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Stereospecific Cross-Coupling Reactions of Aryl-Substituted Tetrahydrofurans, Tetrahydropyrans, and Lactones

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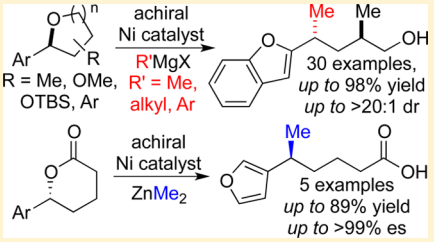
Supporting Information

ABSTRACT: The stereospecific ring-opening of O-heterocycles to provide acyclic alcohols and carboxylic acids with controlled formation of a new C−C bond is reported. These reactions provide new methods for synthesis of acyclic polyketide analogs with complex stereochemical arrays. Stereoselective synthesis of the cyclic template is utilized to control relative configuration; subsequent stereospecific nickel-catalyzed ring-opening affords the acyclic product. Aryl-substituted tetrahydrofurans and tetrahydropyrans undergo nickel-catalyzed Kumada-type coupling with a range of Grignard reagents to furnish acyclic alcohols with high diastereoselectivity. Enantioenriched lactones undergo Negishi-type cross-coupling with dimethylzinc to afford enantioenriched carboxylic acids. Application in a two-step enantioselective synthesis of an anti-dyslipidemia agent is demonstrated.



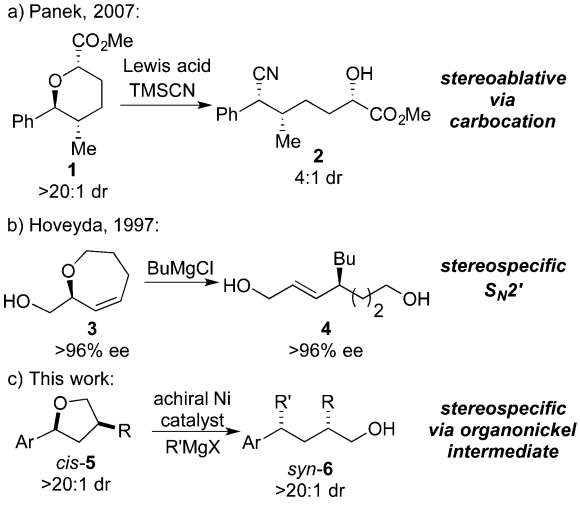
INTRODUCTION

The discovery and asymmetric synthesis of novel polyketides and their unnatural analogs fuel the development of new therapeutic agents. The structural complexity of this class of molecules has inspired and tested synthetic organic chemistry.[1−3] One challenge is control of relative configuration during construction of acyclic fragments. Woodward pioneered the use of cyclic stereocontrol followed by ring-opening to reveal a single diastereomer of an acyclic target.[4] For example, in the first synthesis of erythromycin A, a dithiadecalin template was employed to control relative stereochemistry of ensuing reactions; subsequent ring-opening provided a highly substituted acyclic polyketide. This general strategy has been applied successfully to the synthesis of many natural products.[5]

Ring-opening reactions of tetrahydrofurans and tetrahydropyrans have been developed;[6] however, there are few examples that occur with formation of a new C_{sp^3}−C_{sp^3} bond.[7,8] Panek and co-workers have achieved diastereoselective ring-opening reactions of tetrahydropyrans with cyanide in the presence of a Lewis acid (Scheme 1a).[7a] The stereochemical course is consistent with a stereoablative reaction; minimization of A[1,3] strain in a carbocation intermediate and attack of cyanide on the least hindered face provides the major diastereomer.

A complementary approach to control of relative stereochemistry is via a stereospecific reaction, where stereochemical information is conserved throughout the transformation. Hoveyda and co-workers demonstrated that unsaturated cyclic ethers activated by pendant alcohols undergo stereospecific S_N2' reactions with Grignard reagents to yield enantioenriched acyclic products (Scheme 1b).[9] We sought to expand stereospecific ring-opening reactions to include *saturated* cyclic ethers that are not activated by ring strain.[10,11] We envisioned stereospecific nickel-catalyzed ring-opening reactions of cyclic ethers, based on our enantiospecific Kumada-type cross-coupling of ethers (Scheme 1c).[12,13] We anticipated that cross-coupling would proceed with inversion at the electrophilic carbon. Therefore, by appropriate choice of diastereomer of starting material **5**, either the syn or anti diastereomer of **6** could be obtained selectively. This work would harness diastereoselective synthesis of tetrahydrofurans and tetrahydropyrans to provide complex acyclic fragments. The products would contain a free alcohol that could be further utilized in synthetic sequences. This method would provide stereospecific incorporation of a benzylic methyl substituent, a common motif in medicinal agents.[14] In addition, strategic use of extended

Scheme 1. Stereoselective Ring-Opening and C−C Bond Formation Strategy



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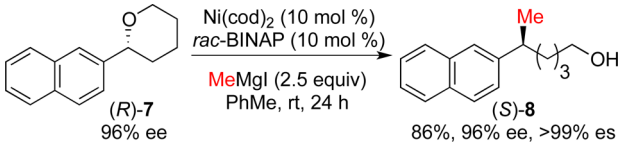
alkyl or aryl Grignard reagents would allow for the generation of a wide range of unnatural polyketide analogs for biological testing. In this manuscript, we report the stereospecific Kumada-type cross-coupling of tetrahydrofurans and tetrahydropyrans with a range of Grignard reagents. We also report stereospecific Negishi-type cross-coupling reactions of benzylic lactones with dimethyl zinc to provide enantioenriched carboxylic acids.

RESULTS AND DISCUSSION

Determination of Reaction Stereospecificity. To establish nickel-catalyzed ring-opening of cyclic ethers and determine the stereospecificity of the reaction, we designed model substrate (*R*)-**7** based on our prior experience developing Kumada-type cross-coupling reactions of benzylic ethers. We chose to first examine coupling with methyl Grignard reagent, as incorporation of "magic" methyl groups is an established strategy to increase potency of certain pharmaceutical agents.[14] Naphthyl-substituted tetrahydropyran (*R*)-**7** is straightforward to prepare in high enantiomeric excess (ee) utilizing the Corey–Bakshi–Shibata (CBS) reduction.[15] We were pleased to see that in the presence of a nickel catalyst and Grignard reagent, (*R*)-**7** provided acyclic alcohol (*S*)-**8** with cross-coupling at the benzylic center (Scheme 2). The reaction

Scheme 2. Enantiospecific Nickel-Catalyzed THP Opening



was highly enantiospecific, providing the product in 96% ee and >99% enantiospecificity (es).[16,17] No reaction occurs in the presence of Grignard reagent in the absence of nickel catalyst.

We envisioned that the most powerful application of this method would be in ring-opening reactions of heterocycles containing multiple stereogenic centers. To test our hypothesis that the nickel-catalyzed ring opening would occur with inversion at the electrophilic carbon, irrespective of the presence of other stereogenic centers, we examined both diastereomers of substituted tetrahydrofuran **9**. In the presence of $Ni(cod)_2$ and DPEphos each diastereomer underwent cross-coupling with clean inversion at the site of oxidative addition (Scheme 3).[18] Tetrahydrofuran *trans*-**9** (dr >20:1) afforded acyclic *anti*-**10** in 93% and a dr of >20:1. The other diastereomer, *cis*-**9** (dr >20:1), afforded *syn*-**10** in 93% yield and >20:1 dr. The relative configuration of tetrahydrofuran *cis*-**9** was determined by X-ray crystallographic analysis. The relative configuration of both diastereomers of acyclic **10** was assigned based on analysis of chemical shifts in the ^1H NMR spectra, based on the pioneering strategy of Kishi for assignment of relative configuration of acyclic polyketide fragments using the Breit model for 1,3-deoxypropionates.[19]

To determine whether or not there is a match/mismatch effect in reactions employing chiral catalysts, we examined ring-opening of both diastereomers of tetrahydrofuran **11** with each enantiomer of BINAP (Table 1). If the reaction proceeds strictly with inversion, regardless of the catalyst chirality, then both enantiomers of BINAP would provide similar results in the ring-opening reactions. However, if the chiral catalyst influences the stereochemical outcome of the cross-coupling

Scheme 3. Diastereoselective Cross-Coupling Reactions

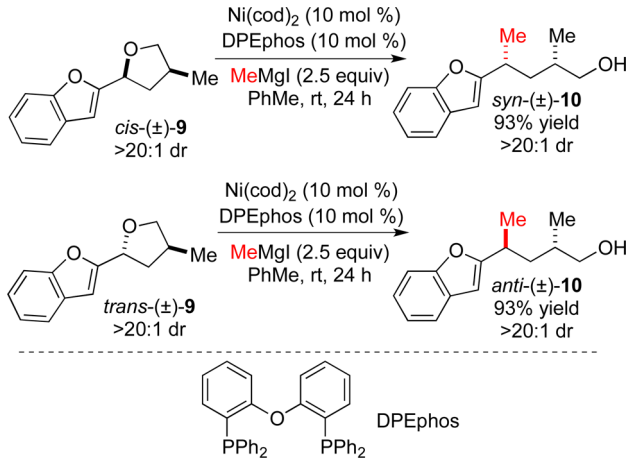
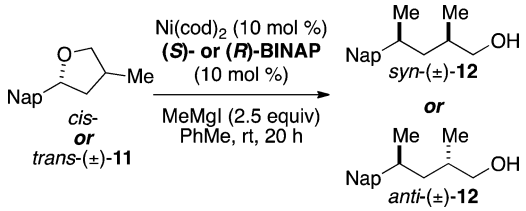


Table 1. Absence of Match/Mismatch Effect



Entry	Starting Material (cis:trans)	Ligand	Yield (%)[a]	dr[b] (syn:anti)
1	*cis*-(±)-**11** 20:1 dr	(*R*)-BINAP	86	20:1
2		(*S*)-BINAP	84	20:1
3	*trans*-(±)-**11** 1:20 dr	(*R*)-BINAP	87	1:20
4		(*S*)-BINAP	86	1:20

[a]Isolated yield after column chromatography. [b]Determined by ^1H NMR.

reaction, then one enantiomer of BINAP should provide diminished or inverted diastereoselectivity. In reactions of tetrahydrofuran *cis*-**11** both enantiomers of BINAP afforded acyclic *syn*-**12** in similar yield and 20:1 dr (entries 1 and 2). Either enantiomer of ligand provided the same diastereomer of product. Similarly, use of either enantiomer of BINAP in reactions of *trans*-**11** provided *anti*-**12** in good yield and 20:1 dr (entries 3 and 4). Therefore, we conclude that there is no match/mismatch between the chirality of the catalyst and substrate. All reactions proceed strictly with inversion without influence by the chirality of the catalyst. These results are consistent with our previous observations of robust substrate control in stereospecific Kumada and Negishi coupling reactions.

Scope of the Reaction: Tetrahydrofurans. We next examined the application of the methodology to a series of substituted tetrahydrofurans with a broad array of substituent patterns and stereochemical relationships found in polyketides.[20] Our starting materials were 2-aryltetrahydrofurans, a motif at the core of natural products such as the lignans sesaminone and pinoresinol.[21] As such, there are outstanding methods for diastereoselective synthesis of highly substituted 2-

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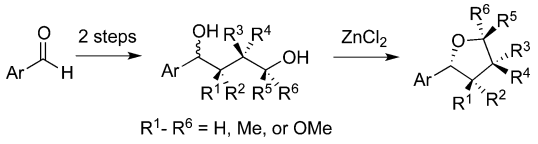
aryltetrahydrofurans.[22] Furthermore, development of methods for their direct derivatization could have application in natural product editing.[23] We prepared substrates using the general strategy outlined in Scheme 4, employing Lewis-acid catalyzed

Scheme 4. Synthesis of Substituted THFs



cyclization of the requisite diols[24] (see SI for full details). This synthesis typically provides access to both diastereomers, important for interrogation of the influence of additional stereogenic centers on the stereochemical course of the cross-coupling reactions. The relative configuration of starting materials and products could be assigned using well established methods typically employed for polyketides, including NOE experiments, analysis of ^{1}H NMR spectra, and X-ray crystallography.[25]

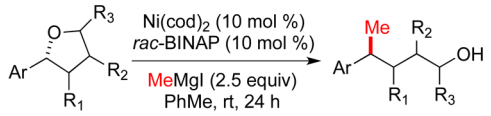
We continued our studies with 2,4-disubstituted tetrahydrofurans, as ring-opening provides the 1,3-dimethyldeoxypropionate fragment (e.g., **9** to **10**, Scheme 3). To determine the stereochemical course of the reaction, we examined reactions of both diastereomers of tetrahydrofuran **11** (Table 2, entries 1 and 2).[26] Under Kumada-type coupling conditions, tetrahydrofuran *trans*-**11** (dr >20:1) afforded acyclic *anti*-**12** in 82% and >20:1 dr (entry 1).[27] The diastereomer, *cis*-**11**, (dr 9:1) gave *syn*-**12** in 86% and 9:1 dr (entry 2). Rigorous assignment of the relative configuration of the starting materials and products demonstrates that the Kumada-type couplings proceeded with inversion.

We next examined introduction of a substituent at the 5-position, to determine whether the method would be amenable to synthesis of secondary alcohols. Both diastereomers of 2,5-disubstituted tetrahydrofuran **13** were synthesized by the Stetter reaction,[28] reduction of the ketones and diol cyclization. Tetrahydrofuran *cis*-**13** (dr 9:1) underwent cross-coupling in 82% yield with inversion to yield *syn*-**14** (dr 9:1, entry 3). The diastereomer *trans*-**13** (dr 8:1), afforded *anti*-**14** with high stereospecificity and in a slightly lower yield of 61% (entry 4). This lower yield is presumably due to steric interactions with the pseudo axial C5 methyl that would be present in the trans diastereomer but not in the cis diastereomer.

Vicinal methyl-bearing stereogenic centers are motifs in natural products such as kalkitoxin and nordihydroguaiaretic acid.[29] We envisioned accessing this motif from 2,3-disubstituted tetrahydrofurans. Starting materials *trans*-**15** and *trans*-**17** were prepared in 9:1 dr using the Nozaki–Hiyama–Kishi reaction as a key step.[30] Using DPEphos as the ligand, *trans*-**15** afforded *syn*-**16** in 65% yield and 9:1 dr (entry 5). We also found that heteroaromatic substituents are well tolerated. In addition to benzofuran-substituted tetrahydrofuran **9**, benzothiophene-substituted *trans*-**17** (dr 9:1) afforded *syn*-**18** in good yield and 9:1 dr (entry 6). While coupling reactions of both **15** and **17** proceed with inversion, more modest yields are likely an impact of steric crowding near the site of oxidative addition.

We examined 4-methoxytetrahydrofurans for synthesis of a 1,3-disubstituted ether unit as found in FK-506 and geldanamycin.[31] We found that methoxy-substituted tetrahydrofurans *trans*-**19** and *cis*-**19** underwent the reaction to afford good yields and excellent transfer of stereochemical information (entries 7 and 8). We attribute slightly diminished yields with both diastereomers of **19** to formation of an allylic ether via β-hydride elimination, which further reacted to a mixture of products under the reaction conditions.[32]

Table 2. Scope of Cross-Coupling Reaction of THFs



Entry	Starting Material	Product	Yield (%)[a]	S.M. dr[b]	Prod. dr[b]
1	*trans*-(±)-**11**	*anti*-(±)-**12**	82	>20:1	>20:1
2	*cis*-(±)-**11**	*syn*-(±)-**12**	86	9:1	9:1
3	*cis*-(±)-**13**	*syn*-(±)-**14**	82	9:1	9:1
4	*trans*-(±)-**13**	*anti*-(±)-**14**	61	8:1	8:1
5[c]	*trans*-(±)-**15**	*syn*-(±)-**16**	65	9:1	9:1
6[c]	*trans*-(±)-**17**	*syn*-(±)-**18**	62	9:1	9:1
7	*trans*-(±)-**19**	*anti*-(±)-**20**	63	>20:1	>20:1
8	*cis*-(±)-**19**	*syn*-(±)-**20**	62	>20:1	>20:1

[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. [c]Reaction performed using DPEphos (10 mol %) instead of *rac*-BINAP. Nap = 2-naphthyl.

Scope of Reaction: Tetrahydropyrans. To further expand the scope and utility of this method to include synthesis of 5-substituted alcohols, we next turned our attention to tetrahydropyrans. We chose to examine *cis*-(±)-2,4-disubstituted tetrahydropyrans, subunits of the calyxin family of natural products.[33] Such cross-coupling reactions would provide synthetic access to *syn*-3,5-disubstituted alcohols. There are several elegant methods for the diastereoselective synthesis of highly substituted tetrahydropyrans.[34] For example, these tetrahydropyrans are easily accessed by diastereoselective Prins cyclization reactions, as outlined in Scheme 5a.[35] Clay-mediated Prins cyclization of 2-napthaldehyde with 4-buten-1-ol in benzene provided *cis*-(±)-**21** in a single step with high diastereoselectivity and reasonable yield.[36]

We developed an alternative two-step diastereoselective strategy to prepare tetrahydropyrans containing a broad range

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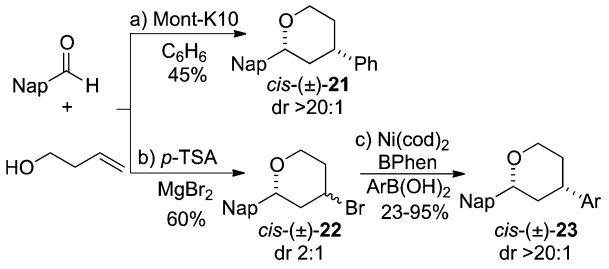
Scheme 5. Diastereoselective Synthesis of Tetrahydropyrans



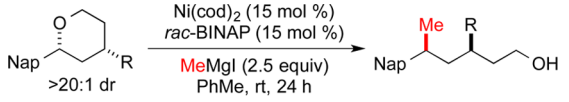
[a](a) Montmorillonite K10 (1.1 equiv), MeOH, C_6H_6, reflux, 18 h; (b) *p*-TSA (1.0 equiv), $MgBr_2$ (1.1 equiv), CH_2Cl_2, rt, 18 h; (c) Ni(cod)$_2$ (10 mol %), bathophenanthroline (BPhen) (20 mol %), ArB(OH)$_2$ (1.2 equiv), KO*t*Bu (1.6 equiv), *s*-BuOH, 60 °C, 24 h.

of aryl substituents at the C4 position (Scheme 5b). 4-Bromotetrahydropyran **22** is easily synthesized as a 2:1 mixture of diastereomers under mild conditions via a $MgBr_2$ and *p*-TsOH-promoted Prins cyclization.[37] To further derivatize **22**, we employed a nickel-catalyzed Suzuki-type cross-coupling reaction.[38] Based on the seminal work of Fu, we hypothesized that the coupling would be stereoconvergent and afford the more stable diastereomer, *cis*-**23**.[39] Indeed, cross-coupling of **22** with a range of commercially available aryl boronic acids afforded a wide variety of 4-aryltetrahydropyrans in high diastereoselectivity. These results are consistent with a stereoablative cross-coupling reaction that proceeds through a radical intermediate,[40] with a strong preference for formation of the thermodynamic product. The relative configuration of these *cis*-2,4-diaryl tetrahydropyrans was assigned by X-ray crystallographic analysis and NOE NMR experiments (see SI for details).

As with the tetrahydrofuran substrates, we examined the transfer of stereochemical information in the cross-coupling reaction by comparing the diastereomeric ratios of the starting materials to those of the acyclic products. We observed that employing a catalyst loading of 15 mol % resulted in good to excellent yields with high diastereomeric ratios (Table 3). Tetrahydropyran **21** (dr >20:1) afforded *syn*-**24** in 84% yield and >20:1 dr (entry 1) indicating the complete transfer of stereochemical information in the cross-coupling. We found that both electron-rich and electron-poor aryl substituents at the C4 position of the tetrahydropyran are well tolerated in the reaction (entries 2 and 3). To further challenge the tetrahydropyran ring-opening, we sought to incorporate biologically relevant moieties in our substrates. For example, the cross-coupling of tetrahydropyran *cis*-**29** proceeded in 81% yield and >20:1 dr to form benzodioxane-substituted product *syn*-**30** (entry 4). 1,4-Benzodioxanes are present in a range of pharmaceutical agents such as piperoxan and idazoxan.[41] We were also pleased to see that 3-furan-substituted tetrahydropyran *cis*-**31** was well tolerated in the reaction. Product *syn*-**32** was formed in high yield and dr and contains a furan substituent that can be readily derivatized by oxidation or cycloaddition reactions (entry 5).[42]

To challenge the method with synthesis of a stereotriad, we examined Kumada coupling of 2,4,6-trisubstituted tetrahydropyran *cis*-**33**. Subjecting *cis*-**33** to the reaction conditions afforded the secondary alcohol *syn*-**34**, containing three stereogenic centers, as a single diastereomer and with good yield (entry 6). This strategy provides a modular three-step synthesis of polyketide analogs where substituents in the C2, C4, and C6 positions can be easily altered by the use of commercially available aldehydes, arylboronic acids, and homoallylic alcohols, respectively.

Table 3. Scope of Cross-Coupling Reaction of THPs



Entry	Starting Material	Product	Yield (%)[a]	Prod. dr[b]
1	*cis*-(±)-**21**	*syn*-(±)-**24**	84	>20:1
2	*cis*-(±)-**25**	*syn*-(±)-**26**	76[c]	>20:1
3	*cis*-(±)-**27**	*syn*-(±)-**28**	72	>20:1
4	*cis*-(±)-**29**	*syn*-(±)-**30**	81[c]	>20:1
5	*cis*-(±)-**31**	*syn*-(±)-**32**	74	>20:1
6	*cis*-(±)-**33**	*syn*-(±)-**34**	63	>20:1
7[d]	*cis*-(±)-**35**	*syn*-(±)-**36**	86	>20:1
8[d]	*cis*-(±)-**37**	*syn*-(±)-**38**	73	>20:1
9[d]	*cis*-(±)-**39**	*syn*-(±)-**40**	86	>20:1

[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. [c]Calculated yield; see SI for details. [d]Reaction performed using Ni(acac)$_2$ (10 mol %) and DPEphos (10 mol %) instead of *rac*-BINAP. Nap = 2-naphthyl.

We set out to determine the compatibility of the reaction conditions with silylethers, common protecting groups. 4-Hydroxytetrahydropyrans are straightforward to prepare in high diastereoselectivity by Prins cyclization employing trifluoroacetic acid.[43] Using DPEphos, we found that benzofuran- and benzothiophene-substituted tetrahydropyrans **35** and **37**

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afforded the acyclic products in good yields and >20:1 dr (entries 7 and 8). To further challenge the ring-opening reaction, we employed a substrate activated by a simple aromatic substituent. 3-Furan-substituted tetrahydropyran *cis*-**39** formed *syn*-**40** in high yield and >20:1 dr (entry 9).

Grignard Reagent Scope. The ability of a synthetic method to easily provide access to analogs with a range of substituent patterns is critical for the discovery of new therapeutics as well as for conducting structure−activity relationship (SAR) studies. We next wanted to examine the scope with respect to the transmetallating agent, which would provide access to a variety of benzylic substituents in the acyclic products. Our laboratory has recently demonstrated that Ni(dppe)Cl_2 is a broadly applicable catalyst for cross-coupling of alkyl and aryl Grignard reagents with benzylic ethers.[12d] To examine the generality of conditions for a range of Grignard reagents, we applied this catalyst system to the cross-coupling reactions of a representative series of tetrahydropyrans and tetrahydrofurans (Table 4).

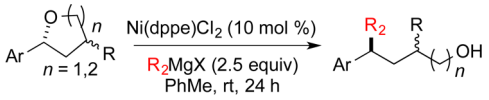
We began with *n*-propylmagnesium iodide, a representative alkyl Grignard reagent. Cross-coupling with tetrahydrofuran **19** afforded the desired product in 75% yield and high dr (entry 1). 3-Phenylpropylmagnesium bromide reacted smoothly with tetrahydropyran **37** to form alcohol **42** in good yield and high dr (entry 2).

We also examined aryl Grignard reagents for synthesis of complex diarylalkanes. Phenylmagnesium bromide underwent successful cross-coupling with tetrahydrofuran **9** and tetrahydropyran **21** (entries 3 and 4). In order to confirm that the reaction proceeded with inversion at the benzylic position, both *trans*-**19** and *cis*-**19** were prepared and subjected to the Kumada couplings with phenylmagnesium bromide. As with methylmagnesium bromide, the products were afforded in good yield and in high dr (entries 5 and 6). The relative configurations of *anti*-**45** and *syn*-**45** were assigned by the preparation of crystalline derivatives that were subjected to X-ray crystallographic analysis (see SI for details). 4-Methoxyphenylmagnesium bromide underwent smooth cross-coupling with tetrahydrofuran **9** and tetrahydropyran **21**. Products **46** and **47** were formed in high yield and dr (entries 7 and 8, respectively).

We have previously demonstrated that diarylalkanes containing a thiophene moiety provide lead compounds with selective anti-breast cancer activity.[12d] We therefore also examined our methodology with 2-thiophenylmagnesium bromide as the nucleophile. With both 2,4-disubstituted tetrahydropyran **21** and tetrahydrofuran **11** the desired product was afforded in excellent yield and dr (entries 9 and 10).

Negishi-Type Cross-Coupling of Lactones. We hypothesized that a similar cross-coupling could be applied to benzylic lactones, based on our recently reported Negishi-type nickel-catalyzed cross-coupling of benzylic esters.[44] Sawama and co-workers have recently demonstrated that aryl substituted lactones undergo Lewis acid-catalyzed ring-opening with allylsilane.[7b] However, to the best of our knowledge, stereoselective ring-opening of lactones with carbon-based nucleophiles has not been reported. As a further benefit, alkyl zinc reagents provide increased functional group tolerance as compared to Grignard reagents. The resulting enantioenriched product would contain a benzylic stereocenter with a distal carboxylic acid. As with the alcohols obtained from the Kumada-type opening of cyclic ethers, this carboxylic acid affords a convenient synthetic handle that can be used for further derivatization. Enantioselective synthesis of lactones provides straightforward access to the requisite starting materials.[45]

Table 4. Scope with Respect to Grignard Reagent



Entry	Grignard Reagent	SM	Product	Yield (%)[a]	S.M. dr[b]	Prod. dr[b]
1	*n*-PrMgI	*trans*-(±)-**19**	*anti*-(±)-**41**	75	>20:1	>20:1
2	MgBr	*cis*-(±)-**37**	*syn*-(±)-**42**	61	>20:1	>20:1
3	MgBr	*trans*-(±)-**9**	*anti*-(±)-**43**	98	>20:1	>20:1
4		*cis*-(±)-**21**	*syn*-(±)-**44**	82[c]	>20:1	>20:1
5		*trans*-(±)-**19**	*anti*-(±)-**45**	65	>20:1	>20:1
6		*cis*-(±)-**19**	*syn*-(±)-**45**	72	>20:1	>20:1
7	MgBr	*trans*-(±)-**9**	*anti*-(±)-**46**	81	>20:1	>20:1
8		*cis*-(±)-**21**	*syn*-(±)-**47**	70	>20:1	>20:1
9	MgBr	*cis*-(±)-**21**	*syn*-(±)-**48**	87[c]	>20:1	>20:1
10		*trans*-(±)-**11**	*anti*-(±)-**49**	88[c]	>20:1	>20:1

[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. [c]Calculated yield; see the SI for details. Nap = 2-naphthyl.

We prepared enantioenriched lactones for cross-coupling by CBS reduction of the benzylic ketones and cyclization of the corresponding 1,5-diols.[46] The absolute configuration of the lactones were assigned as *R* by the accepted CBS model of selectivity of the intermediate alcohols (see SI for details).[15] After examining a series of bidentate ligands and nickel precatalysts, we determined that Ni(acac)$_2$ and Xantphos

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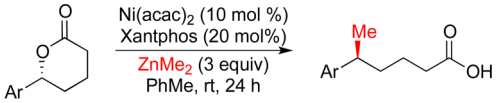
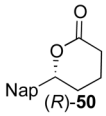
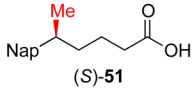
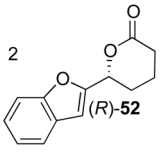
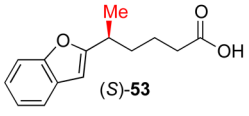
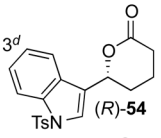
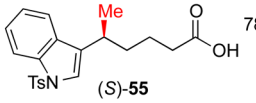
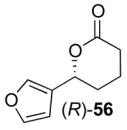
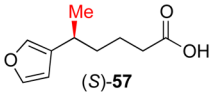
afforded the highest yield of cross-coupled carboxylic acid.[47] Commercially available lactone **50** afforded the cross-coupled product with excellent es (Table 5, entry 1), as did benzofuran-substituted lactone **52** and indole-substituted lactone **54** (entries 2 and 3, respectively).[48]

Table 5. Cross-Coupling Reaction of Lactones



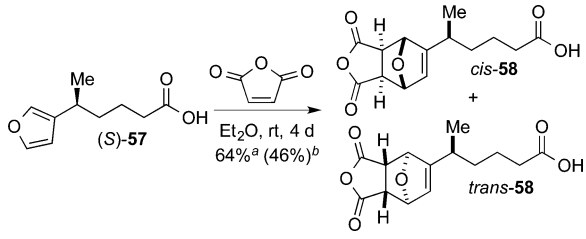
Entry	Starting Material	Product	Yield (%)[a]	S.M. ee[b]	Prod. ee[b]	es (%)[c]
1	 (*R*)-**50**	 (*S*)-**51**	89	97	97	>99
2	 (*R*)-**52**	 (*S*)-**53**	85	96	96	>99
3[d]	 (*R*)-**54**	 (*S*)-**55**	78	96	94	98
4	 (*R*)-**56**	 (*S*)-**57**	84	90	90	>99

[a]Isolated yield after column chromatography. [b]Determined by supercritical fluid chromatography. [c]Enantiospecificity (es) = ($ee_{product}/ee_{substrate}$) × 100%. [d]Reaction performed using DPEphos (20 mol %) instead of Xantphos. Nap = 2-naphthyl.

Furan-substituted δ-valerolactones such as **56** are found in natural products such as ricciocarpin A and salvinorin B;[49] methods for their ring-opening would provide a strategy for synthesis of analogs for biological testing.[23] We anticipated that lactone **56** would undergo straightforward nickel-catalyzed Negishi-type cross-coupling. Our laboratory has observed a strong dependence of the rate of cross-coupling on the identity of the aryl substituent. We hypothesize that arenes possessing lower aromatic stabilization energy[50] are better ligands for the nickel catalyst and stabilize the transition state for oxidative addition. Benzylic ethers and esters activated by extended aromatic rings such as naphthalene and benzofuran are sufficiently reactive, as are those activated by furan.[51] Furthermore, the incorporation of the furan moiety affords a product with two functional group handles: the carboxylic acid and the furan itself.[42] Therefore, we evaluated a 3-furan-substituted lactone and found that (*R*)-**56** underwent the cross-coupling with 84% yield and >99% es (Table 5, entry 4).

To take advantage of the furan's utility for further manipulations, we derivatized product (*S*)-**57** by a Diels–Alder reaction (Scheme 6).[42b,52] The cycloaddition furnished the enantioenriched bicyclic acid **58** in 64% yield as a 1:1 mixture of diastereomers. Based on Woodward's analysis of the thermodynamic product of the reaction, the Diels–Alder reaction is anticipated to be highly exo selective.[52]

Scheme 6. Diels–Alder Reaction of Furan 57

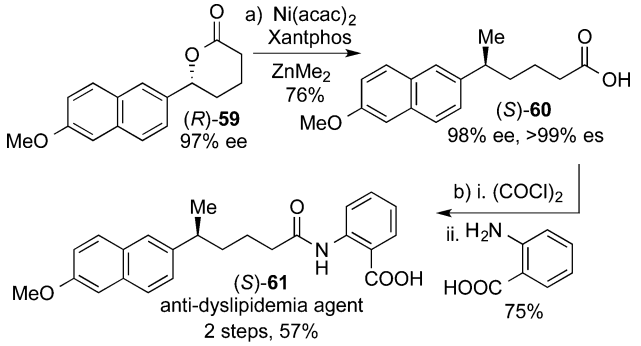


[a]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [b]Isolated yield after column chromatography.

Synthesis of Anti-dyslipidemia Agent 61. Dyslipidemia, a serum lipoprotein level disorder, is implicated in cardiovascular diseases and is often treated with niacin.[53] Anti-dyslipidemia agent **61** was disclosed as part of a campaign for discovery of niacin receptor agonists with reduced side effects.[54] Amide **61** was previously synthesized in seven steps and used chiral chromatography to separate the enantiomers.

We applied our methodology to the asymmetric synthesis of niacin receptor agonist **61** from commercially available lactone (*R*)-**59** (Scheme 7).[55] Utilizing our optimized cross-coupling

Scheme 7. [a] Enantiospecific Synthesis of Anti-Dyslipidemia Agent 61



[a](a) Ni(acac)$_2$ (10 mol %), Xantphos (20 mol %), $ZnMe_2$ (3.0 equiv), PhMe, rt, 24 h; (b) (i) $(COCl)_2$ (1.3 equiv), C_6H_6, rt, 2 h; (ii) anthranilic acid (1.1 equiv), C_6H_6, rt, 3 h.

conditions, carboxylic acid (*S*)-**60** was afforded in 76% yield with >99% es. A subsequent amide coupling directly affords enantioenriched anti-dyslipidemia agent **61** in 75% yield. The other enantiomer can easily be accessed by using (*S*)-**59**. Therefore, using our method either enantiomer of anti-dyslipidemia agent **61** can be prepared in two steps and 57% overall yield from commercially available starting material.

CONCLUSIONS

In summary, we have developed the nickel-catalyzed, stereospecific ring-opening cross-coupling reactions of aryl-substituted tetrahydrofurans, tetrahydropyrans, and lactones. Through judicious choice of starting materials, cyclic ether intermediates have been utilized to set the desired relative stereochemical relationships and allow for the selective synthesis of *syn*- and *anti*- deoxypropionate subunits. We have demonstrated the high stereospecificity of the reaction, where the dr of the product matches the dr of the starting O-heterocycles. The Negishi-type cross-coupling of benzylic lactones has allowed for the enantiospecific synthesis of

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enantioenriched carboxylic acids, which can be further derivatized. Using this methodology, we report the two-step, enantiospecific synthesis of an anti-dyslipidemia agent with easy access to either enantiomer. We are currently investigating the application of these methods toward the implementation of natural product editing to generate a library of unnatural polyketides for SAR studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, including X-ray crystallographic data. For supplementary crystallographic data see CCDC 1017411, 1017412, 1017413, and 1017414. 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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(18) For Kumada couplings of benzylic ethers with MeMgI, we have found that catalysts prepared from *rac*-BINAP, DPEphos, or Xantphos typically provide the highest yields. See ref 12 and the SI Section B for representative data. For most substrates, *rac*-BINAP provides highest yields. However, for heteroaromatic-containing substrates, DPEphos provides the highest yields. When alternative Grignard reagents are employed, the highest-yielding catalyst is typically Ni(dppe)Cl_2 (vide infra, Table 4).

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