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Article

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Ni-Catalyzed Regioselective Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling and Application to the Concise Synthesis of Lignan Natural Products

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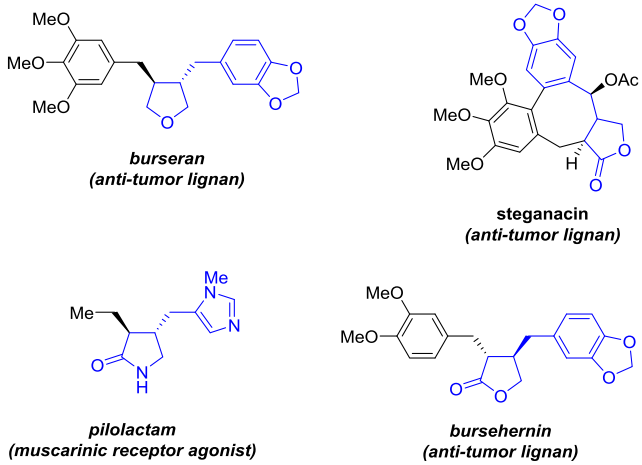
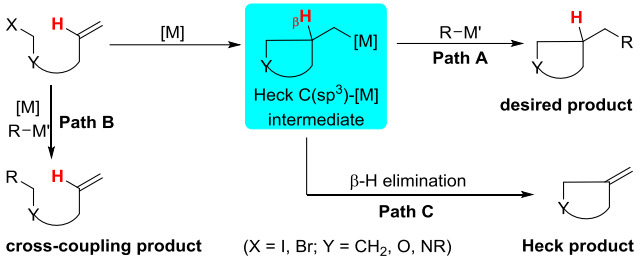
ABSTRACT: We disclose a (terpy)$NiBr_2$-catalyzed reaction protocol that regioselectively difunctionalizes unactivated olefins with tethered alkyl halides and arylzinc reagents. The reaction shows excellent functional group tolerance (such as ketones, esters, nitriles and halides) and moderate to good level of diastereoselectivity. The current cyclization/cross-coupling also tolerates molecules containing base-sensitive racemizable stereocenters, which are preserved without racemization during reaction. This cyclization/cross-coupling provides rapid access to (arylmethyl)carbo- and heterocyclic scaffolds, which occur widely as structural cores in various natural products and bioactive molecules. In order to show synthetic utility and generality, we have applied this new method in gram-scale quantities to the concise synthesis of six lignan natural products containing three different structural frameworks. We further conducted mechanistic investigations with radical probes and selectivity studies, which indicated that the current reaction proceeds via a single electron transfer (SET) process.

INTRODUCTION

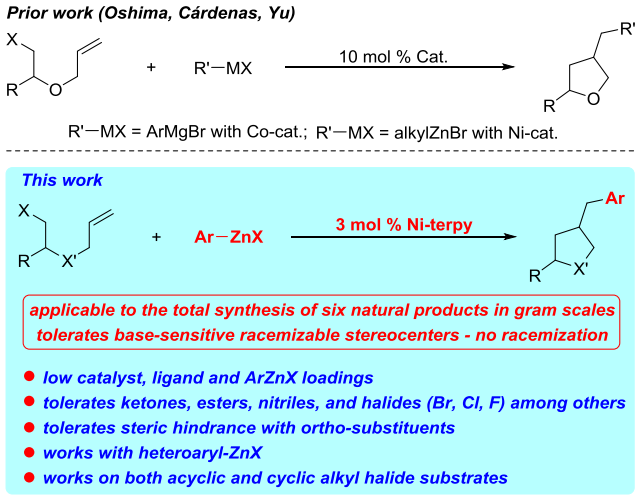
Transition metal (TM)-catalyzed dicarbofunctionalization of unactivated olefins via cross-coupling could afford a straightforward synthetic route to complex molecular structures, natural products and pharmaceuticals. Especially, the functionalization of olefins with tethered organohalides and organometallic reagents via a cyclization/cross-coupling process could furnish complex (carbomethyl)carbo- and heterocyclic scaffolds, such as benzylbutyrolactone, benzylbutyrolactol and benzylfuran, rapidly from simple and readily available chemical feedstock in one synthetic step. Such cyclic frameworks are profusely imbedded as structural cores in a variety of natural products and biologically active molecules such as lignans (Scheme 1).[1] Molecules containing these structural scaffolds generally display a wide range of biological activities including antiviral, antitumor and anti-HIV.[1]



Scheme 1. Lignan natural products and bioactive molecules containing (arylmethyl)heterocyclic cores



Scheme 2. Pathways for olefin dicarbofunctionalization and major side reactions



Scheme 3. Literature precedents and the current work

Despite tremendous synthetic potentials, the regioselective dicarbofunctionalization of unactivated olefins[2] via cross-coupling (Scheme 2, Path A) remains a formidable challenge due to the need to overcome two well-established transformations

that act as side reactions – a) direct cross-coupling of organohalides with organometallic reagents prior to olefin insertion (Scheme 2, Path B), and b) Heck reaction after β-hydride (β-H) elimination from a C(sp^3)-[M] intermediate generated *in situ* after olefin insertion (Scheme 2, Path C).[3] Therefore, the early examples of olefin 1,2-dicarbofunctionalization reactions[4] with organohalides and organometallic reagents generally required substrates without β-H's[5] or utilized conjugated dienes/styrenes to stabilize C(sp^3)-[M] intermediates as π-allyl-[M]/π-benzyl-[M] complexes.[6]

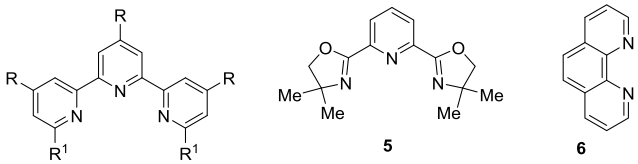
While no general solution has emerged yet,[7] a limited number of reactions have demonstrated that the use of base metal catalysts enables the cyclization/cross-coupling, a reaction that proceeds by a radical process[8] thus expediting olefin insertion and avoiding complications by β-H elimination.[9] In this respect, Oshima et al. disclosed in 2001 a (dppe)$CoCl_2$-catalyzed radical cyclization/cross-coupling of olefin-tethered alkyl halides with aryl Grignard reagents (Scheme 3).[10] In 2007, a similar catalytic system was developed by Cárdenas et al.[11] with pybox/$NiCl_2$ combination for cyclization/cross-coupling of olefin-tethered alkyl iodides with excess alkylzinc reagents.[12] While these early examples represent some progress in this area, the scope and synthetic utility of the cyclization/cross-coupling reactions is still limited especially for their application to the synthesis of natural products.

RESULTS AND DISCUSSION

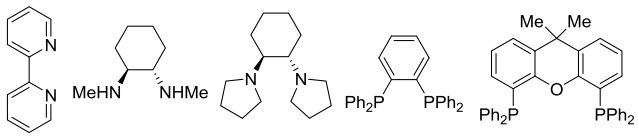
Recently, we reported a Cu-catalyzed cyclization/cross-coupling of alkylzinc reagents derived from olefin-tethered alkyl halides with aryl iodides that furnished (arylmethyl)heterocyclic cores.[13] While the functional group tolerance remained excellent, the reaction was limited to the use of electron-deficient and heteroaryl iodides owing to low reactivity of Cu-catalysts with electron-rich aryl halides. This limitation precluded the application of cyclization/cross-coupling to the synthesis of natural products, such as lignans (Scheme 1), that contain benzylbutyrolactone frameworks with electron-rich polyphenol derivatives. In order to expand the scope of cyclization/cross-coupling to the synthesis of natural products and bioactive molecules, we envisioned to utilize a combination of terpydine (terpy) and NiX_2 that is known to generate (terpy)NiR catalyst in the presence of RZnX and efficiently produce alkyl radicals from alkyl halides during Negishi coupling.[14]

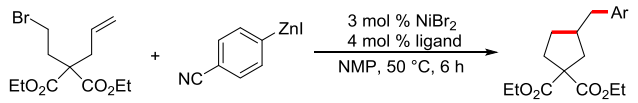
In our efforts to examine the efficacy of (terpy)NiX_2 as a catalyst, we conducted the reaction of olefin-tethered alkyl bromide **12**-Br with (4-cyanophenyl)zinc iodide. We were pleased to find that reaction proceeded with 3 mol% $NiBr_2$ and 4 mol% terpy in NMP at 50 °C affording the cyclization/cross-coupling product **13** in 87% yield (Table 1, entry 1).[15] We further examined *t*Bu, Me and MeO-substituted terpy derivatives **2**-**4**, of which only the *t*Bu-substituted terpy **2** furnished the expected product in comparable yield (entries 2-3). A similar tridentate ligand, pybox **5**, afforded the product only in 12% yield (entry 4). Nitrogen- and phosphorus-based bidentate ligands such as phen **6**, bipy **7**, bis-amines **8**-**9**, dppbz **10** and xantphos **11** also furnished the product in low to moderate yields (entries 5-6). The current reaction is strongly ligand-controlled as only a trace amount of the product **13** was formed in the absence of terpy (entry 7). The reaction also did not proceed in the absence of $NiBr_2$ (entry 8). The product **13** was formed in lower yields in shorter reaction time and at room temperature (entries 9-10), and in moderate yields when $NiBr_2$ was replaced with $Ni(cod)_2$ or $Ni(PPh_3)_4$ (entry 11). While the reaction did not proceed in CH_2Cl_2 and toluene, the product **13** was generated in moderate yields in THF, dioxane, DMF or DMSO (entries 12-14).

Table 1. Optimization of reaction conditions[a]



1, R, R^1 = H; **2**, R = *t*Bu, R^1 = H; **3**, R = H, R^1 = Me; **4**, R = H, R^1 = OMe





12-Br 1.5 equiv (ArZnI) **13**

entry	modified conditions	ligand	yield of **13** (%)
1	none	**1**	87 (81)
2	none	**2**	86
3	none	**3** or **4**	37-46
4	none	**5**	12
5	none	**6**, **7**, **8** or **9**	37-62
6	none	**10** or **11**	16-24
7	none	none	trace
8	no $NiBr_2$	**1**	0
9	3 h	**1**	58
10	room temperature	**1**	42
11	$Ni(cod)_2$ or $(Ph_3P)_4Ni$ instead of $NiBr_2$	**1**	50-62
12	CH_2Cl_2 or toluene instead of NMP	**1**	0
13	DMF or DMSO instead of NMP	**1**	54-72
14	THF or dioxane instead of NMP	**1**	25-35

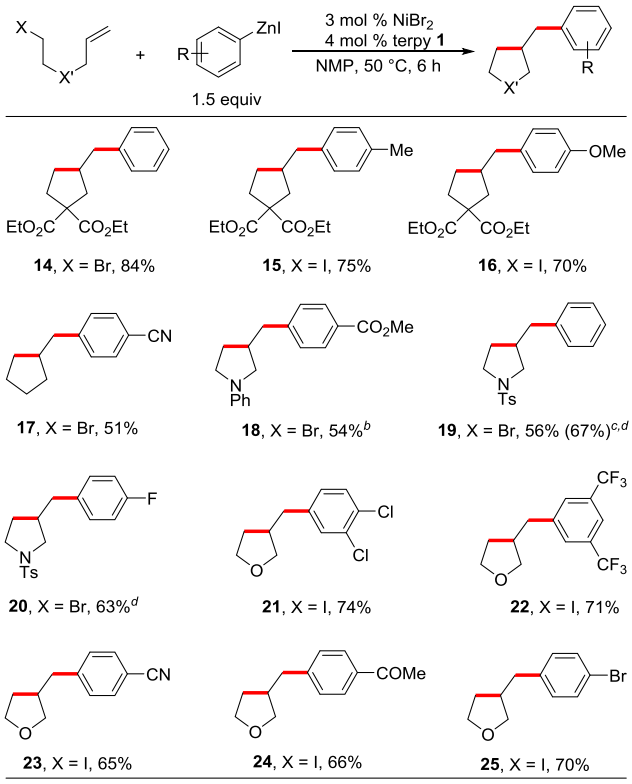
[a]Yields were determined by ^{1}H NMR using pyrene as an internal standard. Value in parenthesis is the isolated yield from a 0.5 mmol scale reaction.

Scope of the Cyclization/Cross-Coupling. With the optimized conditions in hand, we studied the scope of the current cyclization/cross-coupling reaction with respect to both the olefin-tethered alkyl halides and arylzinc reagents (Table 2). A variety of olefin-tethered alkyl halides can be cyclized to furnish carbocycles (**14**-**17**), and *N*- (**18**-**20**) and *O*-heterocycles (**21**-**25**) in good yields.[16,17] The reaction proceeds well with both electron-rich and deficient arylzinc reagents, which affords products in good to excellent yields. Synthetically important functional groups such as nitriles (**17** and **23**), esters (**18**), ketones (**24**) and halides (Br, Cl, F) (**20**, **21** and **25**) are also tolerated on arylzinc reagents.

We further examined the scope of the reaction with respect to olefin-tethered alkyl halides containing pre-existing stereocenters in order to determine diastereoselectivity of the reaction (Table 3). Olefin-tethered alkyl iodides such as *trans*-2-(allyloxy)-3-iodotetrahydrofuran, *trans*-1-(allyloxy)-2-iodocyclohexane, *trans*-2-(allyloxy)-3-iodotetrahydro-2H-pyran, and 1-

(1-(allyloxy)-2-iodoethoxy)butane could be cyclized and cross-coupled with arylzinc reagents bearing electron-donating groups (Me, OMe) (**26**-**31**), electron-withdrawing and highly sensitive groups (CF_3, CN, COMe, Br, Cl) (**33**-**38** and **42**-**45**), and *ortho*-substituents (**27**, **28**, **31**) to furnish bicyclic heterocycles in good to excellent yields. The reaction also tolerates ketones and esters in olefin-tethered alkyl halides, which could be coupled after cyclization with arylzinc reagents containing other sensitive functional groups such as nitrile (**45**). This example demonstrates the tolerance of multiple, highly sensitive and synthetically important functional groups, such as CN, COMe and CO_2Me, together in one molecule. These products were formed in moderate to good levels of diastereoselectivity with the major diastereoisomers containing three contiguous stereocenters in all-*cis* configuration. Olefin-tethered alkyl iodides could also be cyclized and cross-coupled with heteroarylzinc reagents, such as (2-chloropyridin-4-yl)zinc iodide, thiophen-2-ylzinc iodide and di(furan-2-yl)zinc (**38**-**41**), which afforded the products in good to excellent yields with moderate to good degrees of diastereoselectivities.

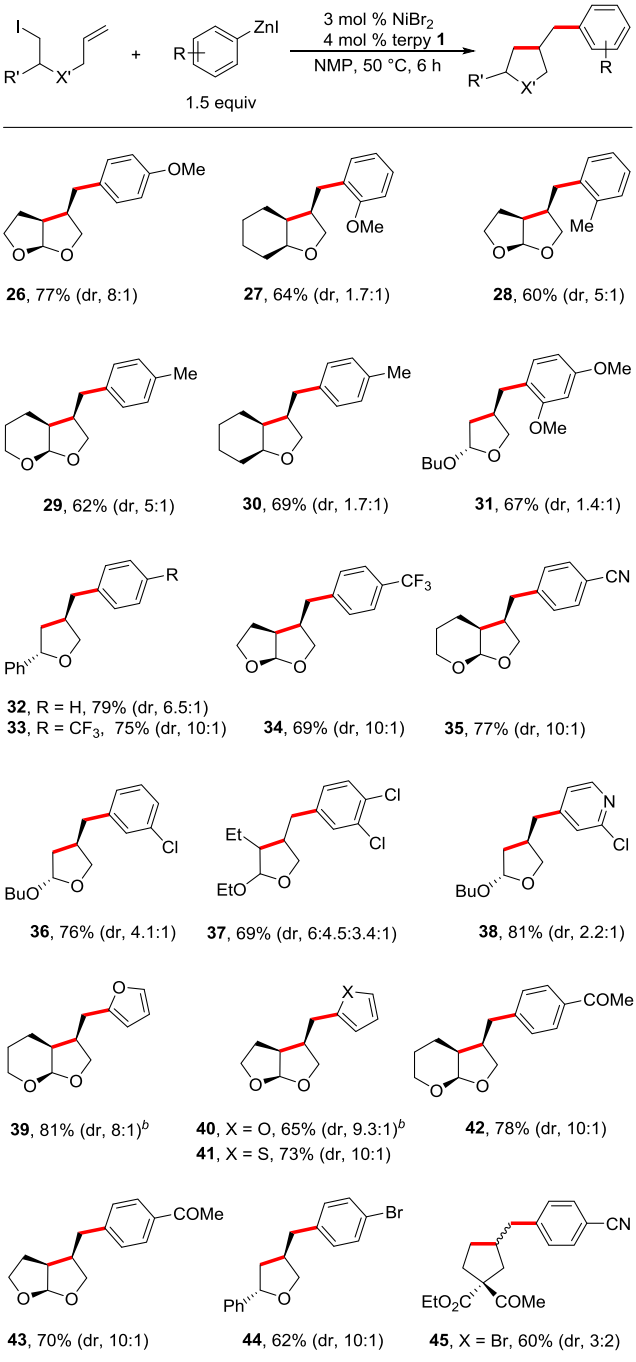
Table 2. Cyclization/cross-coupling of olefin-tethered alkyl halides[a]



[a]Values are isolated yields from 0.5 mmol scale reactions. [b]Room temperature, 12 h. [c]Value in parenthesis is the yield when 1 equiv Ph_2Zn was used instead of PhZnI. [d]8 h.

We further examined the tolerance of molecules containing racemizable stereocenters under our reaction conditions. In this process, we utilized two commercially available, enantiomerically enriched compounds containing one chiral center – *N*-Boc-D-proline methyl ester (**46**, *R*-enantiomer) and (*R*)-dimethylmethylsuccinate (**47**) – as stoichiometric additives in

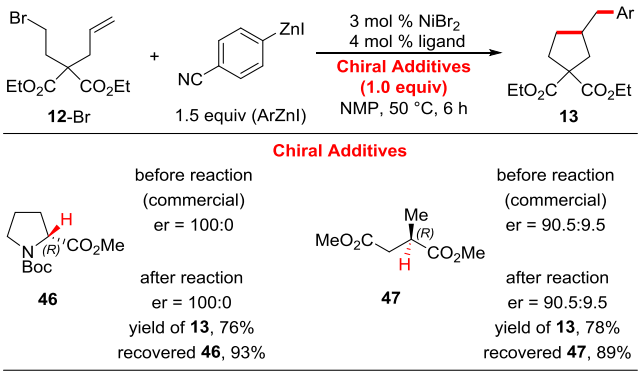
Table 3. Diastereoselective cyclization/cross-coupling[a]



[a]Values are isolated yields from 0.5 mmol scale reactions. dr was determined by ^{1}H NMR and GC. [b]1 equiv di(furan-2-yl)zinc was used. 10 h.

our standard reaction of olefin-tethered alkyl bromide **12**-Br with (4-cyanophenyl)zinc iodide (Table 4). After the reaction was complete, the additives were isolated by column chromatography. Determination of enantiomeric ratios (er's) of the isolated compounds **46** and **47** by chiral high performance liquid chromatography (HPLC) indicated that their er's remained unchanged compared to their er's prior to addition to the reaction. These results confirmed that our cyclization/cross-coupling reaction condition tolerates base sensitive and racemizable stereocenters. These results also clearly demonstrate the importance of our current reaction for the construction or manipulation of synthetically challenging molecules containing base sensitive, enantioenriched chiral centers.

Table 4. Tolerance of base-sensitive and racemizable stereocenters[a]



[a]Reactions were run in 0.4 mmol scale in 2.0 mL NMP with 1.0 equiv of chiral additives. The additives were isolated by column chromatography and their er's were determined by chiral HPLC.

Application to the Synthesis of Natural Products. We also applied the current method to the concise synthesis of six lignan natural products – (±)-dimethylretrodendrin, (±)-kusunokinin, (±)-dimethylmatairesinol, (±)-bursehernin, (±)-yatein and (±)-collinusin – with three different structural frameworks that contain benzylbutyrolactone backbones (Scheme 4-6). These types of lignan natural products containing dibenzylbutyrolactone and aryltetralin scaffolds display a wide range of biological properties such as antibiotic, fungicidal, antiviral, antitumor and anti-HIV.[18] Both (±)-dimethylretrodendrin and (±)-collinusin belong to the class of aryltetralin lignans, which show antitumor activities by functioning as potent inhibitors of human DNA topoisomerase II.[19] Collinusin was isolated from the leaves of *Cleistanthus collinus* (Roxb.) that has insecticidal and piscicidal activities.[20] Kusunokinin shows antitrypanosomal and insecticidal activities.[21] Bursehernin shows potent cytotoxic activities in colon, prostate and breast cancer cell lines among others.[22] Recent studies have shown that yatein exhibits antiproliferative activity[23] and suppresses herpes simplex virus type 1 replication in HeLa cells.[24]

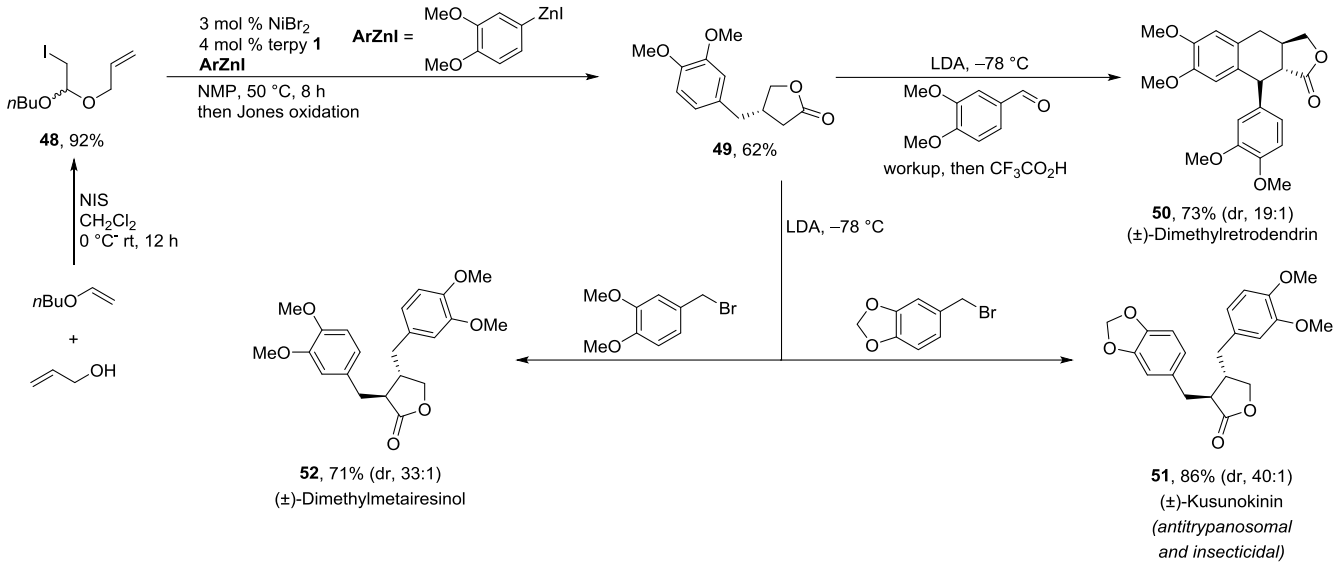
Prior synthesis of these lignan natural products generally required a multi-step process to construct the benzylbutyrolactone skeleton.[25] Our new method allowed us to synthesize the benzylbutyrolactone structure in one-pot two steps in gram-scale quantities. For example, the intermediate lactone **49** was constructed from the cyclization/cross-coupling of 1-(1-(allyloxy)-2-iodoethoxy)butane (**48**) with (3,4-dimethoxyphenyl)zinc iodide followed by oxidation of the crude product with the Jones reagent (Scheme 4). The reaction was conducted in 10 mmol scale, which afforded the lactone **49** in 62% isolated yield (1.464 g). The lactone **49** could then be treated with 3,4-dimethoxybenzaldehyde after deprotonation with lithium diisoproylamide (LDA) at -78 °C followed by Friedel-Crafts alkylation in presence of trifluoroacetic acid to furnish (±)-dimethylretrodendrin (**50**) as a 19:1 diastereomeric mixture in 73% isolated yield (Scheme 4). The intermediate lactone **49** could also be benzylated with (3,4-methylenedioxy)benzyl bromide and 3,4-dimethoxybenzyl bromide to afford (±)-kusunokinin (**51**) and (±)-dimethylmatairecinol (**52**), respectively, in high yields and diastereoselectivities (Scheme 4).

We also constructed the intermediate lactone **53** in a gram-scale quantity (11 mmol, 60% yield, 1.453 g), which was subsequently converted to (±)-bursehernin (**54**) and (±)-yatein (**55**) in high yields and diastereoselectivities after benzylation with 3,4-dimethoxybenzyl bromide and 3,4,5-trimethoxybenzyl bromide, respectively (Scheme 5).

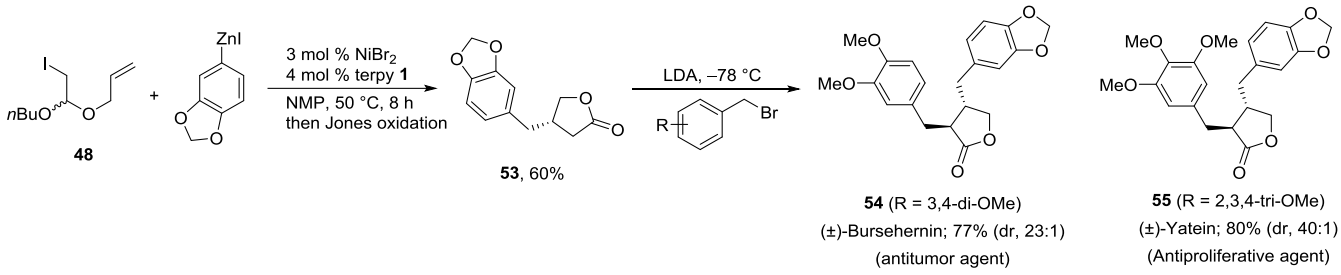
We also utilized the current cyclization/cross-coupling method to synthesize (±)-collinusin in two-pot three steps from readily available starting materials via carbonylbutyrolactone **57** (Scheme 6). The latest known synthesis of a similar lignan natural product required seven linear synthetic sequence to construct the dihydronaphthofuranone core.[26] In our synthesis, we utilized the highly functionalized (2-aryoylaryl)zinc iodide **56** as the coupling partner to construct the carbonylbutyrolactone core **57** in one-pot two steps in 70% yield (2.5 mmol scale, 0.672 g). The corresponding aryl iodide for the arylzinc **56** is readily prepared in one step by the Friedel-Crafts reaction of 1,3-benzodioxole with the commercially available 6-iodoveratric acid (See SI for details). The carbonylbutyrolactone **57** was then treated with lithium diisopropylamide (LDA) followed by $SOCl_2$ to furnish (±)-collinusin (**58**) in 65% yield. We note that the concise synthesis of (±)-collinusin (**58**) by this new method became feasible due to the ability to readily access the arylzinc reagent **56** containing a carbonyl group.

Mechanistic Studies. We have further conducted mechanistic investigations of the current reaction, and proposed a catalytic cycle (Scheme 7) based on our results and prior reports on the Ni/terpy-catalyzed Negishi cross-coupling of alkyl halides with organozinc reagents.[27] Negishi cross-coupling catalyzed by a combination of NiX_2 and terpyridine has been shown by both experiments and density functional theory (DFT) calculations to proceed with the generation of a (terpy)NiX catalyst (**59**) that undergoes transmetalation with organozinc reagents to form a (terpy)NiR species.[14] The alkyl halides are then reduced by a single electron transfer (SET) from (terpy)NiR species followed by recombination of the resultant alkyl radicals with (terpy)Ni(X)(R) and reductive elimination to generate desired products. Under our reaction conditions where olefin-tethered alkyl halides are used, the alkyl radicals generated by electron transfer from a (terpy)NiAr species (**60**) would undergo cyclization onto the tethered olefin to generate a cyclized primary alkyl radical prior to recombination with the (terpy)Ni(X)(Ar) species (**62**) to generate (terpy)Ni(R)(Ar) species (**63**). Reductive elimination from this species **63** then furnishes the desired product with the regeneration of the active (terpy)NiX catalyst (**59**).

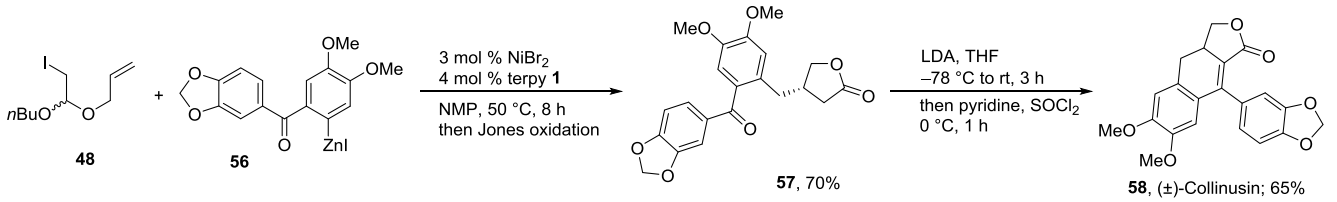
In order to determine the mechanistic similarity of our reaction with the Ni/terpy-catalyzed direct cross-coupling of alkyl halides with organozinc reagents, we conducted selectivity studies by reacting separately *n*-octyl iodide and the olefin-tethered primary alkyl iodide **12**-I with the excess of two electronically biased arylzinc reagents (Schemes 8 and 9). The premise of the experiment is that two separate reactions proceeding via analogous reaction intermediates under otherwise identical reaction conditions would generate similar ratios of products in comp-



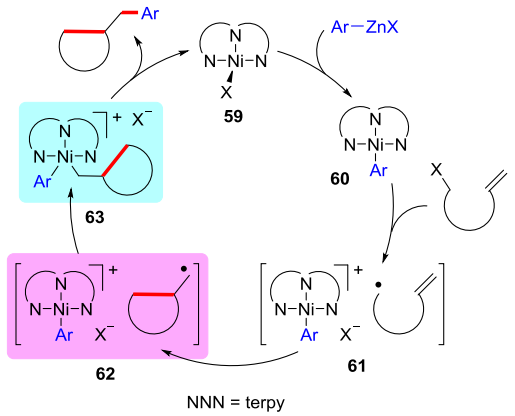
Scheme 4. Concise synthesis of (±)-dimethylretrodendrin, (±)-kusunokinin and (±)-dimethylmatairesinol



Scheme 5. Concise synthesis of (±)-bursehernin and (±)-yatein



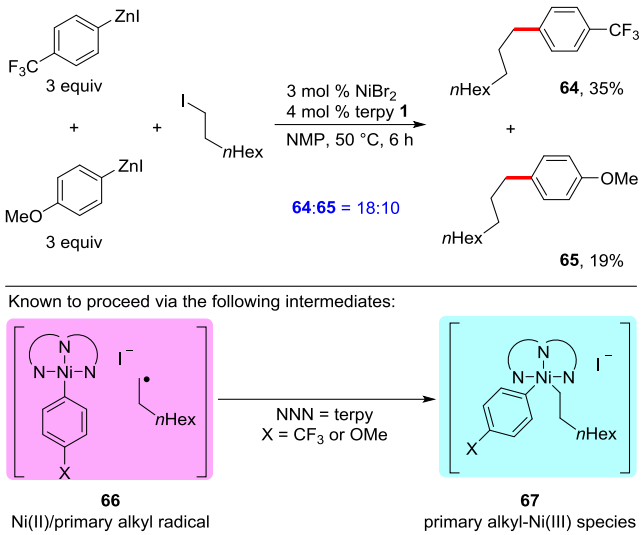
Scheme 6. Concise synthesis of (±)-collinusin



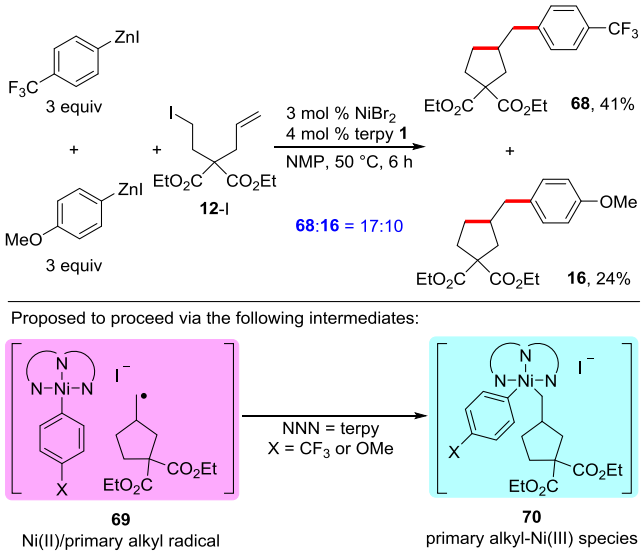
Scheme 7. Proposed catalytic cycle

etition experiments. In one experiment, we allowed *n*-octyl iodide to freely compete for reaction with the excess of (4-(trifluoromethyl)phenyl)zinc iodide and (4-methoxyphenyl)zinc iodide under our standard reaction condition (Scheme 8). This reaction, which is known to proceed via the generation of primary alkyl radical/Ni(II) and primary alkyl-Ni(III) species (**66** and **67**),[14] furnished 4-*n*-octylbenzotrifluoride (**64**) and 4-*n*-octylanisole (**65**) in an 18:10 ratio (combined yield, 54%). In another experiment, a similar olefin-tethered primary alkyl iodide **12**-I was allowed to freely compete for reaction with the excess of (4-(trifluoromethyl)phenyl)zinc iodide and (4-methoxyphenyl)zinc iodide under our standard reaction condition (Scheme 9). This reaction also furnished the corresponding benzotrifloride and anisole products **68** and **16** in

17:10 (combined yield, 65%), a ratio that is similar to the one observed for the competition reaction of *n*-octyl iodide. The results of these competition experiments indicate that the terpy/$NiBr_2$-catalyzed direct cross-coupling of alkyl halides with arylzinc reagents and the cyclization/cross-coupling of olefin-tethered alkyl halides with arylzinc reagents proceed via similar reaction intermediates **66**-**67** and **69**-**70** as indicated in Schemes 8 and 9.



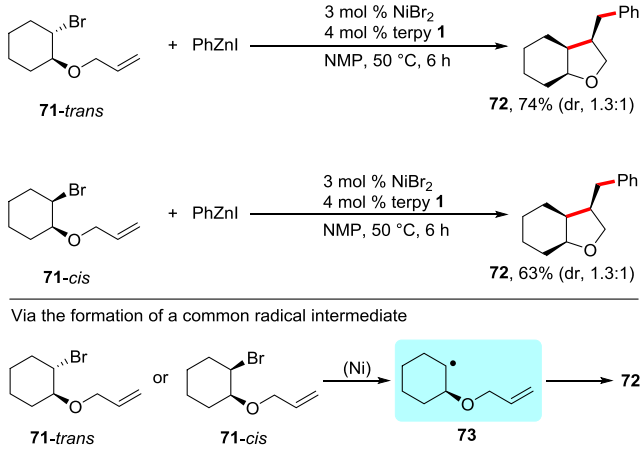
Scheme 8. Selectivity in Negishi cross-coupling of primary alkyl iodide with electronically biased arylzinc reagents



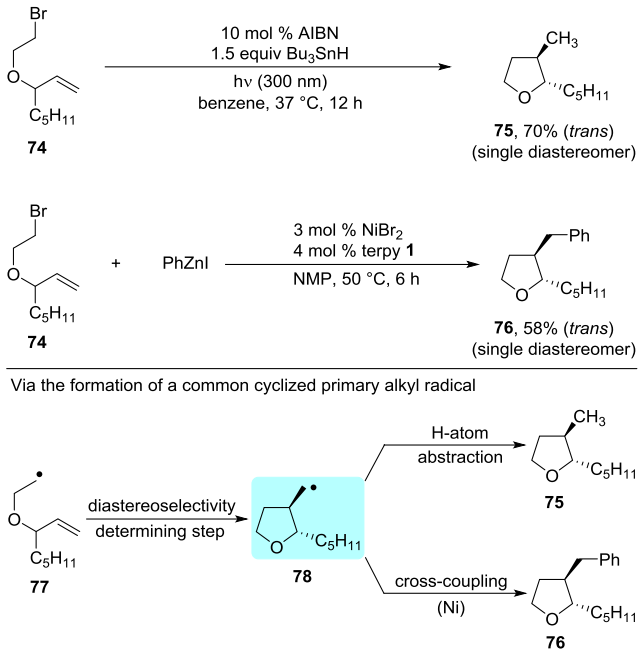
Scheme 9. Selectivity in cyclization/cross-coupling with electronically biased arylzinc reagents

Next, we conducted experiments to determine if the reaction involved alkyl radical intermediates. Our first experiment involved the determination of stereochemical outcomes of a reaction involving the *cis*- and *trans*-isomers of 1-(allyloxy)-2-bromocyclohexane (**71**) (Scheme 10). In this process, we reacted *cis*- and *trans*-1-(allyloxy)-2-bromocyclohexane (**71**) separately with PhZnI under the standard reaction condition. Both *cis*- and *trans*-isomers generated the cyclization/cross-coupling product **72** in 63% and 74% yields, respectively, with the same degree of diastereoselectivity (1.3:1). These results indicate that the reactions of both *cis*- and *trans*-isomers proceed via the formation of the same radical intermediate **73** with the loss of stereochemistry at the C-Br chiral center.

In order to further confirm the formation of alkyl radical intermediates, we also performed an experiment with a racemic, chiral olefin-tethered alkyl bromide **74** under our reaction condition and compared its diastereoselectivity with that of the reaction involving the same alkyl bromide **74** under a condition that is known to generate alkyl radicals as intermediates (Scheme 11). Herein, we reacted the racemic, chiral alkyl bromide **74** with Bu_3SnH in the presence of 10 mol % 2,2′-Azobis(2-methylpropionitrile) (AIBN) as a radical initiator[28] under UV light (300 nm). This reaction, which is known to proceed with the formation of uncyclized and cyclized alkyl radicals **77** and **78**,[28] furnished the *trans*-isomer of the cyclization/H-atom abstraction product **75** as a single diastereomer in 70% yield. In a separate experiment, the racemic, chiral alkyl bromide **74** was subjected to our standard cyclization/cross-coupling reaction condition using PhZnI as a coupling partner. This latter reaction also furnished the *trans*-isomer of the cyclization/cross-coupling product **76** as a single diastereomer in 58% yield. The results of these experiments indicate that the current cyclization/cross-coupling proceeds via the same diastereoselectivity-determining cyclization step as the known AIBN-catalyzed radical cyclization reaction via the formation of the same alkyl radical intermediates **77** and **78** prior to the formation of the cyclization/cross-coupling product **76**.



Scheme 10. Diastereoselectivity studies with *cis*- and *trans*-1-(allyloxy)-2-bromocyclohexane (**71**)



Scheme 11. Diastereoselectivity in the known radical cyclization and the current cyclization/cross-coupling reactions

CONCLUSION

In summary, we have developed an efficient (terpy)$NiBr_2$ catalytic system for cyclization/cross-coupling of olefin-tethered alkyl halides with arylzinc reagents. The reaction tolerates a wide range of synthetically important functional groups and base-sensitive racemizable stereocenters. This method affords (arylmethyl)carbo- and heterocyclic structures that widely occur as structural motifs in a wide range of lignan natural products and bioactive molecules. The use of this method for the concise synthesis of six lignan natural products with three different structural frameworks in gram-scale quantities clearly demonstrates the practical application of the olefin dicarbofunctionalization reaction to the construction of complex natural products, bioactive molecules and pharmaceuticals in short synthetic routes via unprecedented retrosynthetic disconnections. In addition, we have also conducted mechanistic studies with radical probes and competition experiments, which indicate that the current cyclization/cross-coupling reaction proceeds via a SET process.

EXPERIMENTAL SECTION

General Information. All the reactions were set up inside a nitrogen-filled glovebox and all the chemicals were handled under nitrogen atmosphere unless stated otherwise. All the glassware including the 4-dram and 1-dram borosilicate (Kimble-Chase) vials, and pressure vessels were properly dried in an oven before use. Bulk solvents were obtained from EMD and anhydrous solvents (DMF, DMA, DMSO, NMP, dioxane, toluene) were obtained from Sigma-Aldrich, and were used directly without further purification. Deuterated solvents were purchased from Sigma-Aldrich. $NiBr_2$ was purchased from Alfa-Aesar. Aryl halides were purchased from Acros, Sigma-Aldrich, Oakwood, TCI-America, Matrix and Alfa-Aesar. $ZnCl_2$ (99.95%) was obtained from Alfa-Aesar was used as received. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker instrument (300, 75, and 282 MHz respectively) and internally referenced to the residual solvent signals of $CDCl_3$ for ^1H and ^{13}C NMR, and ^{19}F NMR at 7.26, 77.16 ppm, −164.9 ppm respectively. The chemical shifts of NMR and the coupling constants (*J*) for ^1H, ^{13}C, and ^{19}F NMR are reported in δ parts per millions (ppm) and in Hertz, respectively. The following conventions are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; br, broad. High resolution mass spectra for new compounds were recorded at the Mass Spectrometry, Department of Chemistry and Chemical Biology, University of New Mexico (UNM), University of Texas Austin and University of California, Riverside. All NMR spectra were collected at Department of Chemistry and Chemical Biology, University of New Mexico (UNM). The HPLC used was Waters e2695 separations module and Waters 2489 UV/Vis detector. Infrared (IR) spectra were recorded on Bruker Alpha-P ATR-IR at UNM and ν_{max} is reported in cm^{-1}. The starting materials diethyl-2-allyl-2-(2-bromoethyl)malonate[29](**12**-Br), 3-(2-iodoethoxy)prop-1-ene[10c], N-allyl-N-(2-bromoethyl)-4-methylbenzenesulfonamide[30], *N*-allyl-*N*-(2-bromoethyl)aniline[31], *trans*-2-(allyloxy)-3-iodotetrahydrofuran and *trans*-2-(allyloxy)-3-iodotetrahydro-pyran[8g,32], *trans*-1-(allyloxy)-2-iodocyclohexane[33], (1-(allyloxy)-2-iodoethyl)benzene[34], 1-(1-(allyloxy)-2-iodoeth-oxy)butane[8g], 1-(allyloxy)-1-ethoxy-2-iodobutane[8g], 3-(2-bromoethoxy)oct-1-ene[8c], *trans*-1-(Allyloxy)-2-bromocyclohexane[33], *cis*-1-(allyloxy)-2-bromocyclohexane[35] and 3-(2-bromoethoxy)oct-1-ene[8c] were prepared according to the given literature procedure.

General procedure for the preparation of arylzinc reagent

Procedure A.[36] To a Schlenk flask in a glovebox, anhydrous LiCl (210 mg, 5 mmol) and zinc powder (492 mg, 7.5 mmol) was added and the mixture was dried under high vacuum at 150 °C to 170 °C for 2 h outside the glovebox. After 2 h, it was cooled down to room temperature and the reaction flask was flushed with nitrogen. Then it was again taken to a glovebox and anhydrous THF (5mL) was added with stirring the solution at room temperature. Later, zinc was activated with the addition of 5 mol% of $BrCH_2CH_2Br$ and 3 mol% of TMSCl to the zinc/THF suspension and the mixture was stirred for 5 minutes at room temperature. To this stirred solution was added corresponding aryl iodides (5 mmol) (neat) dropwise (liquid) or portion-wise (solid) and the reaction mixture was either heated at 50 °C for heteroaryl iodides for 6 h or refluxed for electron-deficient and electron rich aryl iodides for 12-96 h. The final concentration of the arylzinc reagent was determined by titration with molecular iodine in THF.[37]

Procedure B.[38] Under nitrogen atmosphere, naphthalene (563.9 mg, 4.4 mmol) was dissolved in anhydrous THF (4 ml) in 15 mL pressure vessel, potassium (156.4 mg, 4 mmol) was added to the solution and stirred overnight at room temperature. The solution turned dark green immediately indicating the generation of potassium naphthalenide. Anhydrous $ZnCl_2$ (272.6 mg, 2.0 mmol) was then suspended in dry THF (4 mL) in a separate vial, which was then added dropwise to the potassium naphtalenide solution. The resultant solution was then stirred for 12 h at room temperature. Aryl iodide (1.0 mmol, neat) was added to the stirred solution and stirred again overnight at room temperature. Thus formed organozinc was filtered through Celite upon completion of the reaction (monitored by GC for the remaining starting aryl iodides as well as the protonation product by quenching the organozinc reagents with acetic acid). The final concentration was determined by titration with molecular iodine in THF.[37]

Procedure C.[39] Under nitrogen atmosphere, LiCl (63 mg, 0.3 mmol), $InCl_3$ (30mg, 0.03 mmol) and Zn powder (983 mg, 15 mmol) were weigh out in a dry schlenk-tube equipped with a stir bar. The mixture was heated at 170°C under high vaccum for 3 h. After cooling down to room temperature, the tube was flushed with nitrogen and freshly distilled THF (5mL) and DMPU (5ml) was added and stirred at room temperature. Later TMSCl (3 mol%) and aryl iodide (5 mmol) was added to the suspension. The mixture was further stirred at room temperature for 1 h. The completion of reaction was monitored by GC-analysis of acetic acid-quenched aliquots. The excess zinc dust was allowed to settle down and filtered through celite pad. Finally, the concentration of resulting organozinc was determined by titration with molecular iodine in THF.[37]

General procedure for screening reaction conditions

In a glovebox, THF solution of (4-cyanophenyl)zinc iodide (0.150 mmol) was taken in a 1-dram vial and the solvent was removed under vacuum. To the ArZnI residue was added $NiBr_2$ (0.65 mg, 0.003 mmol), terpyridine (0.9 mg, 0.004 mmol), and diethyl-2-allyl-2-(2-bromoethyl)malonate (30.6 mg, 0.10 mmol). The mixture was then dissolved in 0.5 mL of NMP. The vial was tightly capped and removed from the glovebox. It was placed in a hotplate preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature and 50 µL of pyrene (0.010 mmol, 0.2 M stock solution) as an internal standard was added, diluted with EtOAc (2 mL) and filtered through a short pad of silica gel in a pipette. The filtrate was then analyzed by GC, GC-MS and ^{1}H NMR.

General procedure for large scale reaction

In a glovebox, arylzinc stock solution in THF (0.750 mmol) was taken in a 15mL sealed tube and the solvent was removed under vacuum. To the residue of ArZnI was added $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.020 mmol), and olefin-tethered alkyl halides (0.5 mmol). The mixture was then dissolved in NMP (2.5 mL). The sealed tube was tightly capped and removed from the glovebox. It was then placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent.

Determination of diastereoselectivity and identification of major diastereoisomers. The diastereoselectivity was determined based on crude ^{1}H NMR and crude GC trace. The corresponding GC traces are provided in the respective places. The dr's in the reported ^{1}H NMR spectra of analytically pure compounds do not reflect the actual dr's of the reaction. The diastereomer either contained the other diastereomer in analytically pure samples, or a small fraction of the separated minor diastereomer was contaminated with some other impurities, which are not included in the reported yields. Therefore, the reported ^{1}H NMR show different dr's than those that are actually formed in the reaction. The structures of major diastereomers were determined by comparing ^{1}H NMR spectra and the coupling constants with the same or similar compounds in the literature.[8g,10a,11,13a]

Characterization data for new compounds

*Ethyl 2-acetyl-2-(2-bromoethyl)pent-4-enoate***.** The title compound was prepared according to the modified procedure described in the given literature[40]. To a dry flask, NaH (864 mg, 36 mmol) was weigh out and dry THF (30 mL) was added. The flask was stirred and cooled to 0 °C. To the stirring suspension, ethyl acetoacetate (30 mmol) was added dropwise for 5 minutes. The resulting mixture was stirred at room temperature for an hour. Later, the reaction mixture was again cooled down to 0 °C and allylbromide (2.83 mL, 33 mmol) was added dropwise in the mixture. After the complete addition of allylbromide, the reaction mixture was stirred at room temperature for 12 h. It was diluted with EtOAc (30 mL) and washed with H_2O (15 mL). The ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent and colorless oil of ethyl 2-acetyl-2-(2-bromoethyl)pent-4-enoate was obtained in 90% yield.

To a dry flask, NaH (720 mg, 30 mmol) was weigh out and dry DMF (20 mL) was added. The flask was stirred and cooled to 0 °C. To the stirring suspension, ethyl 2-acetylpent-4-enoate (20 mmol) was added dropwise for 5 minutes. The resulting mixture was stirred at room temperature for an hour. Later, the reaction mixture was again cooled down to 0 °C and dibromoethane (3.5 ml, 40 mmol) was added dropwise in the mixture. After the complete addition of dibromoethane, the reaction mixture was stirred at room temperature for 12 h. It was then diluted with EtOAc (20 mL) and washed with H_2O (10 mL). The ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The title compound was obtained as a colorless oil (3.03 ml, 55% yield) after purification by silica gel column chromatography (Hex : Et_2O = 8:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.28 (t, *J* = 7.5 Hz, 3H), 2.16 (s, 3H), 2.30-2.40 (m, 1H), 2.45-2.56 (m, 1H), 2.64 (d, *J* = 9.0 Hz, 2H), 3.20-3.34 (m, 2H), 4.23 (q, *J* = 7.0 Hz, 2H), 5.07-5.17 (m, 2H), 5.51-5.64 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 26.9 27.0, 35.3, 36.6, 61.9, 63.4, 119.8, 131.6, 171.0, 203.4.

*Diethyl 3-(4-cyanobenzyl)cyclopentane-1,1-dicarboxylate **(13)**:*[13a] This reaction was performed by using organozinc prepared according to procedure A in our standard condition. The title compound **13** was obtained as a yellow oil (133.2 mg, 81% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.22 (q, *J* = 7.9 Hz, 6H), 1.31-1.41 (m, 1H), 1.76-1.84 (m, 2H), 2.11-2.39 (m, 4H), 2.64-2.76 (m, 2H), 4.11-4.21 (m, 4H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 32.0, 33.7, 40.2, 41.2, 41.4, 59.9, 61.5, 109.9, 119.1, 129.5, 132.2, 146.9, 172.5, 172.6; **IR (neat):** 2980, 2937, 2227, 1723, 1607,1249, 1156, 1024; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{19}H_{24}NO_4$ 330.1705; found 330.1694.

*Diethyl 3-benzylcyclopentane-1,1-dicarboxylate **(14)**:*[41] This reaction was performed by using organozinc prepared according to procedure A in our standard condition. The title compound **14** was obtained as a colorless oil (127.6 mg, 84% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.23 (q, *J* = 7.9 Hz, 6H), 1.34-1.44 (m, 1H), 1.80-1.87 (m, 2H), 2.04-2.44 (m, 4H), 2.58-2.72 (m, 2H), 4.12-4.22 (m, 4H), 7.14-7.29 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 32.0, 33.8, 40.4, 41.3,

41.6, 60.0, 61.3, 61.4, 125.9, 128.3, 128.8, 141.3, 172.7, 172.8; **IR (neat):** 2980, 1725, 1453, 1247, 1155, 1096 ; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{18}H_{25}O_4$ 305.1753; found 305.1737.

Diethyl 3-(4-methylbenzyl)cyclopentane-1,1-dicarboxylate ***(15).*** The organozinc prepared for this reaction was according to procedure A. The title compound **15** was obtained as a colorless oil (119.2 mg, 75% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1) **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.23 (q, *J* = 6.9 Hz, 6H), 1.29-1.43 (m, 1H), 1.76-1.86 (m, 2H), 2.08-2.43 (m, 4H), 2.31 (s, 3H), 2.54-2.68 (m, 2H), 4.12-4.22 (m, 4H), 7.03-7.12 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 21.1, 32.0, 33.8, 40.4, 40.9, 41.7, 60.0, 61.3, 128.7, 129.0, 135.3, 138.2, 172.7, 172.8**; IR (neat):** 2980, 1725, 1445, 1366, 1247, 1096; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{19}H_{27}O_4$ 319.1909; found 319.1910.

Diethyl 3-(4-methoxybenzyl)cyclopentane-1,1-dicarboxylate ***(16).*** The organozinc prepared for this reaction was according to procedure A. The title compound **16** was obtained as a colorless oil (116.9 mg, 70% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.23 (q, *J* = 6.9 Hz, 6H), 1.28-1.45 (m, 1H), 1.77-1.84 (m, 2H), 2.08-2.42 (m, 4H), 2.52-2.65 (m, 2H), 3.78 (s, 3H), 4.12-4.21 (m, 4H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 31.9, 33.7, 40.3, 41.8, 55.2, 60.0, 61.3, 113.7, 129.6, 133.3, 157.8, 172.7, 172.8; **IR (neat):** 2980, 1724, 1611, 1443, 1242, 1095; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{19}H_{27}O_5$ 335.1858; found 335.1858.

4-(cyclopentylmethyl)benzonitrile ***(17).***[13a] The organozinc prepared for this reaction was according to procedure A. The title compound **17** was obtained as a colorless oil (47 mg, 51% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$:** δ 1.11-1.27 (m, 2H), 1.49-1.72 (m, 6H), 2.07 (app. septet, *J* = 7.5 Hz, 1H), 2.65 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.0, 32.5, 41.7, 42.3, 109.6, 119.3, 129.6, 132.1, 148.1 ; **IR (neat)**: 2948, 2865, 2226, 1606, 1506.

Methyl 4-((1-phenylpyrrolidin-3-yl)methyl)benzoate ***(18).*** The organozinc prepared for this reaction was according to procedure A. The reaction was done at room temperature for 12 h using standard condition. The title compound **18** was obtained as a white solid (79.6 mg, 54% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.69-1.82 (m, 1H), 2.06-2.16 (m, 1H), 2.62 (app. septet, *J* = 7.5 Hz, 1H), 2.82 (d, *J* = 9 Hz, 2H), 3.02 (t, *J* = 9 Hz, 1H), 3.26-3.45 (m, 3H), 3.93 (s, 3H), 6.54 (d, *J* = 9 Hz, 2H), 6.68 (t, *J* = 9.0 Hz, 1H), 7.21-7.31 (m, 4H), 8.01 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 31.4, 40.0, 40.2, 47.2, 52.1, 53.0, 111.5, 115.6, 128.3, 128.8, 129.2, 129.9, 146.2, 147.8, 167.1; **IR (neat):** 2959, 2822, 1713, 1599, 1505, 1308, 1276, 1107; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{19}H_{22}NO_2$ 296.1651; found 296.1648.

3-Benzyl-1-tosylpyrrolidine ***(19).*** The reaction was conducted using one equiv diphenylzinc (115.5 mg, 67% yield) instead of PhZnI (88.2mg, 56%) in our standard condition for 8 h. The title compound **19** was obtained as a colorless oil after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.40-1.55 (m, 1H), 1.82-1.92 (m, 1H), 2.32 (app. septet, *J* = 7.5 Hz, 1H), 2.25-2.40 (m, 1H), 2.44 (s, 3H), 2.54 (d, *J* = 9 Hz, 2H), 2.92 (t, *J* = 9 Hz, 1H), 3.19 (q, *J* = 7.9 Hz 1H), 3.31-3.42 (m, 2H), 7.05 (d, *J* = 6 Hz, 2H),), 7.16-7.33 (m, 5H), 7.69 (d, *J* = 9 Hz, 2H) ; **^{13}C NMR (75 MHz, $CDCl_3$):** δ 21.6, 31.1, 39.1, 40.4, 47.4, 52.8, 126.3, 127.5, 128.5, 128.6, 129.7, 133.9, 139.8, 143.4; **IR (neat):** 2949, 1733, 1339, 1157, 1027, 1014; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{18}H_{22}NO_2S$ 316.1371; found 316.1363.

3-(4-Fluorobenzyl)-1-tosylpyrrolidine ***(20).*** The organozinc prepared for this reaction was according to procedure A. This reaction was completed in 8 h using our standard condition. The title compound **20** was obtained as a colorless oil (104.8 mg, 63% yield) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.40-1.53 (m, 1H), 1.80-1.91 (m, 1H), 2.28 (app. septet, *J* = 6.9 Hz, 1H), 2.43 (s, 3H), 2.52 (d, *J* = 9 Hz, 2H), 2.89 (q, *J* = 6 Hz, 1H), 3.14-3.22 (m, 1H), 3.28-3.42 (m, 2H), 6.90-7.03 (m, 4H),), 7.32 (d, *J* = 9 Hz, 2H), 7.68 (d, *J* = 9 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 21.6, 31.0, 38.3, 40.5, 47.4, 52.7, 115.3 (d, J_{CF} = 21.0 Hz), 127.6, 129.7, 130.0 (d, J_{CF} = 8.2 Hz), 133.9, 135.4 (d, J_{CF} = 3.0 Hz), 143.4, 161.4 (d, J_{CF} = 243 Hz); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -115.2 **IR (neat):** 1598, 1508, 1448, 1155, 1090, 1014 ; **HRMS (CI) m/z:** $(M+H)^+$ Calcd for $C_{18}H_{21}FNO_2S$ 334.1277; found 334.1284.

3-(3,4-Dichlorobenzyl)tetrahydrofuran ***(21).*** The organozinc prepared for this reaction was according to procedure A. The title compound **21** was obtained as a colorless oil (85.1 mg, 74% yield) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.51-1.63 (m, 1H), 1.93-2.04 (m, 1H), 2.46 (app. septet, *J* = 7.5 Hz, 1H), 2.57-2.70 (m, 2H), 3.42 (t, *J* = 7.5 Hz, 1H), 3.71-3.93 (m, 3H), 6.99 (d, *J* = 6 Hz, 1H), 7.26 (s, 1H), 7.34 (d, *J* = 6 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 32.0, 38.5, 40.7, 67.9, 72.8, 128.2, 130.1, 130.4, 130.6, 132.4, 141.1; **IR (neat):** 2966, 2856, 1470, 1372, 1240, 1130, 1044, 1029; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{11}H_{12}Cl_2O$ 230.0265; found 230.0273.

3-(3,5-Bis(trifluoromethyl)benzyl)tetrahydrofuran ***(22).*** The organozinc prepared for this reaction was according to procedure A. The title compound **22** was obtained as a colorless oil (105.7 mg, 71% yield) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.56-1.67 (m, 1H), 1.97-2.08 (m, 1H), 2.55 (app. septet, *J* = 7.5 Hz, 1H), 2.76-2.90 (m, 2H), 3.47 (t, *J* = 7.5 Hz, 1H), 3.74-3.97 (m, 3H), 7.63 (s, 2H),), 7.73 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 32.0, 39.0, 40.6, 67.9, 72.7, 120.4, 123.4 (q, J_{CF} = 270.9 Hz), 128.9, 131.9 (q, J_{CF} = 32.7 Hz), 143.3 ; **^{19}F NMR (282 MHz, $CDCl_3$)** δ -61.5 **IR (neat):** 2936, 2864, 1622, 1456, 1378, 1274, 1166, 1002; **HRMS (CI) m/z:** $(M+H)^+$ Calcd for $C_{13}H_{13}F_6O$ 299.0871; found 299.0864.

4-((Tetrahydrofuran-3-yl)methyl)benzonitrile ***(23).*** The organozinc prepared for this reaction was according to procedure A. The title compound **23** was obtained as a colorless oil (60.7 mg, 65% yield) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.53-1.65 (m, 1H), 1.94-2.05 (m, 1H), 2.51 (app. septet, *J* = 7.5 Hz, 1H), 2.68-2.81 (m, 2H), 3.44 (t, *J* = 7.5 Hz, 1H), 3.72-3.94 (m, 3H), 7.28 (d, *J* = 6.0 Hz, 2H), 7.58 (d, *J* = 6 Hz, 2H); **^{13}C**

NMR (75 MHz, $CDCl_3$): δ 32.0, 39.4, 40.5, 67.8, 72.7, 110.1, 119.0, 129.5, 132.3, 146.4 ; **IR (neat):** 2965, 2856, 2226, 1606, 1506, 1415, 1177, 1042; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{12}H_{14}NO$ 188.1075; found 188.1081.

1-(4-((tetrahydrofuran-3-yl)methyl)phenyl)ethan-1-one ***(24)***. The organozinc prepared for this reaction was according to procedure C. The title compound **24** was obtained as a colorless oil (67.3mg, 66% yield) after purification by silica gel column chromatography (Hex: EtOAc = 4:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.55-1.67 (m, 1H), 1.94-2.05 (m, 1H), 2.48-2.69 (m, 4H), 2.68-2.75 (d, *J* = 6.0 Hz, 2H), 3.45 (t, *J* = 7.5 Hz, 1H), 3.74-3.94 (m, 3H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.89 (d, *J* = 6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 26.6, 32.2, 39.4, 40.7, 67.9, 72.9,128.7, 129.0, 135.4, 146.6, 197.8 ; **IR (neat):** 2855, 1677, 1605, 1413, 1265, 956; **HRMS (APCI) m/z:** $(M+H)^+$ Calcd for $C_{13}H_{17}O_2$ 205.1229; found 205.1217.

3-(4-bromobenzyl)tetrahydrofuran ***(25).*** The organozinc prepared for this reaction was according to procedure A. The title compound **25** was obtained as a colorless oil (84.0 mg, 70% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.53-1.65 (m, 1H), 1.92-2.04 (m, 1H), 2.47 (app. septet, *J* = 7.0 Hz, 1H), 2.61-2.70 (m, 2H), 3.43 (t, *J* = 7.5 Hz, 1H), 3.71-3.93 (m, 3H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 32.1, 38.8, 40.9, 67.9, 72.9, 119.9, 130.5, 131.6, 139.8 ; **IR (neat):** 2965, 2856, 2226, 1606, 1506, 1415, 1177, 1042; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{11}H_{13}BrO$ 240.0150; found 240.0152.

(±)-(3R,3aS,6aR)-3-(4-Methoxybenzyl)hexahydrofuro[2,3-b]furan ***(26).***[42] The organozinc prepared for this reaction was according to procedure A. The title compound **26** was obtained as a colorless oil (90.0 mg, 77% yield; 8:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.77-2.03 (m, 2H), 2.55-2.79 (m, 4H), 3.52 (t, *J* = 10.5 Hz, 1H), 3.76 (s, 3H), 3.81-3.97 (m, 3H), 5.69 (d, *J* = 6 Hz, 1H), 6.81 (d, *J*=9.0 Hz, 1H), 7.07 (d, *J*=6.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.0, 32.8, 43.9, 45.4, 55.2, 69.0, 72.1, 109.8, 113.9, 129.1, 131.9, 158.0; **IR (neat):** 2952, 1735, 1611, 1511, 1372, 1242, 1178; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{14}H_{19}O_3$ 235.1334; found 235.1330. The actual dr (8:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.69 ppm (major isomer) and δ 5.72 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

(±)-(3R,3aS,7aS)-3-(2-Methoxybenzyl)octahydrobenzofuran ***(27).*** The organozinc prepared for this reaction was according to procedure A. The title compound **27** was obtained as a colorless oil (78.7 mg, 64% yield; 1.7:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.14-1.40 (m, 3H), 1.44-1.64 (m, 4H), 1.71-1.89 (m, 2H), 1.96-2.00 (m, 1x0.37H), 2.26-2.33 (m, 1x0.63H), 2.53-2.62 (m, 1H), 2.67-2.78 (m, 1H), 3.52 (dd, *J* = 9.0, 6.0 Hz, 1x0.63H), 3.64 (t, *J* = 7.5 Hz, 1x0.37H), 3.80 (s, 3H), 3.88-4.11 (m, 2H), 6.73-6.79 (m, 3H), 7.17-7.23 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 20.5, 21.2, 22.2, 23.7, 24.6, 27.5, 28.4, 28.7, 33.7, 39.9, 40.1, 43.1, 45.4, 45.7, 55.2, 70.9, 72.0, 76.2, 78.4, 111.1, 111.2, 114.4, 114.7, 120.9, 121.2, 129.4, 142.3, 142.7, 159.7; **IR (neat):** 2930, 1737, 1584, 1239, 1152, 1043; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{16}H_{23}O_2$ 247.1698; found 247.1691. The actual dr (1.7:1) was calculated using GC. See SI for GC trace.

(±)-(3R,3aS,6aR)-3-(2-Methylbenzyl)hexahydrofuro[2,3-b]furan ***(28).*** The organozinc prepared for this reaction was according to procedure A. The title compound **28** was obtained as a colorless oil (65.4 mg, 60% yield; 5:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1;). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.87-2.08 (m, 2H), 2.32 (s, 3H), 2.62-2.86 (m, 4H), 3.56-3.64 (m, 1H), 3.83-4.00 (m, 3H), 5.73 (d, *J* = 6 Hz, 1H), 7.10-7-16 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 19.5, 25.3, 31.0, 42.3, 45.8, 69.2, 72.2, 109.8, 126.1, 126.4, 128.6, 130.5, 135.8, 138.2 ; **IR (neat):** 2949, 2867, 1603, 1490, 1371, 1180, 1071; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{14}H_{19}O_2$ 219.1385; found 219.1377. The actual dr (5:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.73 ppm (major isomer) and δ 5.74 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

(±)-(3R,3aS,7aR)-3-(4-Methylbenzyl)hexahydro-4H-furo[2,3-b]pyran ***(29).*** The organozinc prepared for this reaction was according to procedure A. The title compound **29** was obtained as colorless oil (71.9 mg, 62% yield; 5:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.49-1.63 (m, 3H), 1.72-1.79 (m, 1H), 1.91-1.99 (m, 1H), 2.32(s, 3H), 2.53-2.74 (m, 3H), 3.63-3.67 (m, 1H), 3.74-3.79 (m, 2H), 3.88 (t, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 3.0 Hz, 1H), 7.04-7.11 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 19.5, 21.0, 23.2, 32.9, 36.5, 42.6, 61.0, 69.9, 102.0, 128.2, 129.2, 135.6, 137.0; **IR (neat):** 2939, 1736, 1515, 1144, 1109, 1018; **HRMS (ESI-TOF) m/z:** $(M+H)^+$ Calcd for $C_{15}H_{21}O_2$ 233.1542; found 233.1537. The actual dr (5:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.27 ppm (major isomer) and δ 5.01 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

(±)-(3R,3aS,7aS)-3-(4-Methylbenzyl)octahydrobenzofuran ***(30).*** The organozinc prepared for this reaction was according to procedure A. The title compound **30** was obtained as a colorless oil (79.3 mg, 69% yield; 1.7:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.18-1.42 (m, 3H), 1.47-1.65 (m, 4H), 1.73-1.89 (m, 2H), 1.98-2.02 (m, 1x0.37H), 2.24-2.31 (m, 1x0.63H), 2.34 (s, 3H), 2.54-2.63 (m, 1H), 2.67-2.79 (m, 1H), 3.54 (dd, *J* = 9.0, 6.0 Hz, 1x0.63H), 3.67 (t, *J* = 7.5 Hz, 1x0.37H), 3.89-4.12 (m, 2H), 7.06-7.13 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 20.5, 21.0, 21.2, 22.2, 23.7, 24.5, 27.5, 28.4, 28.6, 33.1, 39.4, 40.0, 43.0, 45.6, 45.8, 70.9, 72.0, 76.2, 78.4, 128.2, 128.6, 129.1, 135.4, 137.5, 137.9; **IR (neat):** 2926, 2853, 1514, 1446, 1061, 1022; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{16}H_{22}O$ 230.1671; found 230.1669. The actual dr (1.7:1) was calculated using GC. See SI for GC trace.

(±)-(2S,4R)-2-Butoxy-4-(2,4-dimethoxybenzyl)tetrahydrofuran ***(31).*** The organozinc prepared for this reaction was according to procedure A. The title compound **31** was obtained as a colorless oil (98.4 mg, 67% yield; 1.4:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.88-0.96 (m, 3H), 1.30-1.46 (m, 2H), 1.50-1.65 (m, 3H), 1.92-1.98 (m, 1x0.42H), 2.10-2.20 (m,

1x0.58H), 2.45-2.55 (m, 1x0.58H), 2.59 (d, *J* = 6.0 Hz, 1x0.42H), 2.69 (d, *J* = 9.0 Hz, 2H), 3.34-3.42 (m, 1H), 3.54-3.73 (m, 2H), 3.79 (s, 6H), 3.83-3.96 (m, 1H), 5.08-5.12 (m, 1H), 6.38-6.43 (m, 2H), 7.00 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.0, 19.5, 32.0, 33.2, 33.7, 37.5, 38.6, 38.9, 39.2, 55.2, 55.4, 67.2, 67.5, 72.0, 98.5, 103.7, 104.3, 104.7, 121.7, 130.5, 158.4, 159.4; **IR (neat):** 2934, 1738, 1612, 1506, 1456, 1286, 1207, 1155, 1063; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{17}H_{26}O_4$ 294.1831 found 294.1832. The actual dr (1.4:1) was calculated using GC. See SI for GC trace.

*(±)-(2S,4R)-4-Benzyl-2-phenyltetrahydrofuran **(32)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **32** was obtained as a colorless oil (94.0 mg, 79% yield; 6.5:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1).**^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.97-2.07 (m, 1H), 2.11-2.20 (m, 1H), 2.45 (app. septet, *J* = 7.1 Hz, 1x0.13H), 2.71 (app. septet, *J* = 7.5 Hz, 1x0.87H), 2.79 (d, *J* = 9.0 Hz, 2H), 3.70 (t, *J* = 7.5 Hz, 1x0.87H), 3.82 (t, *J* = 7.5 Hz, 1x0.13H), 4.09 (t, *J* = 7.5 Hz, 1x0.13H), 4.20 (t, *J* = 7.5 Hz, 1x0.87H), 4.93 (t, *J* = 7.5 Hz, 1x0.13H), 5.12 (t, *J* = 7.5 Hz, 1x0.87H), 7.20-7.39 (m, 10H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 39.2, 39.5, 40.6, 40.7, 41.9, 42.3, 73.7, 73.8, 80.1, 81.4, 125.5, 125.6, 126.2, 127.1, 128.3, 128.4, 128.5, 128.7, 140.6, 143.8; **IR (neat):** 3061, 2933, 1602, 1494, 1067, 1028; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{17}H_{18}O$ 238.1358; found 238.1357. The actual dr (6.5:1) was calculated using GC. See SI for GC trace.

*(±)-(2S,4R)-2-Phenyl-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran **(33)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **33** was obtained as colorless oil (114.7 mg, 75% yield; 10:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.95-2.05 (m, 1H), 2.08-2.16 (m, 1H), 2.42 (app. septet, *J* = 6.75 Hz, 1x0.10H), 2.66 (app. septet, *J* = 6.90 Hz, 1x0.90H), 2.83 (d, *J* = 9.0 Hz, 2H), 3.65 (t, *J* = 7.5 Hz, 1x0.90H), 3.79 (t, *J* = 7.5 Hz, 1x0.10H), 4.06 (t, *J* = 7.5 Hz, 1x0.10 H), 4.18 (t, *J* = 7.5 Hz, 1x0.90H), 4.92 (t, *J* = 7.5 Hz, 1x0.10H), 5.10 (t, *J* = 7.5 Hz, 1x0.90H), 7.24-7.36 (m, 7H), 7.55 (d, *J* = 9.0 Hz, 2H),; **^{13}C NMR (75 MHz, $CDCl_3$):** δ 39.0, 39.4, 40.5, 40.6, 41.7, 42.0, 73.5, 73.6, 80.1, 81.4, 124.4 (q, J_{CF} = 159.0 Hz), 125.5 (q, , J_{CF} = 12.6 Hz), 127.3, 127.4, 128.4 (q, J_{CF} = 5.3 Hz), 128.9, 129.1, 143.0, 143.6, 144.7; **^{19}F NMR (282 MHz, $CDCl_3$):** δ -61.1; **IR (neat):** 2973, 2867, 1614, 1321, 1151, 1108, 1062; **HRMS (CI) m/z:** $(M-H)^+$ Calcd for $C_{18}H_{16}F_3O$ 305.1153; found 305.1145. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.10 ppm (major isomer) and δ 4.92 ppm (minor isomer).

*(±)-(3R,3aS,6aR)-3-(4-(Trifluoromethyl)benzyl)hexahydrofuro[2,3-b]furan **(34)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **34** was obtained as a colorless oil (93.8 mg, 69% yield; 10:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.79-2.03 (m, 2H), 2.60-2.84 (m, 4H), 3.55 (t, *J* = 9.0 Hz, 1H), 3.82-3.99 (m, 3H), 5.70 (d, *J* = 6.0 Hz, 1H), 7.28 (d, *J* = 6.0 Hz, 2H), 7.54 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.1, 33.6, 43.5, 45.4, 69.0, 71.9, 109.7, 124.2 (q, J_{CF}= 270.4 Hz), 125.5(q, J_{CF}= 3.9 Hz), 128.0, 128.6 (q, J_{CF}= 10.9 Hz), 144.1; **^{19}F NMR (282 MHz, $CDCl_3$)** δ -60.8 **IR (neat):** 2951, 2871, 1321, 1160, 1108, 1065, 997; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{14}H_{16}F_3O_2$ 273.1102; found 273.1093. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.70 ppm (major isomer) and δ 5.74 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*(±)-4-(((3R,3aS,7aR)-Hexahydro-4H-furo[2,3-b]pyran-3-yl)methyl)benzonitrile **(35)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **35** was obtained as colorless oil (93.5 mg, 77% yield; 10:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.48-1.64 (m, 3H), 1.67-1.73 (m, 1x0.90H), 1.81-1.85 (m, 1x0.10H), 1.90-1.98 (m, 1H), 2.62-2.82 (m, 3x0.90H), 2.82-2.85 (m, 3x0.10H), 3.37-3.45 (m, 1x0.10H), 3.60-3.66 (m, 1x0.90H), 3.71-3.79 (m, 2H), 3.85 (t, *J* = 7.5 Hz, 1x0.90H), 4.13 (t, *J* = 7.5 Hz, 1x0.10H), 5.01 (d, *J* = 3.0 Hz, 1x0.10H), 5.25 (d, *J* = 3.0 Hz, 1x0.90H), 7.27 (d, *J* = 6.0 Hz, 2H), 7.57 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 19.6, 23.0, 33.7, 36.5, 42.0, 61.0, 69.6, 101.8, 110.2, 118.8, 129.2, 132.4, 145.8; **IR (neat):** 2940, 2869, 2226, 1716, 1606, 1252, 1177, 1049; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{15}H_{18}NO_2$ 244.1338; found 244.1320. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.27 ppm (major isomer) and δ 5.03 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*(±)-(2S,4R)-2-Butoxy-4-(3-chlorobenzyl)tetrahydrofuran **(36)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **36** was obtained as a colorless oil (101.8 mg, 76% yield; 4.1:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.88-0.96 (m, 3H), 1.30-1.43 (m, 2H), 1.50-1.69 (m, 3H), 1.95-2.02 (m, 1x0.20H), 2.11-2.20 (m, 1x0.80H), 2.46 (app.septet, *J* = 7.9 Hz, 1x0.80H), 2.62-2.65 (m, 1x0.20H), 2.75 (d, *J* = 9.0 Hz, 2H), 3.31-3.42 (m, 1H), 3.51-3.73 (m, 2H), 3.88-4.00 (m, 1H), 5.09-5.13 (m, 1H), 7.03-7.06 (m, 1H), 7.15-7.26 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.0, 19.5, 32.0, 38.5, 39.2, 39.7, 67.5, 71.6, 104.5, 126.3, 126.9, 128.8, 129.7, 134.2, 143.0; **IR (neat):** 2956, 2931, 2869, 1598, 1474, 1430, 1080, 1011; **HRMS (CI) m/z:** $(M)^+$ Calcd for $C_{15}H_{21}ClO_2$ 268.1230; found 268.1221. The actual dr (4.1:1) was calculated using GC. See SI for GC trace.

*(±)-4-(3,4-Dichlorobenzyl)-2-ethoxy-3-ethyltetrahydrofuran **(37)**.* The organozinc prepared for this reaction was according to procedure A. The. title compound **37** was obtained as a colorless oil (104.2 mg, 69% yield; 6: 4.5: 3.4: 1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.85-0.90 (m, 1H), 0.93-1.02 (m, 2H), 1.16-1.23 (m, 3H), 1.32-1.73 (m, 2H), 1.99-2.11 (m, 1H), 2.36-2.86 (m, 3H), 3.39-3.56 (m, 1H), 3.59-3.90 (m, 3H), 4.78 (d, *J* = 2.1 Hz, 1x0.40H), 4.85 (d, *J* = 2.6 Hz, 1x0.23H), 4.95 (d, *J* = 4.8 Hz, 1x0.30H), 4.98 (d, *J* = 4.5 Hz, 1x0.07H), 6.98 (d, *J* = 9.0 Hz, 1H), 7.23-7.34 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 12.2, 12.8, 13.0, 15.3, 15.4, 15.5, 18.0, 19.3, 20.8, 25.5, 32.8, 35.1, 38.5, 40.4, 41.9, 45.8, 48.8, 50.0, 52.9, 63.0, 63.3, 70.6, 71.6, 71.7, 104.1, 107.9, 109.1, 128.1, 128.4, 129.8, 130.1, 130.3, 130.4, 130.6, 130.8, 132.3, 132.4, 140.9, 141.1, 141.2, 142.2; **IR (neat):** 2965, 2874, 1472, 1131, 1044, 1028, 999; **HRMS (CI) m/z:** $(M)^+$ $C_{15}H_{20}Cl_2O_2$ 302.0840;

found 302.0840. The actual dr (6: 4.5: 3.4: 1) was calculated using GC. See SI for GC trace.

*(±)-(2S,4R)-4-((5-Butoxytetrahydrofuran-3-yl)methyl)-2-chloropyridine **(38)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **38** was obtained as a colorless oil (108.9 mg, 81% yield; 2.2:1 dr) by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.87-0.96 (m, 3H), 1.30-1.44 (m, 2H), 1.47-1.64 (m, 3H), 1.97-2.04 (m, 1x0.31H), 2.10-2.19 (m, 1x0.69H), 2.48 (app.septet, *J* = 6.9 Hz, 1x0.69H), 2.64-2.67 (m, 1x0.31H), 2.79 (d, *J* = 9.0 Hz, 2H), 3.33-3.41 (m, 1H), 3.54-3.72 (m, 2H), 3.91-4.01 (m, 1H), 5.09-5.12 (m, 1H), 7.03 (t, *J* = 6.0 Hz, 1H), 7.15 (s, 1H), 8.28 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 13.9, 19.4, 19.5, 31.8, 31.9, 37.8, 38.3, 38.6, 38.7, 39.0, 67.2, 67.5, 71.3, 71.5, 103.9, 104.3, 122.9, 123.0, 124.5, 149.7, 151.8, 152.9, 153.3; **IR (neat):** 2955, 2869, 1592, 1465, 1385, 1085, 1013; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{14}H_{21}ClNO_2$ 270.1261; found 270.1247. The actual dr (2.2:1) was calculated using GC. See SI for GC trace.

*(±)-(3R,3aS,7aR)-3-(Furan-2-ylmethyl)hexahydro-4H-furo[2,3-b]pyran **(39)**.* This reaction was performed by using di(furan-2-yl)zinc (1 eqvt.) in our standard condition. The title compound **39** was obtained as colorless oil (84.2 mg, 81% yield; 8:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.45-1.64 (m, 3H), 1.72-1.80 (m, 1H), 1.96-2.05 (m, 1H), 2.58-2.79 (m, 3H), 3.60-3.67 (m, 1H), 3.72-3.82 (m, 2H), 3.97 (t, *J* = 7.5 Hz, 1H), 5.28 (d, *J* = 3.0 Hz, 1H), 5.99 (d, *J* = 3.0 Hz, 1H), 6.27 (t, *J* = 3.0 Hz, 1H), 7.29 (d, *J* = 3.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 19.5, 23.2, 26.1, 36.7, 39.9, 61.2, 69.9, 102.0, 105.5, 110.2, 141.3, 154.1; **IR (neat):** 2936, 2871, 1769, 1436, 1143, 1047, 1015**; HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{12}H_{17}O_3$ 209.1178; found 209.1174. The actual dr (8:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.30 ppm (major isomer) and δ 5.01 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*(±)-(3R,3aS,6aR)-3-(Furan-2-ylmethyl)hexahydrofuro[2,3-b]furan **(40)**.* This reaction was performed by using di(furan-2-yl)zinc (1 eqvt.) in our standard condition. The title compound **40** was obtained as colorless oil (63.0 mg, 65% yield; 9.3:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.82-2.01 (m, 2H), 2.65-2.89 (m, 4H), 3.54 (t, *J* = 9.0 Hz, 1H), 3.84-3.99 (m, 3H), 5.74 (d, *J* = 6.0 Hz, 1H), 6.01 (d, *J* = 3.0 Hz, 1H), 6.28 (t, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 0.72 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.2, 26.3, 41.1, 45.6, 69.2, 72.2, 105.6, 109.8, 110.3, 141.3, 153.8; **IR (neat):** 2949, 2873, 1716, 1254, 1106, 1072, 996; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{11}H_{15}O_3$ 195.1021; found 195.1015. The actual dr (9.3:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.70 ppm (major isomer) and δ 5.81 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*(±)-(3R,3aS,6aR)-3-(Thiophen-2-ylmethyl)hexahydrofuro[2,3-b]furan **(41)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **41** was obtained as a colorless oil (76.6 mg, 73% yield; 10:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.82-2.04 (m, 2H), 2.64-3.01 (m, 4H), 3.54 (t, *J* = 10.5 Hz, 1H), 3.84-3.99 (m, 3H), 5.74 (d, *J* = 3.0 Hz, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 6.93 (t, *J* = 4.5 Hz, 1H), 7.14 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.2, 28.0, 44.1, 45.4, 69.2, 72.2, 109.9, 123.6, 124.8, 126.9, 142.5; **IR (neat):** 2948, 1438, 1252, 1107, 997, 921; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{11}H_{15}O_2S$ 211.0793; found 211.0792. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.70 ppm (major isomer) and δ 5.80 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*1-(4-(((3R,3aS,7aR)-hexahydro-4H-furo[2,3-b]pyran-3-yl)methyl)phenyl)ethan-1-one **(42)**.* This reaction was performed by using organozinc prepared according to procedure C in our standard condition. The title compound **42** was obtained as white solid (101.4 mg, 78% yield; 10:1 dr) after purification by flash column chromatography (Hex: EtOAc = 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.51-1.61 (m, 3H), 1.72-1.76 (m, 1H), 1.92-1.98 (m, 1H), 2.58 (s, 3H), 2.64-2.82 (m, 3H), 3.64 (t, *J* = 7.5 Hz, 1H), 3.74-3.81 (m, 2H), 3.87 (t, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 6.0 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 19.6, 23.1, 26.6, 33.6, 36.6, 42.2, 61.0, 69.7, 101.9, 128.6, 128.7, 135.5, 145.9, 197.7; **IR (neat):** 2932, 1676, 1355, 1138, 1014, 866**; HRMS (APCI):** $(M+H)^+$ Calcd for $C_{16}H_{21}O_3$ 261.1491; found 261.1481 The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.25 ppm (major isomer) and δ 5.03 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*1-(4-(((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl)methyl)phenyl)ethan-1-one **(43)**.* This reaction was performed by using organozinc prepared according to procedure C in our standard condition. The title compound **43** was obtained as a white solid (86.1 mg, 70% yield; 10:1 dr) after purification by flash column chromatography (Hex: EtOAc = 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.78-2.02 (m, 2H), 2.57 (s, 3H), 2.62-2.84 (m, 4H), 3.54 (t, *J* = 10.5 Hz, 1H), 3.81-3.98 (m, 3H), 5.69 (d, *J* = 6 Hz, 1H), 7.25 (d, *J* = 9 Hz, 2H),), 7.87 (d, *J* = 9 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 25.2, 26.6, 33.9, 43.5, 45.4, 69.1, 72.0, 109.8, 128.6, 128.8, 135.5, 145.7, 197.6; **IR (neat):** 1669, 1415, 1267, 1107, 1003, 921; **HRMS (APCI):** $(M+H)^+$ Calcd for $C_{15}H_{19}O_3$ 247.1334; found 247.1323. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.70 ppm (major isomer) and δ 5.80 ppm (minor isomer). The characterization data given above correspond to the major isomer isolated by column chromatography.

*(2S,4R)-4-(4-bromobenzyl)-2-phenyltetrahydrofuran **(44)**.* This reaction was performed by using organozinc prepared according to procedure A in our standard condition. The title compound **44** was obtained as colorless oil (98.0mg, 62% yield; 10:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.93-2.02 (m, 1H), 2.05-2.14 (m, 1H), 2.41 (app. septet, *J* = 6.0 Hz, 1x0.10H), 2.63 (app. septet, *J* = 6.75 Hz, 1x0.90H), 2.72 (d, *J* = 9.0 Hz, 2H), 3.63 (t, *J* = 7.5 Hz, 1x0.90H), 3.76 (t, *J* = 7.5 Hz, 1x0.10H), 4.04 (t, *J* = 7.5 Hz, 1x0.10H), 4.16 (t, *J* = 7.5 Hz, 1x0.90H), 4.90 (t, *J* = 7.5 Hz, 1x0.10H), 5.07 (t, *J* = 7.5 Hz,

1x0.90H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.25-7.35 (m, 5H), 7.41 (d, *J* = 8.1 Hz, 2H),; **^{13}C NMR (75 MHz, $CDCl_3$):** δ 38.6, 38.9, 40.5, 41.7, 42.1, 73.5, 73.6, 80.0, 81.3, 120.0, 125.5, 125.6, 127.2, 127.4, 128.4 (br, s), 131.6 (br, s), 139.5, 143.6; **IR (neat):** 1558, 1161, 1008, 760, 701, 528; **HRMS (CI):** $(M)^+$ Calcd for : $C_{17}H_{17}BrO$ 316.0463; found 316.0461. The actual dr (10:1) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 5.07 ppm (major isomer) and δ 4.90 ppm (minor isomer).

*ethyl (1R)-1-acetyl-3-(4-cyanobenzyl)cyclopentane-1-carboxylate **(45)**.* The organozinc prepared for this reaction was according to procedure A. The title compound **45** was obtained as a colorless oil (89.7 mg, 60 % yield; 3:2 dr) after purification by silica gel column chromatography (Hex: Et_2O = 8:1). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.21-1.23 (m, 3H), 1.30-1.40 (m, 1H), 1.99-2.13 (m, 4H), 2.22-2.34 (m, 3H), 2.65-2.74 (m, 2H), 4.14-4.21 (m, 2H), 7.26 (d, *J* =7.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 14.1, 26.2, 26.5, 32.0, 32.1, 32.2, 32.3, 38.5, 38.7, 41.2, 41.3, 41.4, 61.6, 66.3, 66.5, 109.9, 119.1, 129.5, 132.2, 146.8, 146.9, 173.3, 173.4, 203.4; **HRMS (CI):** $(M+H)^+$ Calcd for for $C_{18}H_{22}NO_3$ 300.1600; found 300.1590. The actual dr (3:2) of this compound was calculated using crude ^{1}H NMR by integrating peaks at δ 2.10 ppm (major isomer) and δ 2.08 ppm (minor isomer).

*(±)-4-(3,4-Dimethoxybenzyl)dihydrofuran-2(3H)-one **(49)**.* The dicarbofunctionalization reaction was conducted in 10.0 mmol scale in 50 mL NMP in 8 h using the standard procedure. Organozinc ((3,4-dimethoxyphenyl)zinc iodide) for this reaction was prepared according to above procedure B. Under nitrogen atmosphere, (3,4-dimethoxyphenyl)zinc iodide stock solution in THF (15 mmol) was taken in a 150 mL sealed tube and the solvent was removed under vacuum. To the residue of ArZnI was added $NiBr_2$ (30 mg, 0.3 mmol), terpyridine (45 mg, 0.4 mmol), and 1-(1-(allyloxy)-2-iodoethoxy)butane ***(48)*** (10 mmol). The mixture was then dissolved in NMP (50 mL). The sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. The resultant cyclized cross coupled product was oxidized without further purification as follow: The crude reaction mixture (brown color) was diluted with ethyl acetate (30 mL) and washed three times with 10 mL water. The combined EtOAc layer was dried with Na_2SO_4 and solvent was removed. For oxidation, the crude reaction mixture was taken in a reaction flask and 200 mL acetone was added to the flask. 30 mL of Jones reagent (prepared by dissolving 1 gm CrO_3 in 1 mL conc. H_2SO_4 and 3 mL H_2O) was added dropwise to the reaction mixture at 0 °C. The reaction was stirred for 1 h at 0 °C. Then the reaction was quenched with isopropyl alcohol (30 mL) and stirred for a while and filtered. The filtrate was neutralized with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (30 mL). The combined EtOAc layer was dried with Na_2SO_4 and the solvent was pumped off. The title compound **49** was obtained as a colorless oil (1463.2 mg, 62% yield) after purification by silica gel column chromatography (Hex: EtOAc = 4:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.21 (dd, *J* = 18.0, 6.0 Hz 1H), 2.52 (dd, *J* = 18.0, 9.0 Hz 1H), 2.63-2.84 (m, 3H), 3.78 (d, *J* = 3.0 Hz, 6H), 3.95 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.25 (dd, *J* = 9.0, 6.0 Hz, 1H), 6.62-6.65 (m, 2H), 6.75 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 34.0, 37.1, 38.3, 55.7, 72.5, 111.2, 111.7, 120.5, 130.7, 147.6, 148.9, 176.8; **IR (neat):** 2935, 2835, 1767, 1512, 1261, 1138, 1011; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{13}H_{17}O_4$ 237.1127; found 237.1116.

*(3aR,9S,9aR)-9-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1(3H)-one **(50)**.*[25d] Compound **49** (94.4 mg, 0.4 mmol) was dissolved in dry THF (2.5 mL) then the solution was cooled to -78 °C. To the cooled solution, LDA (0.8 mmol, 1.6 ml of 0.5M solution in THF) was added dropwise for 5 minutes. The solution was stirred for 1h at -78 °C which turns the solution to yellow. To the reaction mixture, solution 3,4-dimethoxybenzaldehyde (99.6 mg, 0.6 mmol) in 1.5 mL THF was added dropwise at -50 °C and and stirred at room temperature for 6 h. Then solvent was removed and the reaction crude was dissolved in 1 mL CH_2Cl_2. To the stirring reaction mixture at room temperature, Trifluoroacetic acid (309 µl, 4 mmol) was added dropwise. It was stirred overnight at room temperature and quenched with saturated $NaHCO_3$ (2.0 ml). The reaction mixture was extracted with CH_2Cl_2 (8 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **50** was obtained as a white solid (112.1 mg, 73% yield; 19:1 dr) after purification by flash column chromatography (Hex: EtOAc = 2:1). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 2.50 (dd, *J* = 13.8, 10.8 Hz, 1H), 2.58-2.68 (m, 1H), 2.93 (t, *J* = 13.2 Hz, 1H), 3.00 (dd, *J* = 15.0, 4.5 Hz, 1H), 3.60 (s, 3H), 3.82 (s, 3H), 3.87 (s, 6H), 3.99 (dd, *J* = 10.0, 9.5 Hz, 1H), 4.11 (d, *J* = 11.0 Hz, 1H), 4.52 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.33 (s, 1H), 6.61 (s, 1H), 6.70 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 32.6, 40.1, 45.8, 48.9, 55.8, 55.9, 56.0, 71.0, 111.0, 111.4, 112.4, 112.9, 121.9, 126.9, 131.4, 135.6, 147.7, 147.8, 147.9, 148.8, 175.6, ; **IR (neat):** 1759, 1652, 1514, 1246, 1217, 1102, 981 ; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{22}H_{25}O_6$ 385.1651; found 385.1653. The stereochemistry of the compound was assigned by comparing the spectral data and the *J*-coupling values with the known compound in the literature.[25d] The actual dr (19:1) was calculated using GC and observation of single isomer in crude ^{1}H NMR. See SI for GC trace.

*(±)-(3R,4R)-3-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-(3,4-dimethoxybenzyl)dihydrofuran-2(3H)-one **(51)**.*[43] In a 4 dram vial, compound **49** (94.4 mg, 0.4 mmol) was dissolved in dry THF (4 mL) . The solution was cooled to -78 °C. To the cooled solution, LDA (0.48 mmol, 0.96 ml of 0.5M) solution was added dropwise for 5 minutes. The solution was stirred for 1 h at -78 °C which turns the solution to yellow. To the reaction mixture, solution 5-(bromomethyl)benzo[d][1,3]dioxole[44] (127.8 mg, 0.6 mmol) in 1.5 mL THF was added dropwise at -50 °C followed by addition of HMPA (72 µl, 0.4 mmol) and stirred at room temperature 6 h. The reaction mixture was quenched with NH_4Cl (1 mL) and extracted with EtOAc (10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **51** was obtained as a colorless viscous oil (127.2 mg, 86% yield; 40:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 3:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.46-2.62 (m, 4H), 2.84 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.96 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.82 (s, 3H), 3.85 (s, 3H),), 3.87-3.90 (m, 1H), 4.14 (dd, *J* = 9.0, 6.8 Hz, 1H), 5.92 (dd, *J* = 3.2, 1.4 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 6.55-6.59 (m, 3H), 6.73 (dd, *J* = 15.0, 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 34.8, 38.3, 41.3, 46.5, 55.8, 56.0, 71.3, 101.1, 108.2, 109.5, 111.4, 111.8, 120.7, 122.3, 130.5, 131.4, 146.5, 147.9, 149.1, 178.5; **IR (neat):** 1767, 1732, 1514, 1442, 1236, 1155, 1027; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{21}H_{23}O_6$

371.1495, found 371.1490. The actual dr (40:1) was calculated using GC. See SI for GC trace.

*(±)-(3R,4R)-3,4-Bis(3,4-dimethoxybenzyl)dihydrofuran-2(3H)-one **(52).***[43] In a 4 dram vial, compound **49** (94.4 mg, 0.4 mmol) was dissolved in dry THF (4 mL) . The solution was cooled to -78 °C. To the solution, LDA (0.48 mmol, 0.96 ml of 0.5M) solution was added dropwise for 5 minutes. The solution was stirred for 1 h at -78 °C which turns the solution to yellow. To the reaction mixture, solution of 4-(bromomethyl)-1,2-dimethoxybenzene[45] (, 138 mg, 0.6 mmol) in 1.5 mL THF was added dropwise at -50 °C followed by addition of HMPA (72 µl, 0.4 mmol) and stirred at room temperature 6 h. The reaction mixture was quenched with NH_4Cl (1 mL) and extracted with EtOAc 10 (mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **52** was obtained as a white solid (109.6 mg, 71% yield; 33:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 3:1). **^{1}H NMR (300 MHz, $CDCl_3$);** δ 2.47-2.65 (m, 4H), 2.88-3.00 (m, 2H), 3.81-3.89 (m, 13H), 4.12 (dd, *J* = 9.0, 6.0 Hz, 1H), 6.48 (s, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 6.63-6.67 (m, 2H), 6.75 (dd, *J* = 9.0, 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 34.6, 38.3, 41.1, 46.6, 55.9, 71.3, 111.1, 111.4, 111.9, 112.4, 120.6, 121.4, 130.3, 130.5, 147.9, 148.0, 149.1, 178.8; **IR (neat):** 2935, 1765, 1512, 1452, 1234, 1155, 1014; **IR (neat):** 1765, 1512, 1452, 1234, 1081, 974; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{22}H_{27}O_6$ 387.1808; found 387.1818. The actual dr (33:1) was calculated using GC. See SI for GC trace.

*(±)-4-(Benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one **(53).*** The dicarbofunctionaliz-ation reaction was conducted in 10.0 mmol scale in 50 mL NMP in 8 h using the standard procedure. Organozinc (benzo[d][1,3]dioxol-5-ylzinc iodide) for this reaction was prepared according to procedure B. Under nitrogen atmosphere, benzo[d][1,3]dioxol-5-ylzinc iodide stock solution in THF (15 mmol) was taken in a 150 mL sealed tube and the solvent was removed under vacuum. To the residue of ArZnI was added $NiBr_2$ (30 mg, 0.3 mmol), terpyridine (45 mg, 0.4 mmol), and 1-(1-(allyloxy)-2-iodoethoxy)butane ***(48)*** (10 mmol). The mixture was then dissolved in NMP (50 mL). The sealed tube was tightly capped, and placed in an oil-bath pre-heated to 50 °C with vigorous stirring. The resultant cyclized cross coupled product was oxidized without further purification as follow: The crude reaction mixture (brown color) was diluted with ethyl acetate (30 mL) and washed three times with 10 mL of water. The combined EtOAc layer was dried with Na_2SO_4 and solvent was removed. For oxidation, the crude reaction mixture was taken in a reaction flask and 220 mL acetone was added to the flask. 33 mL of Jones reagent (prepared by dissolving 1 gm CrO_3 in 1 mL conc. H_2SO_4 and 3 mL H_2O) was added dropwise to the reaction mixture at 0°C. The reaction was stirred for 1 h at 0°C. Then the reaction was quenched with isopropyl alcohol (33 ml) and stirred for a while and filtered. The filtrate was neutralized with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (30 mL). The combined EtOAc layer was dried with Na_2SO_4 and the solvent was pumped off. The title compound **53** was obtained as a colorless oil (1452 mg, 60% yield) after purification by silica gel column chromatography (Hex: EtOAc = 4:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.19 (dd, *J* = 18.0, 9.0 Hz 1H), 2.52 (dd, *J* = 18.0, 9.0 Hz 1H), 2.60-2.78 (m, 3H), 3.93 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.25 (dd, *J* = 12.0, 9.0 Hz, 1H), 5.86 (s, 2H), 6.54 (d, *J* = 6.0 Hz, 1H), 6.58 (s, 1H), 6.68 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 33.8, 37.0, 38.3, 72.3, 100.8, 108.2, 108.7, 121.4, 131.9, 146.1, 147.7, 176.7; **IR (neat):** 2906, 1769, 1488, 1238, 1166, 1011; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{12}H_{13}O_4$ 221.0814; found 221.0806.

*(±)-(3R,4R)-4-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(3,4-dimethoxybenzyl)dihydrofuran-2(3H)-one **(54).**[25g]* In a 4 dram vial, compound **53** (88.0 mg, 0.4 mmol) was dissolved in dry THF (4 mL) . The solution was cooled to -78 °C. To the solution, LDA (0.48 mmol, 0.96 ml of 0.5M) solution was added dropwise for 5 minutes. The solution was stirred for 1 h at -78 °C which turns the solution to yellow. To the reaction mixture, solution of 4-(bromomethyl)-1,2-dimethoxybenzene[45] (138 mg, 0.6 mmol) in 1.5 mL THF was added dropwise at -50 °C followed by addition of HMPA (72 µl, 0.4 mmol) and stirred at room temperature 6 h. The reaction mixture was quenched with NH_4Cl (1 mL) and extracted with EtOAc (10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **54** was obtained as a colorless viscous oil (113.9 mg, 77% yield; 23:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 3:1). The actual dr ratio is calculated using GC trace. See SI for GC trace. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.42-2.60 (m, 4H), 2.88 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.96 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.86-3.88 (m, 1H), 4.11 (dd, *J* = 9.0, 6.0 Hz, 1H), 5.92 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.42-6.47 (m, 2H), 6.66-6.70 (m, 3H), 6.79 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 34.7, 38.4, 41.1, 46.6, 55.9, 71.2, 101.1, 108.3, 108.8, 111.2, 112.2, 121.4, 121.6, 130.2, 131.7, 146.4, 148.0, 149.1, 178.7; **IR (neat):** 1766, 1514, 1464, 1236, 1140, 1025; **HRMS (ESI-TOF):** Calcd for $(M+H)^+$ $C_{21}H_{23}O_6$ 371.1495; found 371.1529. The actual dr (23:1) was calculated using GC. See SI for GC trace.

*(±)-(3R,4R)-4-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzyl)dihydrofuran-2(3H)-one **(55).**[25a]* In a 4 dram vial, compound **52** (88 mg, 0.4 mmol) was dissolved in dry THF (4 mL) . The solution was cooled to -78 °C. To the solution, LDA (0.48 mmol, 0.96 mL of 0.5M) solution was added dropwise for 5 minutes. The solution was stirred for 1 h at -78 °C which turns the solution to yellow. To the reaction mixture, solution of 5-(bromomethyl)-1,2,3-trimethoxybenzene[46] (165.6 mg, 0.6 mmol,) in 1.5 mL THF was added dropwise at -50 °C followed by addition of HMPA (72 µl, 0.4 mmol) and stirred at room temperature 6 hrs. The reaction mixture was quenched with NH_4Cl (1 mL) and extracted with EtOAc (10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **55** was obtained as a colorless oil (128.0 mg, 80% yield; 40:1 dr) after purification by silica gel column chromatography (Hex: EtOAc = 3:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.44-2.65 (m, 4H), 2.84-2.96 (m, 2H), 3.82 (s, 9H), 3.84-3.90 (m, 1H), 4.17 (dd, *J* = 9.0, 6.0 Hz, 1H), 5.93 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.35 (s, 2H), 6.45-6.48 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 35.3, 38.4, 41.1, 46.5, 56.1, 60.9, 71.2, 101.1, 106.2, 108.3, 108.8, 121.6, 131.6, 133.4, 136.9, 146.4, 147.9, 153.3, 178.5; **IR (neat):** 1766, 1589, 1489, 1237, 1123, 1010; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{22}H_{25}O_7$ 401.1600; found 401.1594. The actual dr (40:1) was calculated using GC. See SI for GC trace.

Benzo[d][1,3]dioxol-5-yl(2-iodo-4,5-dimethoxyphenyl)methanone **.** The compound was prepared by Friedel-Crafts acylation of 1,3-benzodioxole with 6-iodoveratric acid according to

the literature procedure.[47] The title compound *benzo[d][1,3]dioxol-5-yl(2-iodo-4,5-dimethoxyphenyl)methan-one* was obtained as a white solid (94% yield) after purification by silica gel column chromatography (Hex : EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.80 (s, 3H), 3.88 (s, 3H), 6.03 (s, 2H), 6.78 (d, *J* = 6.0 Hz, 2H), 7.24-7.26 (m, 2H), 7.33 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 56.1, 56.3, 81.5, 102.0, 107.9, 109.4, 111.7, 121.8, 127.9, 130.6, 136.8, 148.3, 148.9, 150.4, 152.3, 195.2; **IR (neat):** 2900, 1635, 1499, 1323, 1179, 1033; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{16}H_{14}IO_5$ 412.9886, found 412.9879. The title compound was used directly for the preparation of organozinc **56** using the standard procedure A.

*(±)-4-(2-(Benzo[d][1,3]dioxole-5-carbonyl)-4,5-dimethoxybenzyl)dihydrofuran-2(3H)-one **(57).*** The dicarbofunctionalization reaction was conducted in 2.50 mmol scale in 12.5 mL NMP using the standard procedure for 8 h. For this reaction, the organozinc **(56**) (2-(benzo[d][1,3]dioxole-5-carbonyl)-4,5-dimethoxyphenyl)zinc iodide was prepared according to the standard procedure A. The resultant product was oxidized without further purification as follows: The crude reaction mixture (brown color) was diluted with ethyl acetate (15 mL) and washed three times with 5 mL water. The aqueous layer was extracted back with EtOAc (10 mL) and all the EtOAc layer were combined and dried with Na_2SO_4 and solvent was removed. For oxidation, the crude reaction mixture was taken in a reaction flask and acetone (70 mL) was added to the flask. 7.5 mL of Jones reagent (prepared by dissolving 1 gm CrO_3 in 1 mL conc. H_2SO_4 and 3 mL H_2O) was added dropwise to the reaction mixture at 0 °C. The reaction was stirred for 1 h at 0 °C. Then the reaction was quenched with isopropyl alcohol (6 mL) and stirred for a while and filtered. The filtrate was neutralized with $NaHCO_3$ (2 mL) and extracted with EtOAc (15 mL). The combined EtOAc layer was dried with Na_2SO_4 and the solvent was pumped off. The title compound **57** was obtained as a white solid (672.0 mg, 70% yield) after purification by silica gel column chromatography (Hex: EtOAc = 3:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.14 (dd, *J* = 18.0, 6.0 Hz 1H), 2.37 (dd, *J* = 18.0, 9.0 Hz 1H), 2.66-2.80 (m, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 3.86 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.13 (dd, *J* = 9.0, 6.0 Hz, 1H), 5.91 (s, 2H), 6.64-6.69 (m, 2H), 6.73 (s, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 7.17 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 33.8, 35.3, 37.1, 55.7, 72.3, 101.8, 107.4, 108.9, 112.4, 112.9, 126.8, 130.2, 131.1, 132.2, 146.3, 147.9, 150.2, 151.7, 176.7, 195.3; **IR (neat):** 2935, 1771, 1646, 1436, 1225, 1032; **HRMS (ESI-TOF):** $(M+H)^+$ Calcd for $C_{21}H_{21}O_7$ 385.1287; found 385.1276.

*(±)9-(Benzo[d][1,3]dioxol-5-yl)-6,7-dimethoxy-3a,4-dihydronaphtho[2,3-c]furan-1(3H)-one **(58).***[48] Compound **57** (76.8 mg, 0.25 mmol) was dissolved in dry THF (2.5 mL) and the solution was cooled to -78 °C. To the cooled solution, LDA (0.5 mmol, 1.0 mL of 0.5M solution in THF) was added dropwise for 5 minutes. The solution was stirred for 1 h at -78 °C which turns the solution to yellow. To the same reaction mixture, HMPA (45 µl, 0.25 mmol) was added dropwise and stirred at room temperature for additional 3 h. Then the solvent was removed and the crude reaction was dissolved in 2.4 mL pyridine solution. The reaction mixture was cooled back to 0 °C and $SOCl_2$ (182 µl, 2.5 mmol,) was added dropwise. It was stirred for 1 h at 0 °C and was diluted with CH_2Cl_2 (10 mL) and quenched with 1M HCl (2.5 ml). The reaction mixture was extracted with additional 10 mL CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvent was removed. The title compound **58** was obtained as a white solid (59.4 mg, 65% yield) after purification by silica gel column chromatography (Hex: EtOAc = 1:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 2.79 (t, *J* = 9.9 Hz, 1H), 2.93 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.33-3.46 (m, 1H), 3.67 (s, 3H), 3.92 (s, 3H), 4.00 (t, *J* = 9.0 Hz, 1H), 4.69 (t, *J* = 9.0 Hz, 1H), 6.02 (d, *J* = 3.0 Hz, 2H), 6.54 (s, 1H), 6.78 (br.s, 3H), 6.86 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 33.0, 35.8, 56.1, 71.05, 101.3, 107.9, 110.6, 111.2, 112.5, 119.6, 123.9, 127.9, 128.6, 129.3, 147.1, 147.2, 147.7, 147.9, 150.3, 168.4; **IR (neat):** 2915, 2849, 1745, 1683, 1540, 1378, 1063 ; **HRMS (ESI):** $(M+H)^+$ Calcd for $C_{21}H_{19}O_6$ 367.1182; found 367.1190.

*1-octyl-4-(trifluoromethyl)benzene **(64).***[49] The organozinc prepared for this reaction was according to procedure A. Under nitrogen atmosphere, in a sealed tube, (4-(trifluoromethyl)phenyl)zinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of ArZnI, $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.02 mmol), and iodooctane (0.5 mmol) were added successively. Then the mixture was dissolved in NMP (2.5 mL). Later, sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The title compound **64** was obtained as a colorless oil (78.1 mg, 88% yield) after purification by silica gel column chromatography in hexane. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.87 (t, *J* = 6.0 Hz, 3H), 1.25-1.33 (m, 10H), 1.56-1.63 (m, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.2, 22.8, 29.4, 29.5, 31.3, 32.0, 35.98, 123.5 (q, *J* = 72.0 Hz), 125.3 (q, *J* = 4.1 Hz), 126.8 (q, *J* = 63.7 Hz), 128.8, 147.1; **^{19}F NMR (282 MHz, $CDCl_3$)** δ -62.3. The NMR data are consistent with the reported values.

*1-methoxy-4-octylbenzene **(65)**.*[49] The organozinc prepared for this reaction was according to procedure A. Under nitrogen atmosphere, in a sealed tube, (4-((4-methoxyphenyl)zinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of ArZnI, $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.020 mmol), and iodooctane (0.5 mmol) were added successively. Then the mixture was dissolved in NMP (2.5 mL). Later, sealed tube was tightly capped and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The title compound **65** was obtained as a colorless oil (46.5 mg, 69% yield) after purification by silica gel column chromatography (Hex: EtOAc = 32:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.90 (t, *J* = 6.3 Hz, 3H), 1.28-1.35 (m, 10H), 1.54-1.64 (m, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 3.80 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.2, 22.8, 29.4, 29.6, 31.9, 32.0, 35.2, 55.3, 113.7, 129.3,

135.2, 157.7. The NMR data are consistent with the reported values.

diethyl 3-(4-(trifluoromethyl)benzyl)cyclopentane-1,1-dicarboxylate **(68)**.[13a] The organozinc prepared for this reaction was according to procedure A. Under nitrogen atmosphere, in a sealed tube, (4-(trifluoromethyl)phenyl)zinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of ArZnI, $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.02 mmol), and diethyl-2-allyl-2-(2-Iodoethyl)malonate (**12-I**) (0.5 mmol) were added successively. Then the mixture was dissolved in NMP (2.5 mL). Later, sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The title compound **68** was obtained as a colorless oil (148.8 mg, 80% yield) after purification by silica gel column chromatography (Hex: EtOAc = 9:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.17-1.25 (m, 6H), 1.28-1.41 (m, 1H), 1.76-1.84 (m, 2H), 2.07-2.40 (m, 4H), 2.62-2.75 (m, 2H), 4.10-4.20 (m, 4H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.51 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 32.1, 33.7, 40.3, 41.1, 41.4, 60.0, 61.5, 122.6, 125.4(q, J_{CF}= 3.8 Hz), 126.0 (q, J_{CF}= 31.5 Hz), 128.4 (q, J_{CF}= 34.1 Hz), 129.1, 145.4, 172.6, 172.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.8; **IR (neat):** 2981, 2944, 2855, 1725, 1617.

Test for the tolerance of base-sensitive racemizable stereocenter in *N*-Boc D-proline methyl ester (46) In a sealed tube, (4-cyanophenyl)zinc iodide stock solution in THF (0.60 mmol) was taken and the solvent was removed under vacuum. To the residue of ArZnI was added $NiBr_2$ (2.5 mg, 0.012), terpyridine (3.6 mg, 0.016 mmol), and diethyl-2-allyl-2-(2-bromoethyl)malonate (**12-Br**) (0.4 mmol) respectively. The chiral additives N-Boc D-Proline methyl ester (0.4 mmol) was then added in the mixture. Then the mixture was dissolved in NMP (2.0 mL). The sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by column chromatography using 20% EtOAc in hexane. The compound diethyl 3-(4-cyanobenzyl)cyclopentane-1,1-dicarboxylate (**13**) was obtained in 76% yield with the recovery of chiral additives *N*-Boc D-proline methyl ester in 93% yield. After the reaction, the racemization was checked using chiral HPLC. At first, the racemic mixture of N-Boc proline methyl ester in chiral HPLC were separated by chiral pak IA-3 in 1% IPA in hexane with the flow of 1.0 mL/min with detection by UV detector at 210 nm. The two peaks of (*S*)- and (*R)*-compounds were observed at 11.1 min and 12.8 min. Then pure *N*-Boc D-proline methyl ester {(*R*)-enantiomer)} appeared as a single peak at 12.8 min with 100:0 enantiomeric ratio (er). Later, *N*-Boc D-proline methyl ester recovered from our reaction was analyzed with the chiral HPLC which showed a single peak at 12.8 min with 100:0 er. For complete picture of both enantiomer, their % area and retention time see SI.

Test for the tolerance of base-sensitive racemizable stereocenter in (*R*)-Dimethylmethylsuccinate (47) To a sealed tube, (4-cyanophenyl)zinc iodide stock solution in THF (0.6 mmol) was taken and the solvent was removed under vacuum. To the residue of ArZnI, $NiBr_2$ (2.5 mg, 0.012 mmol), terpyridine (3.6 mg, 0.016 mmol), and diethyl-2-allyl-2-(2-bromoethyl)malonate (**12-Br**) (0.4 mmol) were added respectively. The chiral additives (*R*)-dimethylmethylsuccinate (0.5 mmol) was then added in the mixture. Then the mixture was dissolved in NMP (2.0 mL). Later, the tube was sealed and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by column chromatography using 15% EtOAc in hexane. The compound diethyl 3-(4-cyanobenzyl)cyclopentane-1,1-dicarboxylate **(13)** was obtained in 78% yield with the recovery of chiral additives (*R*)-dimethylmethylsuccinate in 89% yield. After this reaction, the epimerization of chiral additives was checked using chiral HPLC. At first, racemic mixture of (*R,S*)-dimethylmethylsuccinate were separated in HPLC by using Chiral-Pak-IB in 5% IPA in hexane with the flow of 0.5ml/min at 210 nm wavelength. The two peaks of (*R)*- and (*S)*- configuration were observed at 10.9 and 13.9 min. Then pure (*R*)-dimethylmethylsuccinate appeared as a peak at 10.9 and minor at 13.9 min with 90.5:9.5 er. Later, (*R*)-dimethylmethylsuccinate which is recovered from our reaction was analyzed through chiral HPLC. It shows two peaks at 10.9 and 13.9 min with 90.5:9.5 er which is exactly same with the value of (*R*)-dimethylmethylsuccinate before reaction. For complete picture of both enantiomer, their % area and retention time see SI.

Selectivity study in Negishi cross-coupling reaction: To a dry 1dram vial, arylzinc stock solution in THF, (4-(trifluoromethyl) phenyl)zinc iodide (0.6 mmol) and (4-methoxyphenyl)zinc iodide (0.6 mmol) was taken and the solvent was removed under vacuum. To the residue of mixture of ArZnI, $NiBr_2$ (1.3 mg, 0.006 mmol), terpyridine (1.8 mg, 0.008 mmol), and iodooctane (0.2 mmol) were added respectively. Then the mixture was dissolved in NMP (1.0 mL). The sealed tube was tightly capped, and placed in a hot plate preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (6 mL) and filtered through silica pad. The peaks of cross coupling product of 4-(trifluoromethyl)phenyl)zinc iodide with iodooctane and (4-methoxyphenyl)zinc iodide with iodooctane were analyzed using GC and GC/MS using pyrene as an internal standard. The ratio of **64**:**65** was found as 18: 10 which was calculated after calibration from the factor using pyrene as an internal standard.

Selectivity study in the cyclization/cross-coupling reaction: To a dry 1 dram vial, arylzinc stock solution in THF, (4-(trifluoromethyl)phenyl)zinc iodide (0.6 mmol) and (4-methoxyphenyl)zinc iodide (0.6 mmol) was taken and the solvent was removed under vacuum. To the residue, $NiBr_2$ (1.3 mg, 0.006 mmol), terpyridine (1.8 mg, 0.008 mmol), and Diethyl-2-allyl-2-(2-iodoethyl)malonate (**12-I**) (0.2 mmol) were added respectively. The mixture was dissolved in NMP (1.0 mL) as a solvent

then sealed tube was tightly capped and placed in a hot plate preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through silica pad. The clear solution was run in GC using pyrene as an internal standard. The product peak of cyclization cross coupled product of 4-(trifluoromethyl)phenyl)zinc iodide with **12-I** and (4-methoxyphenyl)zinc iodide with **12-I** were analyzed by GC and GC/MS using pyrene as an internal standard. The ratio of **68**:**16** was found as 17: 10 which was calculated after calibration of their value from the factor using pyrene as an internal standard.

Diastereoselectivity study of *trans*-1-(allyloxy)-2-bromocyclohexane: The organozinc prepared for this reaction was according to procedure A. In a sealed tube, phenylzinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of PhZnI was added $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.020 mmol), and *trans*-1-(allyloxy)-2-bromocyclohexane (**71**) (0.5 mmol) respectively. Then the mixture was dissolved in NMP (2.5 mL). The sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) extracted with ethyl acetate. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The crude reaction solution was analyzed in GC and GC/MS and their diastereomeric ratio was calculated. The diastereomeric ratio of the product from this reaction was found to be 1.3:1. The product (3R,3aS,7aS)-3-benzyloctahydrobenzofuran (**72**) was purified by column chromatography in 63% yield using 5% EtOAc in hexane. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.06-1.39 (m, 3H), 1.44-1.62 (m, 4H), 1.71-1.87 (m, 2H), 1.95-2.05 (m, 1x0.43H), 2.23-2.34 (m, 1x0.57H), 2.55-2.63 (m, 1H), 2.69-2.80 (m, 1H), 3.52 (dd, *J* = 6.0, 3.0 Hz, 1x0.57H), 3.65 (t, *J* = 8.5 Hz, 1x0.43H), 3.86-4.10 (m, 2H), 7.14-7.30 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 20.5, 21.2, 22.3, 23.7, 24.6, 27.6, 28.5, 28.7, 33.7, 39.9, 40.1, 43.1, 45.6, 45.8, 71.2, 72.0, 76.3, 78.4, 126.0, 126.1, 128.5, 128.8, 140.7, 141.0; **IR (neat):** 2926, 1452, 1022, 749, 698; **HRMS (CI):** $(M)^+$ Calcd for $C_{15}H_{20}O$ 216.1514; found 216.1503.

Diastereoselectivity study of *cis*-1-(allyloxy)-2-bromocyclohexane: In a sealed tube, phenylzinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of PhZnI was added $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.020 mmol), and *cis*-1-(allyloxy)-2-bromocyclohexane (**71**) (0.5 mmol) respectively. Then the mixture was dissolved in NMP (2.5 mL). The sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) extracted with ethyl acetate. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The clear solution was analyzed in GCand GC/MS and their diastereomeric ratio was calculated. The diastereomeric ratio of the product from this reaction was found to be 1.3:1. The product (3R,3aS,7aS)-3-benzyloctahydrobenzofuran (**72**) was purified by column chromatography in 74% yield using 5% EtOAc in hexane.

Diastereoselectivity study in radical cyclization.[28] Under nitrogen**,** in a quartz glass tube, AIBN (6.4 mg, 0.04 mmol), Bu_3SnH (175 mg, 0.6 mmol) and 3-(2-bromoethoxy)oct-1-ene (**74**) (105 µL, 0.4 mmol) were added respectively. The mixture was dissolved in benzene (1.0 mL). Then the quartz tube was tightly capped, and placed in UV light of 300 nm at 37 °C with vigorous stirring. After 12 h, the reaction mixture was cooled to room temperature and the solvent was pumped off. The diastereoselectivity of the reaction was analyzed through GC and ^{1}H NMR where the trans-isomer of the cyclization/H-atom abstraction product **75** was formed as a single diastereomer. The title compound **75** was obtained as a colorless oil (54.6 mg, 70% yield) after purification by silica gel column chromatography in Hexane. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.28-1.56 (m, 9H), 1.70-1.84 (m, 1H), 2.00-2.51 (m, 1H), 3.23-3.30 (m, 1H), 3.73-3.85 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 17.4, 22.7, 26.3, 32.2, 34.5, 34.9, 39.1, 66.7, 86.1; **IR (neat):** 2925, 1655, 1457, 1300, 1076, 661; **HRMS (CI):** $(M+H)^+$ Calcd for $C_{10}H_{21}O$ 157.1592; found 157.1590.

Diastereoselectivity study in cyclization/cross-coupling reaction: The organozinc prepared for this reaction was according to procedure A. To a sealed tube, phenylzinc iodide stock solution in THF (0.750 mmol) was taken and the solvent was removed under vacuum. To the residue of PhZnI, $NiBr_2$ (3.3 mg, 0.015 mmol), terpyridine (4.7 mg, 0.02 mmol), and 3-(2-bromoethoxy)oct-1-ene (**74**) (0.5 mmol) were added respectively. Then the mixture was dissolved in NMP (2.5 mL). The sealed tube was tightly capped, and placed in an oil-bath preheated to 50 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (15 mL) and H_2O (10 mL). The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The diastereomer was analyzed through ^{1}H NMR and GC. The diastereoselectivity of the reaction was analyzed through GC and ^{1}H NMR where the trans-isomer of the cyclization/cross-coupling product **76** was formed as a single diastereomer. The title compound **76** was obtained as a colorless oil (67.2 mg, 58% yield) after purification by silica gel column chromatography (Hex: EtOAc = 19:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.25-1.44 (m, 8H), 1.57-1.68 (m, 1H), 1.89-2.11 (m, 2H), 2.54 (dd, *J* = 12.0, 9.0 Hz, 1H), 2.77 (dd, *J* = 12.0 Hz, *J* = 9.0 Hz, 1H), 3.49-3.55 (m, 1H), 3.80 (t, *J* = 6.0 Hz, 2H), 7.15-7.31 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 14.1, 22.7, 26.1, 32.0, 32.6, 34.8, 39.5, 46.32, 66.8, 84.3, 126.1, 128.4, 128.9, 140.8; **IR (neat):** 2926, 1453, 1079, 754, 689; **HRMS (ESI-TOF):** Calcd for $C_{16}H_{24}ONa$ $(M+Na)^+$ 255.1725; found 255.1720.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of new compounds, and GC and HPLC traces. 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 interests.

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(16) We also examined 5-bromo-1-pentene and 7-bromo-1-heptene as substrates, which did not form 4- and 6-membered cyclization/cross-coupling products.

(17) We also examined 2,2-disubstituted terminal and 1,2-disubstituted internal olefins such as 1-(2-iodo-1-((2-methylallyl)oxy)ethoxy)butane and (*E*)-(3-(1-butoxy-2-iodoethoxy)prop-1-en-1-yl)benzene. However, no cyclization/cross-coupling product was observed in either case.

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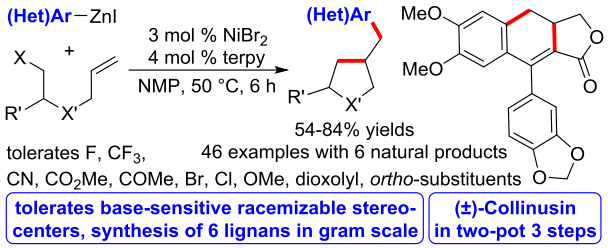
(Het)Ar—ZnI
X
+
R'
X'
3 mol % NiBr2
4 mol % terpy
NMP, 50 °C, 6 h
(Het)Ar
R'
X'
MeO
MeO
O
O
O
O
54-84% yields
46 examples with 6 natural products
tolerates F, CF3,
CN, CO2Me, COMe, Br, Cl, OMe, dioxolyl, ortho-substituents
tolerates base-sensitive racemizable stereo-centers, synthesis of 6 lignans in gram scale
(±)-Collinusin in two-pot 3 steps