 mg, 0.094 mmol, 15 mol%) in CH_2Cl_2 (5 mL) was added 1-(diphenylphosphino)-2-[(diphenylphosphino)methyl]benzene (**L3**; 43 mg, 0.094 mmol, 15 mol%) under an argon atmosphere. This was stirred at r.t. for 1 h to form completely the **L3**–$Cu(OTf)_2$ complex. To this was added a soln of 2,5-dimethylhex-5-en-1-ol (**20**; 100 mg, 0.78 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 76 μL, 0.62 mmol, 1 equiv) in CH_2Cl_2 (5 mL) via cannula. The reaction was stirred at r.t. for 18 h. Upon completion the reaction was diluted with CH_2Cl_2 (10 mL) and washed with aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (10% EtOAc–hexanes) to provide tetrahydropyran **69** (76 mg, 49%); dr ~7:1 (^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.62 (d, *J* = 10.2 Hz, 2 H), 4.07 (d, *J* = 10.0 Hz, 1 H), 3.99 (ddd, *J* = 11.1, 4.3, 2.4 Hz, 1 H), 3.78 (s, 3 H), 3.16 (t, *J* = 11.0 Hz, 1 H), 2.63–2.55 (m, ~0.14 H, methyl diastereomer), 2.38 (ddd, *J* = 12.0, 10.0, 3.3 Hz, 1 H), 1.91 (m, 2 H), 1.45 (s, 3 H), 1.35 (q, *J* = 12.2 Hz, 1 H), 1.26 (d, *J* = 7.0 Hz, ~0.42 H methyl diastereomer), 0.87 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.93, 146.20, 133.18, 128.39 (2 C), 113.35 (2 C), 111.82, 83.44, 74.99, 55.07, 53.33, 50.30, 39.12, 31.18, 21.28, 17.00.

MS (EI): *m*/*z* = 121, 161, 246 [M^+].

MS (CI): *m*/*z* = 121, 139, 247 [M + H].

***trans*-3-Isopropenyl-2-(2-methoxyphenyl)tetrahydro-2*H*-pyran (37)**

Following the typical procedure using 5-methylhex-5-en-1-ol (**1**; 143 mg, 1.25 mmol) and 2-anisaldehyde (**36**; 136 mg, 1 mmol) with **L3** gave **37** (79 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.5, 1.8 Hz, 1 H), 7.25 (td, *J* = 8.3, 1.8 Hz, 1 H), 6.98 (t, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 4.84 (d, *J* = 10.2 Hz, 1 H), 4.54 (d, *J* = 7.9 Hz, 2 H), 4.16–4.08 (m, 1 H), 3.83 (s, 3 H), 3.65 (td, *J* = 11.8, 2.2 Hz, 1 H), 2.52 (td, *J* = 10.7, 3.5 Hz, 1 H), 1.97–1.67 (m, 4 H), 1.59 (s, 3 H).

^{13}C (125 MHz, $CDCl_3$): δ = 156.72, 146.22, 129.58, 128.51, 127.89, 120.66, 111.64, 110.50, 68.97, 55.33, 50.22, 30.31, 26.43, 20.42.

MS (EI): *m*/*z* = 124, 232 [M^+].

MS (CI): *m*/*z* = 125, 233 [M + H].

***trans*-3-Isopropenyl-2-[3,4-(methylenedioxy)phenyl]tetrahydro-2*H*-pyran (39)**

Following the typical procedure using 5-methylhex-5-en-1-ol (**1**; 143 mg, 1.25 mmol) and piperonal (**38**; 150 mg, 1 mmol) with **L3** gave **39** (111 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (s, 1 H), 6.84–6.56 (m, 2 H), 5.94 (d, *J* = 3.4 Hz, 2 H), 4.67 (d, *J* = 15.2 Hz, 2 H), 4.12 (d, *J* = 9.9 Hz, 2 H), 3.60 (td, *J* = 11.8, 2.1 Hz, 1 H), 2.32 (ddd, *J* = 11.6, 9.6, 3.7 Hz, 1 H), 2.01–1.62 (m, 4 H), 1.51 (s, 3 H).

^{13}C (125 MHz, $CDCl_3$): δ = 147.37, 146.88, 146.27, 135.24, 120.96, 112.05, 107.76, 107.62, 100.83, 84.18, 68.85, 50.56, 30.25, 26.29, 21.42.

MS (EI): *m*/*z* = 124, 246 [M^+].

MS (CI): *m*/*z* = 125, 247 [M + H].

(2*S,3*S**,6*S**)-3-Isopropenyl-6-isopropyl-2-[(*E*)-styryl]tetrahydro-2*H*-pyran (52)**

Following the typical procedure using 2,7-dimethyloct-7-en-3-ol (**51**; 112 mg, 0.725 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 73 μL, 0.58 mmol, 1 equiv) with **L3** gave **52** (88 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (dd, *J* = 7.7, 1.6 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 6.66 (d, *J* = 15.9 Hz, 1 H), 6.25 (dd, *J* = 15.9, 5.9 Hz, 1 H), 4.81 (s, 2 H), 3.94 (ddd, *J* = 10.1, 5.9, 1.5 Hz, 1 H), 3.16 (ddd, *J* = 11.2, 6.5, 2.1 Hz, 1 H), 2.08 (ddd, *J* = 12.3, 10.1, 3.8 Hz, 1 H), 1.89 (dd, *J* = 13.2, 3.5 Hz, 1 H), 1.84–1.76 (m, 2 H), 1.74 (s, 3 H), 1.68 (dd, *J* = 12.5, 3.9 Hz, 1 H), 1.38 (tdd, *J* = 12.8, 11.1, 3.9 Hz, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.50, 137.39, 130.24, 129.45, 128.38, 127.20, 126.48, 112.02, 82.66, 80.47, 50.16, 33.17, 30.17, 27.93, 20.90, 18.96, 18.38.

(2*S,3*S**,6*S**)-6-*tert*-Butyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (54)**
Following the typical procedure using 2,2,7-trimethyloct-7-en-3-ol (**53**; 113 mg, 0.667 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 66 μL, 0.533 mmol, 1 equiv) with **L3** gave **54** (72 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 2 H), 7.33–7.29 (t, *J* = 8.5, 6.8 Hz, 8 H), 7.23 (m, *J* = 7.3 Hz, 3 H), 6.68–6.63 (dd, *J* = 16.0, 1.5 Hz, 1 H), 6.28–6.23 (dd, *J* = 15.9, 5.2 Hz, 1 H), 4.81 (d, *J* = 6.1 Hz, 2 H), 3.95–3.91 (ddd, *J* = 10.1, 5.2, 1.6 Hz, 1 H), 3.08–3.04 (dd, *J* = 11.2, 1.8 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.93–1.83 (m, 1 H), 1.74 (s, 3 H), 1.73–1.62 (m, 2 H), 1.41 (m, 1 H), 0.97 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.55, 137.48, 129.73, 129.28, 128.33, 127.03, 126.36, 111.87, 85.15, 80.08, 50.17, 34.17, 30.38, 26.14, 25.34, 20.90.

MS (EI): *m*/*z* = 96, 133, 154, 269, 284 [M^+].

MS (CI): *m*/*z* = 133, 267, 285 [M + H].

(2*S,3*S**,6*S**)-6-Allyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (56)**
Following the typical procedure using 8-methylnona-1,8-dien-4-ol (**55**; 68 mg, 0.44 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 44 μL, 0.35 mmol, 1 equiv) with **L3** gave **56** (32 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 6.66 (d, *J* = 15.9 Hz, 1 H), 6.23 (dd, *J* = 15.9, 6.3 Hz, 1 H), 5.93 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1 H), 5.21–5.04 (m, 2 H), 4.82 (s, 2 H), 3.97 (ddd, *J* = 9.9, 6.3, 1.4 Hz, 1 H), 3.52 (dtd, *J* = 11.1, 6.4, 2.1 Hz, 1 H), 2.53–2.42 (m, 1 H), 2.36–2.25 (m, 1 H), 2.12 (ddd, *J* = 12.1, 10.2, 3.7 Hz, 1 H), 1.94–1.83 (m, 1 H), 1.83–1.76 (m, 1 H), 1.74 (s, 3 H), 1.69 (td, *J* = 13.0, 4.1 Hz, 1 H), 1.41 (tdd, *J* = 12.9, 11.1, 4.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.26, 137.20, 134.95, 130.90, 129.04, 128.38, 127.32, 126.53, 116.69, 112.18, 109.73, 80.77, 77.13, 49.92, 40.81, 30.98, 29.91, 20.89.

MS (EI): *m*/*z* = 105, 131, 284 [M^+].

MS (CI): *m*/*z* = 123, 197, 269 [M + H].

(2*S,3*S**,6*S**)-6-Benzyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (58)**
Following the typical procedure using 6-methyl-1-phenylhept-6-en-2-ol (**57**; 100 mg, 0.49 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 49 μL, 0.39 mmol, 1 equiv) with **L3** gave **58** (42 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.5 Hz, 2 H), 7.40–7.23 (m, 6 H), 6.71 (d, *J* = 15.9 Hz, 1 H), 6.28 (dd, *J* = 16.0, 6.0 Hz, 1 H), 4.84 (s, 2 H), 4.01 (dd, *J* = 9.8, 6.0 Hz, 1 H), 3.71 (dt, *J* = 10.5, 5.5 Hz, 1 H), 3.13 (dd, *J* = 13.4, 5.9 Hz, 1 H), 2.79 (dd, *J* = 13.4, 7.1 Hz, 1 H), 2.16 (ddd, *J* = 12.1, 10.3, 3.8 Hz, 1 H), 1.92–1.77 (m, 1 H), 1.75 (s, 3 H), 1.68–1.40 (m, 4 H), 1.16 (qd, *J* = 12.8, 5.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.24, 138.72, 137.27, 130.84, 129.57 (2 C), 129.03, 128.44 (2 C), 128.22 (2 C), 127.36, 126.54 (2 C), 126.16, 112.25, 80.65, 78.55, 71.54, 49.93, 42.96, 30.85, 20.91.

MS (EI): *m*/*z* = 91, 117, 131, 188, 303, 318 [M^+].

MS (CI): *m*/*z* = 107, 117, 301, 319 [M + H].

(2*S,3*S**,6*S**)-6-Phenyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (60)**
Following the typical procedure using 5-methyl-1-phenylhex-5-en-1-ol (**59**; 138 mg, 0.735 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 74 μL, 0.588 mmol, 1 equiv) with **L3** gave **60** (85 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.20 (m, 10 H), 6.74–6.71 (dd, *J* = 15.9 Hz, 1 H), 6.34–6.28 (dd, *J* = 15.9, 6.2 Hz, 1 H), 4.88 (s, 2 H), 4.57–4.54 (dd, *J* = 11.4, 2.1 Hz, 1 H), 4.17 (dd, *J* = 9.6, 6.4 Hz, 1 H), 2.29–2.20 (ddd, *J* = 13.6, 10.0, 3.7 Hz, 1 H), 2.00 (m, 2 H), 1.95–1.84 (m, 1 H), 1.80 (s, 3 H), 1.78–1.66 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.11, 142.97, 137.17, 130.87, 128.93, 128.36, 128.24, 127.29, 126.49, 125.97, 125.88, 112.33, 81.10, 79.57, 49.76, 33.86, 30.37, 20.94.

MS (EI): *m*/*z* = 104, 133, 286, 304 [M^+].

MS (CI): *m*/*z* = 133, 173, 227, 287, 305 [M + H].

(2*R,3*S**,6*R**)-3-Isopropenyl-2-(4-methoxyphenyl)-6-methyltetrahydro-2*H*-pyran (61)**
Following the typical procedure using 6-methylhept-6-en-2-ol (**16**; 54 mg, 0.49 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 41 μL, 0.34 mmol, 1 equiv) with **L3** gave **61** (47 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.65 (d, *J* = 13.3 Hz, 2 H), 4.23 (d, *J* = 10.0 Hz, 1 H), 3.81 (s, 3 H), 3.67 (dtt, *J* = 12.3, 6.1, 3.1 Hz, 1 H), 2.29 (ddd, *J* = 11.9, 9.9, 3.8 Hz, 1 H), 1.97–1.88 (m, 1 H), 1.84–1.71 (m, 2 H), 1.52–1.43 (m, 1 H), 1.48 (s, 3 H), 1.27 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.94, 146.57, 133.78, 128.56, 113.44, 111.82, 83.67, 74.31, 55.17, 50.13, 33.65, 30.50, 22.18, 21.44.

MS (EI): *m*/*z* = 136, 246 [M^+].

MS (CI): *m*/*z* = 139, 247 [M + H].

(2*R,3*S**,6*S**)-3-Isopropenyl-6-isopropyl-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran (62)**
Following the typical procedure using 2,7-dimethyloct-7-en-3-ol (**51**; 65 mg, 0.419 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 41 μL, 0.335 mmol, 1 equiv) with **L3** gave **62** (54 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (d, *J* = 2.0 Hz, 2 H), 6.84–6.82 (d, *J* = 2.0 Hz, 2 H), 4.64–4.60 (d, *J* = 17.3 Hz, 2 H), 4.19–4.16 (d, *J* = 9.9 Hz, 1 H), 3.79 (s, 3 H), 3.25–3.12 (dd, *J* = 11.3, 5.8 Hz, 1 H), 2.22–2.16 (t, *J* = 10.7 Hz, 1 H), 1.95–1.89 (m, 1 H), 1.77–1.70 (m, 4 H), 1.45 (s, 3 H), 0.94 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.67, 146.69, 134.23, 128.33, 113.15, 111.61, 83.39, 82.82, 55.05, 50.72, 32.83, 30.43, 27.37, 21.47, 18.69, 17.96.

MS (EI): *m*/*z* = 137, 274 [M^+].

MS (CI): *m*/*z* = 137, 167, 275 [M + H].

(2*R,3*S**,6*S**)-6-Allyl-2-(4-methoxyphenyl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-pyran (63)**
Following the typical procedure using 8-methylnona-1,8-dien-4-ol (**55**; 100 mg, 0.65 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 63 μL, 0.52 mmol, 1 equiv) with **L3** gave **63** (65 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.24 (d, *J* = 8.6 Hz, 2 H), 6.86–6.84 (d, *J* = 8.6 Hz, 2 H), 5.97–5.85 (m, 1 H), 5.15–4.99 (m, 2 H), 4.65–4.61 (d, *J* = 14.2 Hz, 2 H), 4.22–4.19 (d, *J* = 10.4, 3.4 Hz, 1 H), 3.79 (s, 3 H), 3.57–3.52 (m, 1 H), 2.43–2.38 (m, 1 H), 2.31–2.23 (m, 2 H), 1.92–1.89 (m, 1 H), 1.82–1.70 (m, 2 H), 1.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.83, 146.45, 134.93, 133.71, 128.43, 116.53, 113.28, 111.80, 83.58, 77.57, 55.07, 50.32, 40.76, 30.93, 30.27, 21.42.

(2*R,3*S**,6*S**)-6-Benzyl-2-(4-methoxyphenyl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-pyran (64)**
Following the typical procedure using 6-methyl-1-phenylhept-6-en-2-ol (**57**; 100 mg, 0.49 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 47 μL, 0.39 mmol, 1 equiv) with **L3** gave **64** (76 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 7 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.65 (d, *J* = 21.2 Hz, 2 H), 4.26 (d, *J* = 10.0 Hz, 1 H), 3.83 (s, 3 H), 3.74 (m, 1 H), 3.07 (dd, *J* = 13.5, 5.1 Hz, 1 H), 2.76 (dd, *J* = 13.4, 7.7 Hz, 1 H), 2.34–2.20 (m, 1 H), 1.90 (m, 2 H), 1.83–1.50 (m, 3 H), 1.47 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.91, 146.48, 138.67, 133.81, 129.60 (2 C), 128.48 (2 C), 128.13 (2 C), 126.05, 113.35 (2 C), 111.85, 83.70, 78.99, 55.14, 50.41, 42.93, 30.74, 30.27, 21.47.

MS (EI): *m*/*z* = 91, 117, 136, 188, 231, 322 [M$^+$].

MS (CI): *m*/*z* = 121, 137, 215, 305, 323 [M + H].

(2*R,3*S**,6*R**)-2-(Benzyloxymethyl)-3-isopropenyl-6-methyltetrahydro-2*H*-pyran (65) and 8-(Benzyloxymethyl)-2,6-dimethyl-3,4,7,8-tetrahydro-2*H*-oxocin (66)**

Following the typical procedure using 6-methylhept-6-en-2-ol (**16**; 105 mg, 0.82 mmol, 1.25 equiv) and benzyloxyacetaldehyde (**47**; 92 μL, 0.66 mmol, 1 equiv) with **L1** gave **65** (94 mg, 55%) and less-polar oxocin **66** (19 mg, 11%).

Tetrahydropyran 65

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 4.79–4.73 (m, 2 H), 4.60 (dd, *J* = 15.35, 12.35 Hz, 2 H), 3.63–3.56 (m, 2 H), 3.53 (ddd, *J* = 11.1, 6.2, 2.0 Hz, 1 H), 3.47 (dd, *J* = 11.1, 6.9 Hz, 1 H), 2.11 (ddd, *J* = 11.9, 10.0, 3.9 Hz, 1 H), 1.81–1.77 (m, 1 H), 1.69 (s, 3 H), 1.68–1.57 (m, 2 H), 1.42–1.31 (m, 1 H), 1.27 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.61, 138.60, 128.21 (2 C), 127.68 (2 C), 127.36, 111.92, 79.56, 73.73, 73.34, 71.86, 45.66, 33.27, 30.12, 22.05, 20.13.

MS (EI): *m*/*z* = 91, 107, 139, 260 [M$^+$].

MS (CI): *m*/*z* = 91, 111, 261 [M + H].

Oxocin 66

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 5.49–5.42 (m, 1 H), 4.62 (q, *J* = 12.0 Hz, 2 H), 3.62–3.50 (m, 3 H), 3.49–3.40 (m, 1 H), 2.53–2.41 (m, 2 H), 2.00 (dd, *J* = 13.9, 1.4 Hz, 1 H), 1.98–1.91 (m, 1 H), 1.81 (s, 3 H), 1.70–1.59 (m, 1 H), 1.53 (dddd, *J* = 13.7, 12.5, 4.8, 3.5 Hz, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.55, 135.30, 128.30 (2 C), 127.59 (2 C), 127.47, 124.99, 79.18, 75.52, 74.03, 73.28, 38.11, 36.99, 25.37, 24.27, 22.21.

MS (EI): *m*/*z* = 91, 107, 139, 260 [M$^+$].

MS (CI): *m*/*z* = 91, 111, 153, 261 [M + H].

(2*R,3*S**,5*S**)-2-(4-Methoxyphenyl)-5-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-pyran (69)**

Following the typical procedure using 2,5-dimethylhex-5-en-1-ol (**20**; 100 mg, 0.78 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 76 μL, 0.62 mmol, 1 equiv) with **L3** gave **69** (76 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.62 (d, *J* = 10.2 Hz, 2 H), 4.07 (d, *J* = 10.0 Hz, 1 H), 3.99 (ddd, *J* = 11.1, 4.3, 2.4 Hz, 1 H), 3.78 (s, 3 H), 3.16 (t, *J* = 11.0 Hz, 1 H), 2.63–2.55 (m, ~0.14 H, methyl diastereomer), 2.38 (ddd, *J* = 12.0, 10.0, 3.3 Hz, 1 H), 1.91 (m, 2 H), 1.45 (s, 3 H), 1.35 (q, *J* = 12.2 Hz, 1 H), 1.26 (d, *J* = 7.0 Hz, ~0.42 H methyl diastereomer), 0.87 (d, *J* = 6.4 Hz, 3 H); dr ~7:1.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.93, 146.20, 133.18, 128.39 (2 C), 113.35 (2 C), 111.82, 83.44, 74.99, 55.07, 53.33, 50.30, 39.12, 31.18, 21.28, 17.00.

MS (EI): *m*/*z* = 68, 95, 112, 121, 135, 161, 246 [M$^+$].

MS (CI): *m*/*z* = 121, 139, 247 [M + H].

(2*S,3*S**,5*S**)-5-Methyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (70)**

Following the typical procedure using 2,5-dimethylhex-5-en-1-ol (**20**; 100 mg, 0.78 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 79 μL, 0.62 mmol, 1 equiv) with **L3** gave **70** (65 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.2 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 6.62 (d, *J* = 16.1 Hz, 1 H), 6.18 (dd, *J* = 16.0, 6.3 Hz, 1 H), 4.79 (d, *J* = 1.5 Hz, 2 H), 3.98 (ddd, *J* = 11.2, 4.2, 2.3 Hz, 1 H), 3.82 (ddd, *J* = 10.3, 6.4, 1.3 Hz, 1 H), 3.11 (t, *J* = 11.1 Hz, 1 H), 2.17 (ddd, *J* = 12.3, 10.0, 3.3 Hz, 1 H), 1.90–1.74 (m, 2 H), 1.71 (s, 3 H), 1.29 (q, *J* = 12.1 Hz, 1 H), 0.86 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.98, 137.04, 131.06, 128.72, 128.33 (2 C), 127.30, 126.40 (2 C), 112.10, 80.35, 74.33, 50.14, 38.65, 30.98, 20.76, 16.98.

MS (EI): *m*/*z* = 68, 95, 112, 131, 227, 242 [M$^+$].

MS (CI): *m*/*z* = 139, 243 [M + H].

(2*R,3*S**,5*S**)-5-Methyl-2-(4-nitrophenyl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-pyran (71)**

Following the typical procedure using 2,5-dimethylhex-5-en-1-ol (**20**; 100 mg, 0.78 mmol, 1.25 equiv) and 4-nitrobenzaldehyde (**6**; 94 mg, 0.62 mmol, 1 equiv) with **L3** gave **71** (48 mg, 29%). Colorless solid; mp 58–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.6 Hz, 2 H), 7.46 (d, *J* = 8.6 Hz, 2 H), 4.65 (s, 1 H), 4.55 (s, 1 H), 4.21 (d, *J* = 10.0 Hz, 1 H), 4.02 (ddd, *J* = 11.3, 4.3, 2.4 Hz, 1 H), 3.17 (t, *J* = 11.0 Hz, 1 H), 2.26 (ddd, *J* = 12.1, 10.1, 3.2 Hz, 1 H), 1.97–1.88 (m, 2 H), 1.45 (s, 3 H), 1.43–1.30 (m, 1 H), 1.26 (d, *J* = 6.9 Hz, ~0.5 H, methyl diastereomer), 0.89 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.44, 147.23, 144.81, 127.95 (2 C), 123.12 (2 C), 112.89, 82.70, 74.74, 51.19, 38.63, 30.98, 21.34, 16.89.

MS (EI): *m*/*z* = 68, 95, 112, 246, 262 [M$^+$].

MS (CI): *m*/*z* = 112, 262 [M + H].

(2*R,3*S**,4*S**)-2-(4-Methoxyphenyl)-4-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-pyran (72)**

Following the typical procedure using 3,5-dimethylhex-5-en-1-ol (**24**; 118 mg, 0.918 mmol, 1.25 equiv) and *p*-anisaldehyde (**10**; 89 μL, 0.734 mmol, 1 equiv) with **L3** gave **72** (22 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.18 (d, *J* = 8 Hz, 2 H), 6.83–6.79 (d, *J* = 8 Hz, 2 H), 4.66 (s, 1 H), 4.56 (s, 1 H), 4.14–4.04 (m, 2 H), 3.78 (s, 3 H), 3.66–3.57 (td, *J* = 12.1, 2.3 Hz, 1 H), 1.92–1.89 (t, *J* = 10.3 Hz, 1 H), 1.79 (m, 1 H), 1.73–1.59 (m, 2 H), 1.56–1.46 (m, 1 H), 1.43 (s, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.83, 144.00, 133.46, 128.33, 113.90, 113.26, 83.42, 77.14, 68.37, 58.10, 55.07, 34.46, 33.89, 19.81.

MS (EI): *m*/*z* = 85, 112, 135, 161, 246 [M$^+$].

MS (CI): *m*/*z* = 121, 139, 247 [M + H].

(2*S,3*S**,4*S**)-4-Methyl-3-(prop-1-en-2-yl)-2-styryltetrahydro-2*H*-pyran (73)**

Following the typical procedure using 3,5-dimethylhex-5-en-1-ol (**24**; 122 mg, 0.950 mmol, 1.25 equiv) and *trans*-cinnamaldehyde (**30**; 95 μL, 0.757 mmol, 1 equiv) with **L3** gave **62** (24 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.19 (m, 5 H), 6.62–6.52 (dd, *J* = 15.9 Hz, 1 H), 6.20–6.13 (dd, *J* = 16.0, 6.3 Hz, 1 H), 4.84–4.78 (d, *J* = 24.0 Hz, 2 H), 4.10–4.06 (dd, *J* = 11.4, 4.4 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.64–3.55 (m, 1 H), 1.76–1.69 (m, 2 H), 1.69–1.59 (m, 5 H), 1.41 (m, 1 H), 0.89 (d, *J* = 5.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.76, 137.11, 130.73, 128.98, 128.33, 127.26, 126.40, 126.17, 80.25, 77.14, 67.87, 57.72, 34.29, 33.10, 19.66.

MS (EI): *m*/*z* = 67, 82, 112, 131, 227, 242 [M$^+$].

MS (CI): *m*/*z* = 139, 225, 243 [M + H].

Acknowledgment

Financial support by the National Institutes of Health is gratefully acknowledged.

References

(1) (a) Reymond, S.; Ferrie, L.; Guerinot, A.; Capdevielle, P.; Cossy, J. *Pure Appl. Chem.* **2008**, *80*, 1683. (b) Sanz, M. A.; Voigt, T.; Waldmann, H. *Adv. Synth. Catal.* **2006**, *348*, 1511. (c) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301. (d) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (e) Gademann, K.; Portmann, C. *Curr. Org. Chem.* **2008**, *12*, 326.

(2) (a) Carrillo, R.; Leon, L. G.; Martın, T.; Martın, V. S.; Padron, J. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6135. (b) Singh, P.; Bhardwaj, A. *J. Med. Chem.* **2010**, *53*, 3707. (c) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (d) List, B.; Castello, C. *Synlett* **2001**, 1687.

(3) (a) Ghosh, A. K.; Anderson, D. D. *Future Med. Chem.* **2011**, *3*, 1181. (b) Wender, P. A.; Baryza, J. L.; Brenner, S. E.; Clarke, M. O.; Gamber, C. G.; Horan, J. C.; Jessop, T. C.; Kan, C.; Pattabiraman, K.; Williams, T. J. *Pure Appl. Chem.* **2003**, *75*, 143.

(4) (a) Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Steffey, M. P.; Walters, D. E.; Koh, Y.; Amano, M.; Mitsuya, H. *J. Med. Chem.* **2011**, *54*, 622. (b) Ide, K.; Aoki, M.; Amano, M.; Koh, Y.; Yedidi, R. S.; Das, D.; Leschenko, S.; Chapsal, B.; Ghosh, A. K.; Mitsuya, H. *Antimicrob. Agents Chemother.* **2011**, *55*, 1717.

(5) Tietze, L. F.; Kettschau, G.; Gewer, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19.

(6) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839.

(7) Yadav, J. S.; Purnima, K. V.; Reddy, B. V. S.; Nagaih, K.; Ghamdi, A. K. *Tetrahedron Lett.* **2011**, *52*, 6709.

(8) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, 1218.

(9) Smith, A. B. III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675.

(10) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Org. Biomol. Chem.* **2005**, *3*, 3551.

(11) (a) Ghosh, A. K.; Nicponski, D. R. *Org. Lett.* **2011**, *13*, 4328. (b) Ghosh, A. K.; Nicponski, D. R.; Kass, J. *Tetrahedron Lett.* **2012**, *53*, 3699.

(12) Miura, K.; Horiike, M.; Inoue, G.; Ichikawa, J.; Hosomi, A. *Chem. Lett.* **2008**, *37*, 270.

(13) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669.

(14) For examples of Lewis acid catalyzed ene reactions, see: Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.

(15) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536.

(16) Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003.

(17) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(19) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(20) Kocovsky, P.; Ahmed, G.; Srogl, J.; Malkov, A. V.; Steele, J. *J. Org. Chem.* **1999**, *64*, 2765.

(21) Gesinski, M. R.; Van Orden, L. J.; Rychnovsky, S. D. *Synlett* **2008**, 363.

(22) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839.

(23) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092.

(24) Inoue, S.; Asami, M.; Honda, K.; Miyazaki, H. *Chem. Lett.* **1996**, *10*, 889.

(25) Rychnovski, S. D.; Jasti, R. *J. Am. Chem. Soc.* **2006**, *128*, 13640.

(26) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.