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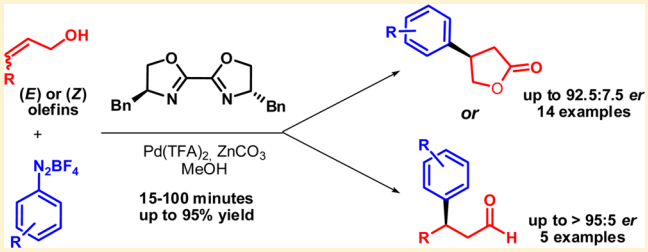
Intermolecular Enantioselective Heck–Matsuda Arylations of Acyclic Olefins: Application to the Synthesis of β-Aryl-γ-lactones and β-Aryl Aldehydes

Caio C. Oliveira, Ricardo A. Angnes, and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP. 13083-970, Campinas, São Paulo, Brazil

Supporting Information

ABSTRACT: We describe herein a synthetically useful method for the enantioselective intermolecular Heck–Matsuda arylation of acyclic allylic alcohols. Aryldiazonium tetrafluoroborates were applied as arylating agents in the presence of $Pd(TFA)_2$ and a chiral, commercially available, bisoxazoline ligand. The methodology is straightforward, robust, scalable up to a few grams, and of broad scope allowing the synthesis of a range of β-aryl-carbonyl compounds in good to high enantioselectivities and yields. This new enantioselective Heck–Matsuda arylation allowed the synthesis of β-aryl-γ-lactones and β-aryl aldehydes, which play a vital role as key intermediates in the synthesis of the biologically active compounds, such as (*R*)-baclofen, (*R*)-rolipram, (*S*)-curcumene, (*S*)-dehydrocurcumene, and (*S*)-tumerone.



INTRODUCTION

The enantioselective intermolecular Heck arylations of cyclic olefins was first reported by Hayashi in 1991.[1] Because of its intrinsic synthetic value, these reactions rapidly became a powerful tool in organic synthesis.[2] The conventional enantioselective Heck reaction requires a chiral chelating ligand and a cationic palladium species generated from an aryl triflate or an aryl halide using silver salts as additive. As the carbopalladation and β-hydrogen elimination steps proceed with *syn* stereospecificity, cyclic olefins were the first substrate choices for these Heck arylations since the newly created stereogenic sp^3 center is normally preserved during the double-bond migration process. On the other hand, acyclic olefins proved to be rather challenging substrates for such reactions as both vicinal hydrogens can participate in the β-elimination step, thus leading to mixtures of the allylic and styrenil products (Scheme 1).[3]

In spite of the remarkable advances in the field of Heck reactions,[4] there are only a few and scattered examples for the enantioselective intermolecular reaction using acyclic olefins. The first report was published by Shibasaki in the arylation of (*Z*)-buten-1,4-diol (**1**) with phenyl triflate (**2**) using $Pd(OAc)_2$ and (*S*)-BINAP. The Heck product, the lactol **3**, was obtained in a modest 24% yield after 12 days, in an enantiomeric ratio (*er*) of 68:32 (Scheme 2a).[5] The second example was described by Uemura in the arylation of (*E*)-crotyl alcohol (**4**) using the chiral phosphinite-oxazoline ligand **6**.[6] In their best case, the β-phenyl aldehyde **7** was obtained in 23% yield after 3 days, in a 58.5:41.5 *er* (Scheme 2b). These methods also suffer from harsh reaction conditions and provide the Heck adducts in low yields, making them less attractive in organic synthesis. Very recently, Sigman reported good results on the enantioselective arylation of secondary allylic and homoallylic alcohols using aryldiazonium hexafluorophosphates (Scheme 2c). In spite of the good yields and enantioselectivities, the arylation method requires dry solvents, inert atmosphere and rather long reaction times.[7] Herein we report an efficient and straightforward intermolecular enantioselective arylation of acyclic allylic alcohols employing aryldiazonium tetrafluoroborates in good to excellent enantiomeric ratios and yields. Our protocol uses palladium trifluoroacetate, $Pd(TFA)_2$, and the commercial chiral bisoxazoline **14** as ligand, out of the bottle solvent (MeOH), no need for inert atmosphere, mild conditions, short reaction times (15–100 min), broad scope, and the possibility of scaling up in an ordinary laboratory environment (Scheme 2d).

In 2012 we described the first examples of the enantioselective Heck–Matsuda reaction for the desymmetrization of cyclic unactivated olefins using chiral bisoxazolines (BOX) as ligands and arenediazonium tetrafluoroborates as arylating agents.[8] One major advantage of the Heck–Matsuda reactions is the fast oxidative addition of Pd(0) to aryldiazonium salts to generate a reactive cationic aryl-Pd(II) intermediate, which often favors high reactivity under mild conditions.[9] To further demonstrate the scope and versatility of this method, as well as its synthetic potential, we investigated the application of our previous protocol to the more challenging intermolecular arylation of acyclic olefins.

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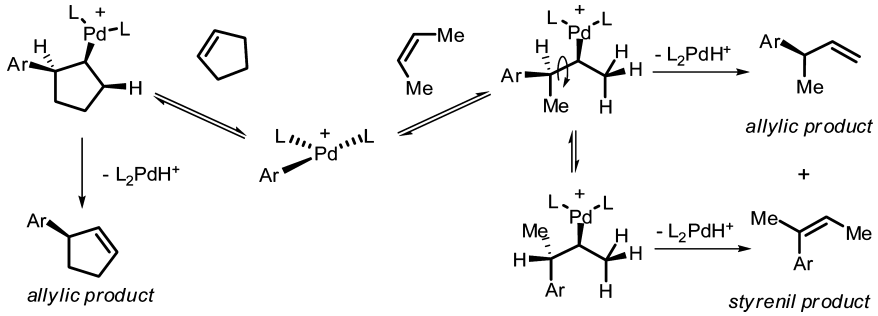
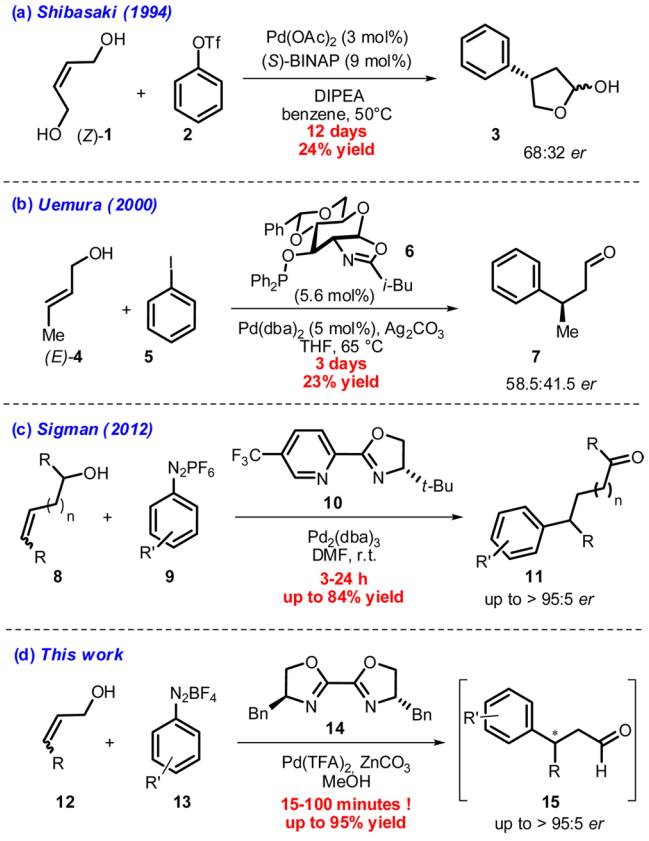
Scheme 1. Comparing the Intermolecular Heck Reactions of Cyclic and Acyclic Olefins



Scheme 2. Precedents for the Enantioselective Heck Arylation of Acyclic Olefins



RESULTS AND DISCUSSION

Our initial studies started with the reaction of diol **1** with *p*-chloro-benzenediazonium tetrafluoroborate (**13a**). When applying our previously reported conditions[8] ($Pd(TFA)_2$ (10 mol %), BOX ligand **14** (20 mol %), 1 equiv of 2,6-di-*t*-buytl-4-methyl-pyridine (DTBMP) as base, in methanol at 60 °C), the *O*-methyl lactol **16a** was obtained in 91% yield and an *er* of 92.5:7.5 for both diastereoisomers (Table 1, entry 1). In the absence of the palladium catalyst, no Heck products could be detected (entry 2). It is worth mentioning that these unoptimized reaction conditions already represent one of the best examples of an intermolecular enantioselective Heck reaction with an acyclic olefin.

Replacement of $Pd(TFA)_2$ by $Pd(OAc)_2$ or the cationic $Pd(MeCN)_4(BF_4)_2$ had a detrimental effect on the *er* values, although the chemical yields remained good (entries 3−4). Somewhat surprisingly, the use of $Pd(dba)_2$ provided yields and enantioselectivities comparable to those obtained with $Pd(TFA)_2$ (entries 1 and 5). The disadvantage when using $Pd(dba)_2$ is the frequent contamination of the Heck products with free dba.[10] MeOH was considered a good solvent for the Heck reaction not only for its high polarity but also for its capability of reducing Pd(II) to Pd(0) in situ. Nevertheless, a few mixtures of MeOH with other solvents were also evaluated. The use of the "green solvent" dimethyl carbonate/MeOH led to *O*-methyl lactol **16a** in 88% yield and 91:9 *er* (entry 6), which indicated DMC as a good alternative.[11]

As we have previously observed that zinc salts seem to have an accelerating effect in the Heck−Matsuda reactions, we decided to further explore it as base.[8] Replacing DTBMP for $ZnCO_3$ in DMC proved ineffective. However, in MeOH as solvent the *O*-methyl lactol **16a** was obtained in 95% yield and 90:10 *er* after only 15 min (entries 7 and 8). Because of its lower cost, effectiveness, and cleaner reactions, we decided to keep $ZnCO_3$ as our optimal base.

The best $Pd(TFA)_2$:BOX ligand ratio was found to be 1:2.2 (entry 9). This was done empirically, probing the system. Decreasing the catalyst loading to 5%, and the ligand to 11 mol %, led to a lower yield (58%) and *er* (81:19) (entry 10). We then hypothesized that the formation of the key complex Pd/BOX (see compound A in Scheme 4) could be under equilibrating conditions. Gratifyingly, when we raised the concentration of the reaction from 0.14 to 0.27 M, the *O*-methyl lactol **16a** was obtained in 92% yield and 92.5:7.5 *er*, after only 15 min (entry 11). At higher concentration (0.54M), both yield and *er* were significantly reduced (entry 12), probably because of the limited solubility of the aryldiazonium salt in the reaction medium. Absence of base led to a significant erosion of the *er* (67:33), whereas the yield was kept at a good 88% (entry 13). We speculate that without an effective base, the ligand bisoxazoline may function as such, liberating ligand-free palladium to the reaction medium. Finally, arylations were best carried out at 60 °C, using 2 equiv of the aryldiazonium salt.[12] Remarkably, these reactions are all very clean (see chromatograms S58 of the Supporting Information). The key *O*-methyl lactol **16a**, a precursor of the GABA agonist baclofen, was produced in high yield and good *er* after a single filtration through a short plug of silica gel even in a 10 mmol scale (Scheme 3).

A rationale for the formation of *O*-methyl lactols **16** and the stereochemical outcome is shown in Scheme 4. The catalytic cycle starts with the oxidative addition of the chiral palladium complex **A** to aryldiazonium **13** to form the cationic aryl-palladium **B**. The preferential formation of the *R* isomer can be rationalized by the approach of olefin **1** to complex **B** as depicted in **C**, probably avoiding interaction of the carbinolic

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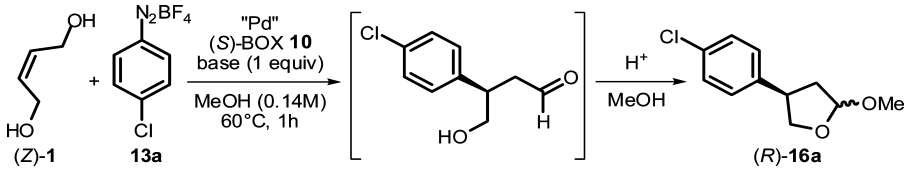
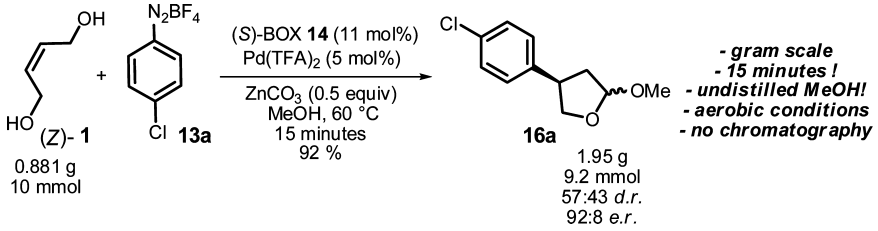
Table 1. Evaluation of the Intermolecular Heck Arylation



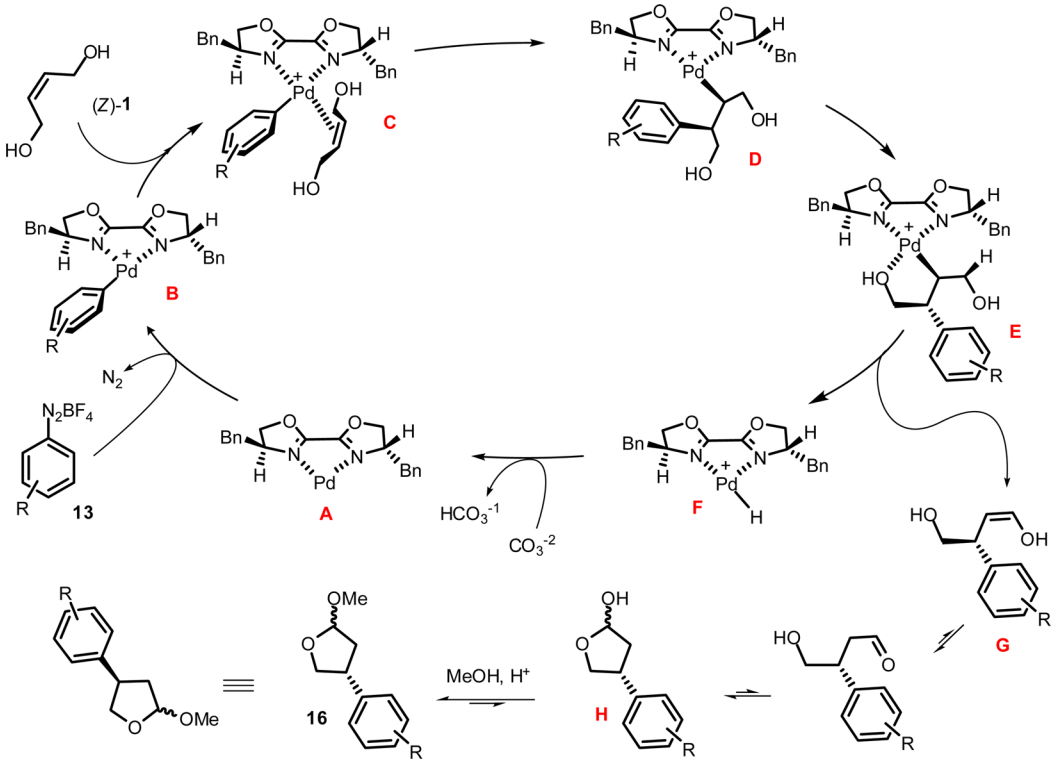
entry	"Pd" (mol %)	(*S*)-BOX (mol %)	solvent	base	yield (%)[a]	*dr*[b]	*er*[b,c]
1	$Pd(TFA)_2$ (10)	20	MeOH	DTBMP	91	54:46	92.5:7.5
2	—	—	MeOH	DTBMP	—		—
3	$Pd(OAc)_2$ (10)	20	MeOH	DTBMP	90	58:42	86:14
4	$Pd(MeCN)_4(BF_4)_2$ (10)	20	MeOH	DTBMP	80	60:40	65:35
5	$Pd(dba)_2$ (10)	20	MeOH	DTBMP	77	59:41	92:8
6	$Pd(TFA)_2$ (10)	20	DMC/MeOH (95:5)	DTBMP	88	61:39	91:9
7	$Pd(TFA)_2$ (10)	20	MeOH	$ZnCO_3$	95	59:41	90:10
8	$Pd(TFA)_2$ (10)	20	DMC/MeOH (95:5)	$ZnCO_3$	5	61:39	72:28
9[d]	$Pd(TFA)_2$ (10)	22	MeOH	$ZnCO_3$	95	59:41	93:7
10[d]	$Pd(TFA)_2$ (5)	11	MeOH	$ZnCO_3$	58	59:41	81:19
11[d,e]	**$Pd(TFA)_2$ (5)**	**11**	**MeOH**	**$ZnCO_3$**	**92**	**57:43**	**92.5:7.5**
12[d,f]	$Pd(TFA)_2$ (5)	11	MeOH	$ZnCO_3$	40	58:42	82:18
13	$Pd(TFA)_2$ (5)	11	MeOH	—	88	58:42	67:33

[a]Determined by ^{1}H NMR. [b]Determined by chiral GC analysis. [c]Both diastereoisomers display the same enantiomeric ratios (see Scheme 4 for the proposed mechanism). [d]Reaction time was 15 min. [e]Reaction performed at 0.27 M. [f]Reaction performed at 0.54 M.

Scheme 3. Synthesis of 16a on Gram Scale



Scheme 4. Rationale for the Catalytic Cycle and Stereochemical Outcome



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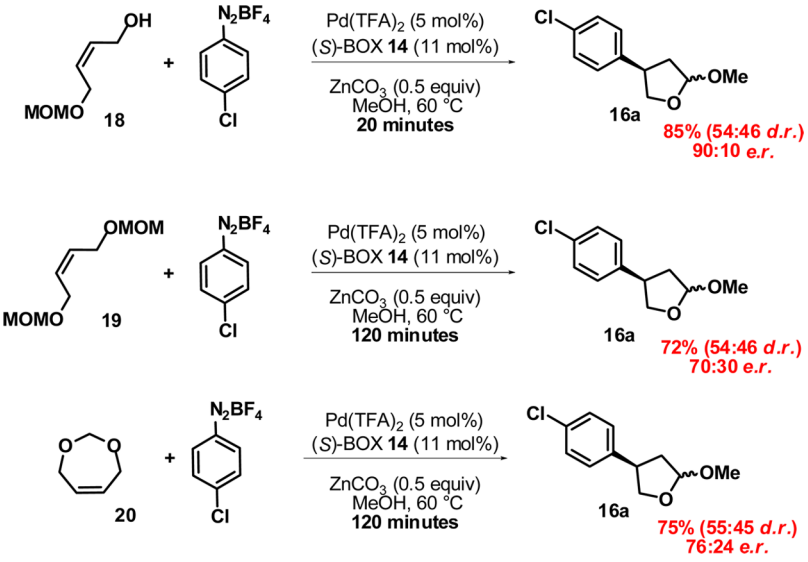
Scheme 5. Heck–Matsuda Arylation of Mono- and Bis-Protected Derivatives of Diol 1

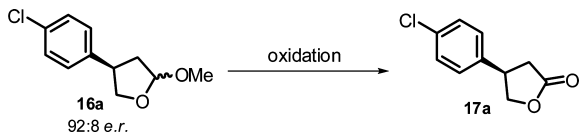


groups present in olefin (*Z*)-**1** with one of the benzyl groups of ligand (*S*)-BOX-14. *Syn*-carbopalladation then generates intermediate **D**. Since a free hydroxyl group seems to be critical for effective transformation, we propose the intermediacy of complex **E**, a five-membered "oxy-complex" with one of the free carbinol group (participation of the carbinol next to palladium leads to a more constrained four-membered oxy-complex).[13a] The hydrogens on the free carbinol group then become available for β-syn-elimination furnishing the palladium hydride intermediate **F** and the enol **G**. Intermediate **F** is deprotonated by base regenerating Pd(0), while **G** undergoes tautomerization followed by intramolecular cyclization to form lactol **H**. Acid catalysis by the Lewis acid Zn^{2+} and/or HCO_3^-/H_2CO_3 in the presence of methanol (solvent) then leads to the Heck product *O*-methyl lactols **16** as a mixture of diastereomers.

To evaluate the participation of a free hydroxyl group in the catalytic process, we performed the Heck–Matsuda arylation of the mono- and bis-protected derivatives **18** and **19**, as well as of the dioxepin **20** (Scheme 5). The monoprotected substrate **18** led to the formation of *O*-methyl lactol **16a** after 15 min with yield and enantiomeric ratio comparable to that observed for the arylation of diol **1**, whereas the diprotected substrate **19** and the dioxepin **20** led to the same Heck product in lower yields and *er* after 120 min. These longer reaction times for the arylation of compounds **19** and **20** strongly suggest the active participation of a free carbinol group favoring the catalytic cycle, possibly through stabilization of intermediate **E**, as indicated in Scheme 4. These data also indicate that higher enantiomeric ratios and yields are associated with the presence of a free carbinolic group, but that its absence is not an impediment for the Heck arylation reaction.

The *O*-methyl lactols **16** were obtained as inseparable mixtures of diastereomeric compounds (single spot on TLC). However, since our main objective was the synthesis of the respective lactones, we investigated the direct conversion of methyl lactols **16** into the corresponding 4-aryl-γ-lactones **17** (Table 2). We first evaluated the method described by Cacchi [*m*-CPBA (**21**), $BF_3{\cdot}OEt_2$ in CH_2Cl_2], but these conditions led to moderate yields (~50%) of lactone **17a** and, surprisingly, to extensive racemization of the product.[13b] We rationalize this

Table 2. Evaluated Procedures for the Oxidation of *O*-Methyl Lactol 16a into 17a



entry	conditions	yield (%)	*er*
1	*m*-CPBA (**21**), $BF_3{\cdot}Et_2O$, DCM, rt, 16 h	50	70:30
2	(1) HCl, MeCN, rt 1 h; (2) PCC (**22**), DCM, rt, 6 h	62	92:8
3	Jones, acetone/H_2O, 0 °C to rt, 2 h	88	92:8

rather unusual result by the participation of radical species in the oxidation process, thus leading to benzylic hydrogen abstraction and consequent partial racemization of the product. A two-step procedure was also adopted: acidic hydrolysis with HCl followed by oxidation with pyridinium chlorochromate (PCC) (**22**). In this case, a good *er* was observed but with only a marginal increase in the yield of lactone **17a**. A much better result was obtained with diluted Jones solution at 0 °C followed by warming to room temperature. In this case, lactone **17a** was isolated in 88% yield and 92:8 *er*. This lactone can be obtained with an *er* higher than 95:5 after a single recrystallization.

With an efficient protocol established for the oxidation of the diastereomeric mixture of methyl lactols to the corresponding lactones, we then evaluated the scope of the Heck–Matsuda toward several aryldiazonium tetrafluoroborates (Table 3). These reactions exhibited broad scope and efficiency providing the *O*-methyl lactols **16a–n** in yields ranging from 69 to 95%. Complete chemoselectivity was achieved in the presence of halogen-substituted aryldiazonium salt (Table 3, entries 1–6). For example, the 4-iodo-phenyl *O*-methyl lactol **16f** was obtained in 90% yield and 92:8 *er*, making this product a valuable substrate for further cross-coupling reactions (entry 6). Electron-rich aryldiazonium salts furnished the products in excellent yields and enantioselectivities (entries 7–13). The efficiency of the reaction was not affected by steric effects as demonstrated in entries 4 and 8. Electronic effects may play an important role in the process as electron-deficient aromatic

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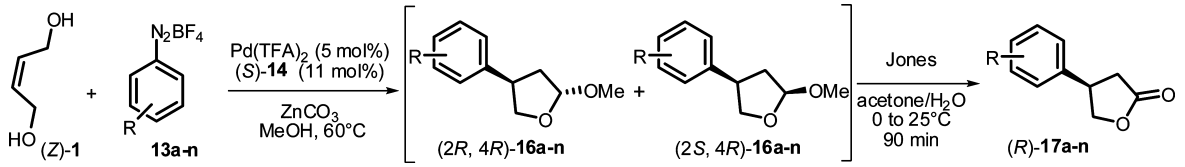
Table 3. Enantioselective Heck–Matsuda Arylation of (*Z*)-Diol 1 Followed by Oxidation to Produce the Enantioenriched 4-Aryl-γ-lactones 17



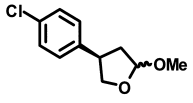
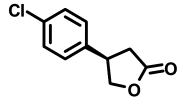
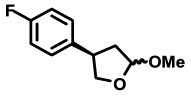
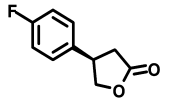
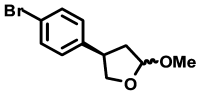
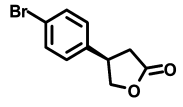
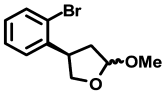
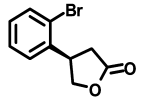
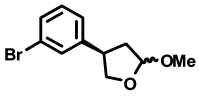
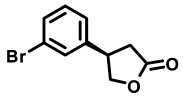
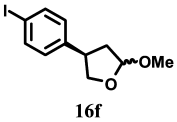
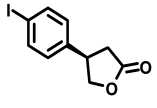
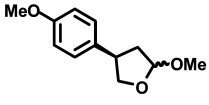
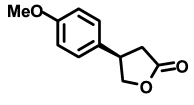
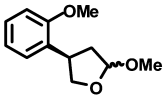
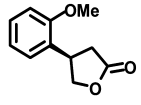
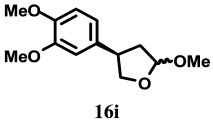
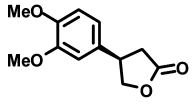
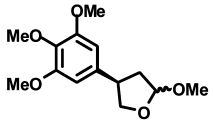
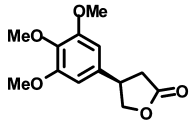
entry	R	time (min)	16a-n	*d.r.*[a] (2*R*, 4*R*)/ (2*S*, 4*R*)	Yield[b] (%)	17a-n	yield[c] (%)	*e.r.*[a]
1	4-Cl	15	 **16a**	57:43	92 (90)[d]	 **17a**	81 (81)[f,g]	92.5:7.5
2	4-F	20	 **16b**	58:42	85	 **17b**	78	89.5:10.5
3	4-Br	40	 **16c**	57:43	95	 **17c**	71	91:9
4	2-Br	40	 **16d**	62:38	90	 **17d**	77	90:10
5	3-Br	30	 **16e**	59:41	94	 **17e**	83[f]	82:18
6	4-I	25	 **16f**	59:41	90	 **17f**	73[f]	92:8
7	4-OMe	40	 **16g**	59:41	91 (90)[d]	 **17g**	79 (81)[f,g]	91:9
8	2-OMe	105	 **16h**	67:33	90 (88)[d]	 **17h**	72	91:9
9	3,4-OMe	30	 **16i**	59:41	95 (92)[d]	 **17i**	58	91:9
10	3,4,5-OMe	100	 **16j**	58:42	69 (65)[d]	 **17j**	50[f]	89.5:10.5

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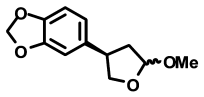
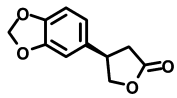
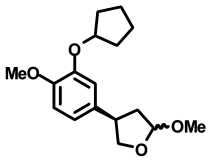
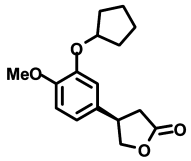
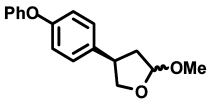
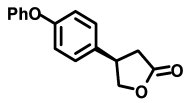
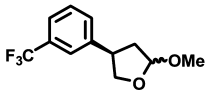
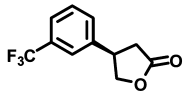
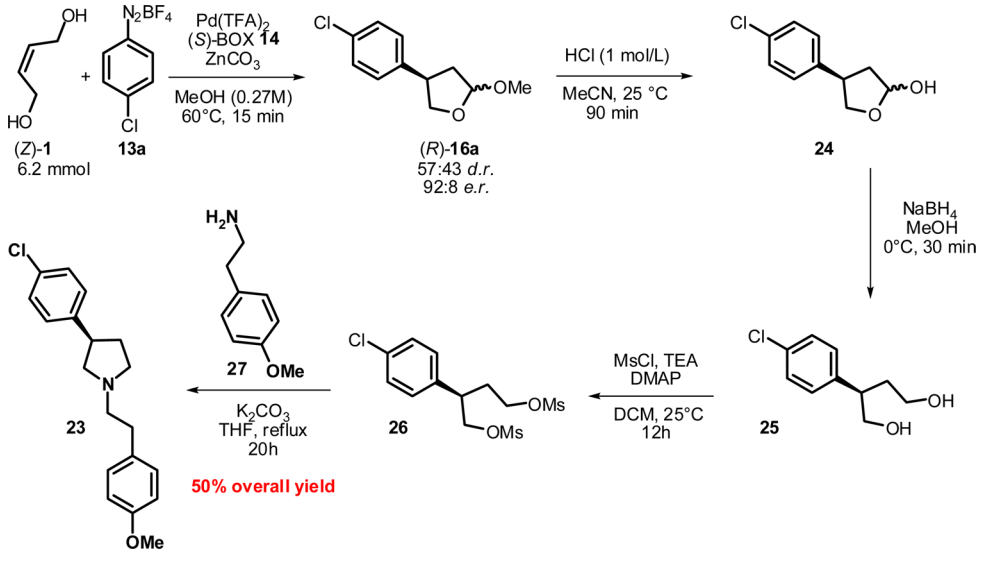
Table 3. continued

entry	R	time (min)	16a-n	*d.r.*[a] (2*R*, 4*R*)/ (2*S*, 4*R*)	Yield[b] (%)	17a-n	yield[c] (%)	*e.r.*[a]
11	3,4-OCH_2O	60	 **16k**	59:41	95	 **17k**	61	92:8
12	3-O*c*Pn-4-OMe	100	 **16l**	64:36	90	 **17l**	61	90:10
13	4-OPh[e]	30	 **16m**	73:27	95	 **17m**	87	91:9
14	3-CF_3	15	 **16n**	57:43	80	 **17n**	72	84:16

[a]Determined by chiral GC and/or HPLC analysis. [b]Determined by ^{1}H NMR. [c]Isolated yield after two steps (1 mmol scale). [d]Isolated yield of **16** in parentheses. [e]Enantiomeric ratio determined after conversion to the corresponding lactone. [f]Enantiomeric ratio >95:5 after a single recrystallization. [g]Isolated yield at 10 mmol scale.

Scheme 6. Enantioselective Synthesis of the Aryl-pyrrolidine 23



rings were transferred with slightly lower enantioselectivity (entries 5, and 14). Gratifyingly, the protocol adopted for the oxidation of the *O*-methyl lactols proved compatible with the presence of electron-rich phenyl groups furnishing good to excellent yields (50−87%) of lactones **17** in good enantiomeric ratios (Table 3). The absolute stereochemistry of lactones **17a**, **17d**, and **17g** were assigned by comparison to previously reported synthesis of these compounds,[14] and all others were determined by analogy.

It is worth pointing out that the enantioenriched 4-aryl-γ-lactones **17** are versatile building blocks for the construction of bioactive compounds. For example, lactone **17a** was used as a key intermediate for the total synthesis of the $GABA_B$ agonist (*R*)-baclofen,[15] an amino acid used to treat spasticity and alcoholism, whereas lactone **17l** is a precursor to the antidepressant and anti-inflammatory lactam (*R*)-rolipram.[16] Since our method promotes a significant increase in structural complexity, we believe that it will complement the current methods for the synthesis of these lactones, such as the laborious asymmetric Baeyer−Villiger oxidation of prochiral cyclobutanones,[14] and the Rh-catalyzed 1,4-addition of boronic acids to α−β-unsaturated lactones.[17] Additionally, as aryl pyrrolidines are common structural motifs among several bioactive compounds and drugs,[18] the chiral *N*-substituted-3-

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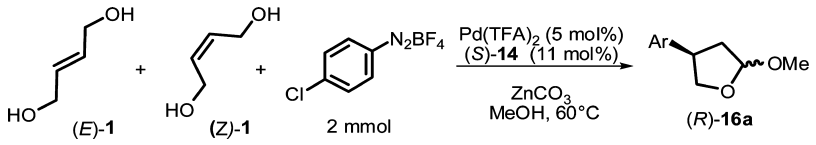
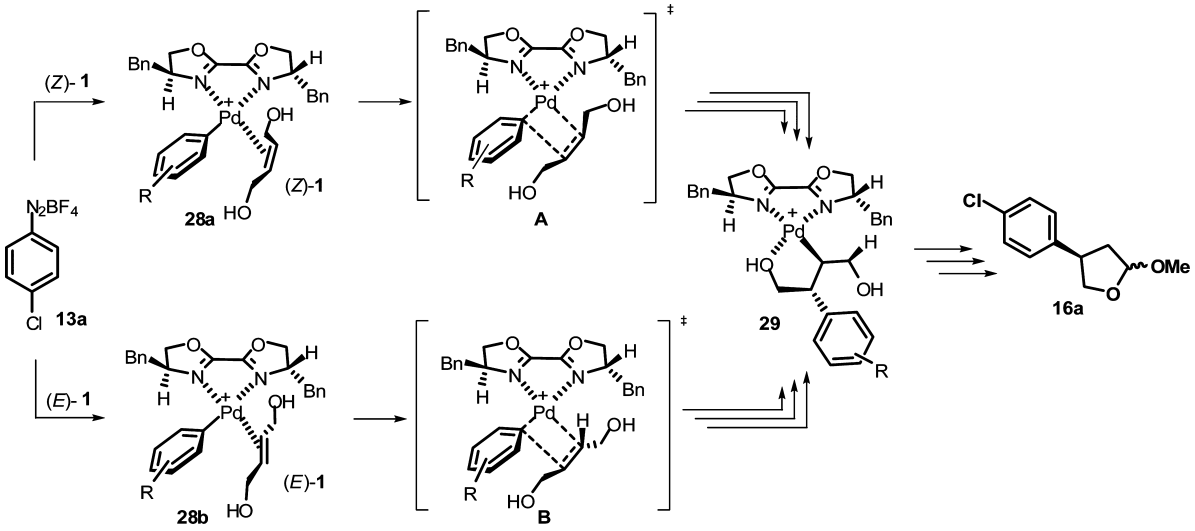
Table 4. Stereoconvergent Heck–Matsuda Reaction



entry	(*E*)-**1** (mmol)	(*Z*)-**1** (mmol)	*er*	yield (%)
1	1	—	89.5:10.5	82
2	0.75	0.25	91:9	52
3	0.5	0.5	90:10	65
4	0.25	0.75	91:9	80
5	—	1	92:8	92

Scheme 7. Rationale for the Stereoconvergency of Diols (*Z*)- and (*E*)-1



aryl-pyrrolidine **23** was obtained in a straightforward manner by the hydrolysis of *O*-methyl lactol **16a** in HCl,[19] followed by reduction of the lactol **24** with $NaBH_4$. Mesylation of diol **25** provided the bis-electrophile **26**, which underwent a double S_N2 reaction with amine **27** to provide pyrrolidine **23** in 50% overall yield after five steps from diol **1** (Scheme 6).[18] This route is easily scalable, and no chromatographic purifications were required along the route, except for the last step.

Somewhat surprisingly, the (*E*)-diol **1** provided the same *O*-methyl lactol enantiomer as its (*Z*)-isomer. The *O*-methyl lactol (*R*)-**16a** was obtained with the same levels of enantioselectivity starting from the *Z* or *E* isomer, or from mixtures of both isomeric diols **1** (Table 4). This interesting phenomenon is somewhat rare, and to the best of our knowledge, there is only a single example of that in the literature for the Heck reaction.[6] In the present case, it can be explained by the preferential orthogonal approach of both stereoisomeric diols to the plane of the ligand to minimize repulsion between the carbinol groups in **1** and the benzyl group in the ligand (**28a,b**, Scheme 7). The two putative transition states for the carbopalladation step (**A** and **B**) provide the newly formed benzylic center with the same absolute configuration, as depicted in the oxy-complex **29**, the precursor for the formation of the *O*-methyl lactol **16a** (Scheme 7).

Encouraged by these results, we extended the arylations to the (*E*) and (*Z*) crotyl alcohols **4** and the (*Z*)-2-penten-1-ol **30** (Table 5). Heck reactions proceeded smoothly in moderate to excellent yields (54–90%) and enantioselectivities (88:12 to >95:5) but only with modest regioselectivities (~1:1 up to ~3:1) to provide the β-aryl dimethylacetals **31** and the α-aryl dimethylacetals **32** as the primary Heck adducts.[20] We would also like to highlight the fact that the *er* of both dimethylacetals were very similar as determined by chiral GC analysis of this clean but inseparable mixture of regioisomers (88:12 to >95:5 *er*, see Supporting Information for details). In particular, the enantioselectivities observed for the regioisomeric dimethylacetals **32** are intriguing and pose interesting questions. The arylation process implicates the formation of σ-palladium intermediates in equilibrium with a tightly bounded chiral palladium hydride. Palladium hydride migration along the carbon chain terminates with the formation of the aldehyde function, but it maintains to a great extent the newly created stereogenic center at the α-position (see Supporting Information for a mechanistic proposal regarding these transformations). Unfortunately, acid hydrolysis of most dimethylacetals **32** led to extensive decomposition and racemization of the corresponding aldehydes **34**. Another aspect that is worth pointing out is the lack of stereoconvergency as observed for bis-diols **1**. The (*Z*)-mono allylic alcohols **4** and **30** led to the *S* configuration of the stereocenter present in aldehydes **33**, whereas the (*E*)-stereoisomers led to the opposite *R* configuration.

Because of the instability of aldehydes **34**, we initially focused our attention on the major regioisomeric β-aryl aldehydes **33**, which could be obtained in moderate overall yields (over 2 steps from the allylic substrates) in good to high enantiomeric

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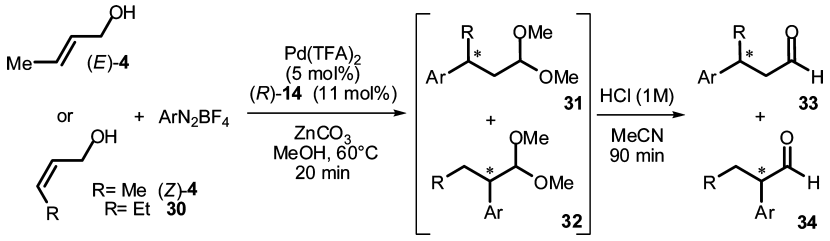
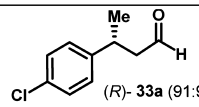
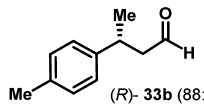
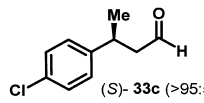
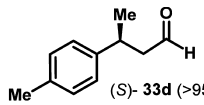
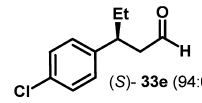
Table 5. Heck–Matsuda Arylation of Allylic Alcohols to Produce the Chiral β-Aryl Aldehydes 33 and α-Aryl Aldehydes 34



entry	olefin	Ar	yield (31+32) (%)[a]	31/32	regioisomer 33 (e.r.)[b]	yield (%)[c]
1	(E)- 4	4-Cl-Ph	90	58:42	 (R)- 33a (91:9)	49
2	(E)- 4	4-Me-Ph	54	51:49	 (R)- 33b (88:12)	26
3	(Z)- 4	4-Cl-Ph	87	61:39	 (S)- 33c (>95:5)	49
4	(Z)- 4	4-Me-Ph	66	63:37	 (S)- 33d (>95:5)	37
5	30	4-Cl-Ph	58	77:23	 (S)- 33e (94:6)	42

[a]Determined by ^{1}H NMR. [b]Determined by chiral GC analysis. [c]Isolated yield of β-aryl aldehyde **33** over two steps (1 mmol scale).

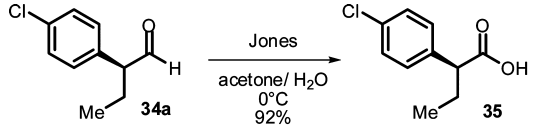
ratios, especially when the (*Z*)-**4** and (*Z*)-**30** were used (entries 3–5, Table 5). In spite of the moderate yields, these reactions are operationally simpler alternatives to the usual enantioselective 1,4-addition of dialkylzinc to cinnamaldehyde derivatives.[21] β-Alkyl substituted aldehydes are also versatile building blocks in organic synthesis. An illustrative example is the previously reported total synthesis of the anticancer bisabolane sesquiterpenes (*S*)-curcumene, (*S*)-dehydrocurcumene and (*S*)-tumerone employing the chiral, nonracemic aldehyde **33d** as a common precursor.[21a]

As mentioned previously, aldehydes **34** are rather unstable and volatile compounds. However, aldehydes **34c** and **34d** could be isolated in pure form to allow their full spectroscopic and spectrometric characterization. The original *er* values of these aldehydes could be estimated from their corresponding dimethylacetals and from the hydrolysis products by chiral capillary GC analysis (see Supporting Information for details). Additionally, the absolute stereochemistry of **34c** (obtained by the arylation of *E*-**4** with (*S*)-Box **14** as ligand) was assigned as (*S*) after its oxidation to the known carboxylic acid **35** (Scheme 8).[22]

CONCLUSION

In conclusion, we successfully developed an efficient and enantioselective intermolecular Heck–Matsuda arylation of acyclic olefins. Structurally diverse allylic alcohols were arylated under mild conditions in high yields and good enantioselectivity to provide structurally complex *O*-methyl lactols, 5-membered lactones, and α- and β-arylated aldehydes, which play a key role as intermediates in organic synthesis. A rationale concerning the mechanism and the absolute enantioselectivity of these arylations was also presented in order to give some insight on these interesting reactions. Additional work extending the scope of this arylation method and the elucidation of the reaction mechanism is ongoing and will be reported in due course.

Scheme 8. Oxidation of the Aldehyde 34a



EXPERIMENTAL SECTION

General Methods. Flash column chromatography was performed using silica gel (230–400 mesh). Thin layer chromatography (TLC) was performed using silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with phosphomolibdic acid, followed by heating. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a

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positive atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe techniques. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 250, 500, and 600 MHz. Spectra were recorded in $CDCl_3$ solutions. Data were reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz (Hz) and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 62.5, 125, and 150 MHz. Spectra were recorded in $CDCl_3$ solutions. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), hp (heptet), dd (double doublet), ddd (double double-doublet), dt (double triplet), td (triple of doublet), m (multiplet) and bs (broad signal). 1,3-Bis(trifluoromethyl)-5-bromobenzene was used as internal standard for the determination of chemical yields by ^{1}H NMR. High resolution mass spectra (HRMS) were recorded by an electron impact ionization mass spectrometer with a Q-TOF analyzer. Optical rotations were measured in a digital polarimeter. The chiral GC and HPLC methods were calibrated with the corresponding racemates. Except when noted, enantiomeric ratios were determined for the corresponding *O*-methyl lactols **16** by chiral GC analysis using a Chirasil-DEX CB column (25 m × 320 μm × 0.25 μm nominal) under the following conditions: Inlet temperature 220 °C; T_0 = 100 °C (2 min), then at 15 °C/min until 135 °C (25 min), then at 5 °C/min until 180 (40 min).

Enantioselective Heck–Matsuda Reaction. In a 15 mL pressure tube equipped with a magnetic stirring bar were added, in this order: $Pd(TFA)_2$ (16.6 mg, 0.05 equiv, 0.05 mmol), (*S*)-BOX-10 (35.2 mg, 0.11 equiv, 0.11 mmol) and methanol (3.7 mL). The reaction mixture was then immersed in a previously heated oil bath (60 °C) and kept under stirring for 5 min. After this period, the tube was removed from the oil bath and added to the reaction mixture, in this order: $ZnCO_3$ (62.7 mg, 0.5 equiv, 0.5 mmol), the diol **1** (88 mg, 82.2 μL, 1 equiv, 1 mmol) and the aryldiazonium salt (2 equiv, 2 mmol). After addition, the tube was sealed and immersed again in the oil bath. The suspension formed was kept under vigorous stirring until the reaction mixture became homogeneous (by this point diol **1** was totally consumed). The reaction flask was then allowed to cool down to room temperature, and the reaction mixture was transferred to a 100 mL round-bottom flask, followed by removal of the solvent in vacuo. The product was extracted from the resulting residue by successive washes with hexanes:ethyl acetate (1:1) in portions (6 × 50 mL). The combined organic extract was filtered through a plug of silica gel (2.5 × 3 cm) under pressure, and the filtrate was concentrated in vacuo. The crude product was used in the next step without further purification.

Jones Oxidation. To a 100 mL round-bottom flask equipped with a magnetic stirring bar was added the crude Heck–Matsuda reaction followed by acetone:water = 3:1 (20 mL). The reaction mixture was cooled in an ice bath and stirred over 5 min. Next, 2.2 mL of the Jones solution (see below) were added. The mixture was allowed to cool at 0 °C for 30 min and then left at the rt for 90 min. Isopropanol was added (10 mL) resulting in the formation of a green suspension, which was stirred for 10 min. The volatiles were then removed in vacuo, and the resulting suspension transferred to a separatory funnel. The suspension was diluted with ethyl acetate (40 mL) and washed with brine (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtrated and rotaevaporated. The crude product was purified by column chromatography in silica gel (EtOAc:Hexanes = 1:4) to furnish the lactones **17**. Except when noted the products were obtained as pale yellow oils. Solid lactones (**17a–c**, **17f,g**, **17i**, **17l**) were further purified by recrystallization using ethyl acetate/hexanes.

Preparation of the Jones Reagent Solution. To a 100 mL beaker (A) was added 25 g of powdered CrO_3. The chromium trioxide was suspended in concentrated H_2SO_4 (25 mL) under constant stirring with a glass rod. After addition, a reddish slurry was formed containing some insoluble CrO_3 at the bottom. The crude mixture was carefully and slowly transferred to another 250 mL beaker (B) containing water (75 mL). ***Caution!*** *Strongly exothermic reaction.* The resulting orange solution formed in beaker (B) was also used to dissolve the remaining CrO_3 in beaker (A).

(2*R*,4*R*)-4-(4-Chlorophenyl)-2-methoxytetrahydrofuran and (2*S*,4*R*)-4-(4-Chlorophenyl)-2-methoxytetrahydrofuran (16a). 90% yield (191 mg). Diastereomeric ratio (57:43). Obtained as a pale yellow oil after chromatography [hexanes:ethyl acetate (90:10)]: ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) *(major diastereomer)* 7.27 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 5.14 (dd, J = 2.5 and 5.8 Hz, 1H), 4.29 (t, J = 8.3 Hz, 1H), 3.79 (dd, J = 6.8 and 8.4 Hz, 1H), 3.60 (m, 1H), 3.38 (s, 3H), 2.32 (dd, J = 7.8 and 13.2 Hz, 1H), 2.03 (ddd, J = 5.0, 9.3, and 13.2 Hz, 1H); *(minor diastereomer)* 7.27 (m, 4H), 5.16 (d, J = 4.4 Hz, 1H), 4.17 (t, J = 8.3 Hz, 1H), 3.71 (dd, J = 8.7 and 9.8 Hz, 1H), 3.42 (s, 3H), 3.35 (m, 1H), 2.58 (ddd, J = 5.6, 10.4, and 13.7 Hz, 1H), 1.91 (ddd, J = 2.5, 7.6, and 10.2 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 141.3, 140.3, 132.3, 132.3, 129.1, 128.7, 128.6, 128.4, 105.6, 105.4, 73.7, 72.9, 54.9, 54.7, 43.6, 42.1, 41.4, 41.1; HRMS calcd for ($C_{11}H_{13}ClO_2$) 212.0604, found 212.0598.

(2*R*,4*R*)-4-(4-Methoxyphenyl)-2-methoxytetrahydrofuran and (2*S*,4*R*)-4-(4-Methoxyphenyl)-2-methoxytetrahydrofuran (16g). 90% yield (187 mg). Diastereomeric ratio (59:41). Obtained as a pale yellow oil after chromatography [hexanes:ethyl acetate (90:10)]: ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) *(major diastereomer)* 7.15 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.14 (dd, J = 3 and 8.7 Hz, 1H), 4.28 (t, J = 8.3 Hz, 1H), 3.78 (m, 1H), 3.77 (s, 3H), 3.58 (m, 1H), 3.38 (s, 3H), 2.29 (dd, J = 7.6 and 12.9 Hz, 1H), 2.04 (ddd, J = 5.1, 9.7, and 13.1 Hz, 1H); *(minor diastereomer)* 7.22 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.15 (d, J = 4.6 Hz, 1H), 4.14 (t, J = 8.1 Hz, 1H), 3.77 (s, 3H), 3.72 (dd, J = 8.7 and 10 Hz, 1H), 3.42 (s, 3H), 3.33 (m, 1H), 2.57 (ddd, J = 5.6, 10.1, and 13.7 Hz, 1H), 1.91 (ddd, J = 2.8, 8.3, and 11 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 158.3, 158.3, 134.4, 133.1, 128.6, 128.0, 114.0, 113.9, 105.8, 105.5, 74.1, 73.1, 55.2, 55.2, 54.9, 54.6, 43.5, 41.8, 41.4, 41.1. The spectroscopic data of the minor isomer (2*S*,4*R*) were consistent with the data reported in the literature.[13b]

(2*R*,4*R*)-4-(2-Methoxyphenyl)-2-methoxytetrahydrofuran and (2*S*,4*R*)-4-(2-Methoxyphenyl)-2-methoxytetrahydrofuran (16h). 88% yield (183 mg). Diastereomeric ratio (67:33). Obtained as a pale yellow oil after chromatography [hexanes:ethyl acetate (90:10)]: ^{1}H NMR $CDCl_3$, 600 MHz, δ (ppm) *(major diastereomer)* 7.20 (m, 2H), 6.93 (m, 1H), 6.85 (m, 1H), 5.15 (m, 1H), 4.32 (t, J = 8.2 Hz, 1H), 3.96 (m, 1H), 3.81 (s, 3H), 3.79 (m, 1H), 3.39 (s, 3H), 2.23 (ddd, J = 0.9, 7.7, and 12.8 Hz, 1H), 2.16 (ddd, J = 5.0, 9.5, and 12.8 Hz, 1H); *(minor diastereomer)* 7.33 (dd, J = 1.6 and 7.6 Hz, 1H), 7.20 (m, 1H), 6.92 (m, 1H), 6.85 (m, 1H), 5.15 (m, 1H), 4.17 (td, J = 0.97 and 7.1 Hz, 1H), 3.81 (s, 3H), 3.79 (m, 1H), 3.75 (m, 1H), 3.41 (s, 3H), 2.54 (ddd, J = 5.6, 9.4, 13.9 Hz, 1H), 1.97 (ddd, J = 3.0, 8.3, and 11.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 157.5, 157.4, 130.4, 129.0, 127.5, 127.4, 127.4, 126.9, 120.7, 120.6, 110.3, 110.3, 105.8, 105.4, 72.6, 71.6, 55.3, 55.2, 55.0, 54.6, 39.2, 38.9, 37.0, 36.4; HRMS calcd for ($C_{12}H_{16}O_3$) 208.1099, found 208.1102.

(2*R*,4*R*)-4-(3,4-Dimethoxyphenyl)-2-methoxytetrahydrofuran and (2*S*,4*R*)-4-(3,4-Dimethoxyphenyl)-2-methoxytetrahydrofuran (16i). 92% yield (219 mg). Diastereomeric ratio (59:41). Obtained as a yellow oil after chromatography [hexanes:ethyl acetate (90:10)]: ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) *(major diastereomer)* 6.88 (m, 1H), 6.80 (m, 2H), 5.15 (dd, J = 2.7 and 5.8 Hz, 1H), 4.29 (t, J = 8.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (m, 1H), 3.58 (m, 1H), 3.39 (s, 3H), 2.31 (dd, J = 7.7 and 13 Hz, 1H), 2.07 (ddd, J = 5.1, 9.6, and 13.2 Hz, 1H); *(minor diastereomer)* 6.80 (m, 3H), 5.16 (d, J = 4.8 Hz, 1H), 4.16 (t, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.74 (m, 1H), 3.43 (s, 3H), 3.35 (m, 1H), 2.58 (ddd, J = 5.6, 10.1, and 13.7 Hz, 1H), 1.94 (ddd, J = 2.7, 8.0, and 10.7 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 149.0, 148.9, 147.6, 147.6, 135.1, 133.8, 120.7, 119.6, 118.9, 111.2, 111.0, 110.7, 110.2, 105.6, 105.4, 73.9, 73.1, 55.8, 55.7, 55.7, 54.8, 54.5, 43.8, 42.2, 41.4, 41.0; HRMS calcd for ($C_{13}H_{18}O_4$) 238.1205, found 238.1230.

(2*R*,4*R*)-4-(3,4,5-Trimethoxyphenyl)-2-methoxytetrahydrofuran and (2*S*,4*R*)-4-(3,4,5-Trimethoxyphenyl)-2-methoxytetrahydrofuran (16j). 65% yield (175 mg). Diastereomeric ratio (58:42). Obtained as a yellow oil after chromatography [hexanes:ethyl acetate (90:10)]: ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) *(major diastereomer)* 6.48 (s, 2H), 5.18 (dd, J = 2.6 and 5.5 Hz, 1H), 4.32 (t, J = 8.3 Hz, 1H), 3.89 (m, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 3.59 (qn, J = 8.2 Hz,

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1H), 3.42 (s, 3H), 2.35 (dd, J = 7.7 and 12.9 Hz, 1H), 2.10 (ddd, J = 5, 9.3, and 13.3 Hz, 1H); *(minor diastereomer)* 6.58 (s, 2H), 5.20 (d, J = 5 Hz, 1H), 4.20 (t, J = 8.3 Hz, 1H), 3.88 (s, 6H), 3.85 (s, 3H), 3.79 (m, 1H), 3.46 (s, 3H), 3.35 (m, 1H), 2.61 (ddd, J = 5.5, 10.2, and 13.8 Hz, 1H), 1.99 (ddd, J = 2.5, 7.8, and 10.3 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm)153.3, 153.2, 138.6, 137.2, 136.6, 105.7, 105.4, 104.6, 104.0, 104.0, 73.8, 73.1, 60.8, 56.1, 56.1, 56.1, 55.0, 54.6, 44.6, 43.1, 41.6, 41.0; HRMS calcd for ($C_{14}H_{20}O_5$) 268.1311, found 268.1317.

(*R*)-4-(4-Chlorophenyl)dihydrofuran-2(3*H*)-one (17a). 81% yield (159 mg). Obtained as white needles after flash chromatography: mp 71−72 °C; $[\alpha]_D^{20}$ = −47 (c = 1.36, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.37 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.68 (dd, J = 8 and 9 Hz, 1H), 4.26 (dd, J = 8 and 9 Hz, 1H), 3.80 (qn, J = 8 Hz, 1H), 2.95 (dd, J = 8.5 and 17.5 Hz, 1H), 2.65 (dd, J = 8.5 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 175.9, 137.9, 133.5, 129.2, 128.0, 73.7, 40.4, 35.6. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[14b]

(*R*)-4-(4-Fluorophenyl)dihydrofuran-2(3*H*)-one (17b). 78% yield (140 mg). Obtained as a yellow powder after flash chromatography: mp 59−60 °C; $[\alpha]_D^{20}$ = −35 (c = 0.77, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.21 (m, 2H), 7.06 (m, 2H), 4.66 (t, J = 8.3 Hz, 1H), 4.24 (t, J = 8.6 Hz, 1H), 3.79 (qn, J = 8.3 Hz, 1H), 2.93 (dd, J = 8.7 and 17.4 Hz, 1H), 2.63 (dd, J = 8.9 and 17.4 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.1, 162.1 (d, J = 237.5 Hz), 135.2 (d, J = 12.5 Hz), 128.2 (d, J = 12.5 Hz), 116.0 (d, J = 25 Hz), 73.9, 40.4, 35.7. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[14c]

(*R*)-4-(4-Bromophenyl)dihydrofuran-2(3*H*)-one (17c). 71% yield (171 mg). Obtained as a white solid after flash chromatography: mp 82−83 °C; $[\alpha]_D^{20}$ = −45 (c = 1.2, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.50 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 4.65 (dd, J = 7.9 and 8.9 Hz, 1H), 4.23 (dd, J = 7.7 and 9.1 Hz, 1H), 3.75 (qn, J = 8.2 Hz, 1H), 2.93 (dd, J = 8.6 and 17.5 Hz, 1H), 2.62 (dd, J = 8.9 and 17.8 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 175.9, 138.5, 132.3, 128.4, 121.6, 73.7, 40.6, 35.6. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[23]

(*R*)-4-(2-Bromophenyl)dihydrofuran-2(3*H*)-one (17d). 77% yield (186 mg). Obtained as a pale yellow oil after flash chromatography: $[\alpha]_D^{20}$ = −28 (c = 1.75, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.61 (dd, J = 0.95 and 8 Hz, 1H), 7.35 (td, J = 0.9 and 7.8 Hz, 1H), 7.29 (dd, J = 1.4 and 7.8 Hz, 1H), 7.17 (td, J = 1.6 and 7.9 Hz, 1H), 4.69 (dd, J = 7.4 and 9.1 Hz, 1H), 4.31 (dd, J = 6 and 9.2 Hz, 1H), 4.23 (qn, J = 7.6 Hz, 1H), 2.97 (dd, J = 8.8 and 17.6 Hz, 1H), 2.67 (dd, J = 6.8 and 17.6 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.0, 138.8, 133.4, 129.1, 128.2, 126.6, 124.3, 72.8, 40.1, 34.6. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[24]

(*R*)-4-(3-Bromophenyl)dihydrofuran-2(3*H*)-one (17e). 83% yield (200 mg). Obtained as pale yellow oil after flash chromatography: $[\alpha]_D^{20}$ = −24 (c = 2.54, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.44 (dd, J = 0.6 and 7.9 Hz, 1H), 7.39 (s, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 4.66 (dd, J = 8 and 9 Hz, 1H), 4.25 (dd, J = 7.8 and 9.1 Hz, 1H), 3.77 (qn, J = 8.3 Hz, 1H), 2.93 (dd, J = 8.8 and 17.4 Hz, 1H), 2.65 (dd, J = 8.8 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 175.8, 141.8, 130.8, 130.7, 129.9, 125.2, 123.1, 73.5, 40.6, 35.4. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[14c]

(*R*)-4-(4-Iodophenyl)dihydrofuran-2(3*H*)-one (17f). 73% yield (210 mg). Obtained as a white solid after flash chromatography: mp 86−87 °C; $[\alpha]_D^{20}$ = −39 (c = 0.7, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.69 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 4.65 (dd, J = 8 and 9 Hz, 1H), 4.23 (dd, J = 7.8 and 9 Hz, 1H), 3.74 (qn, J = 8.3 Hz, 1H), 2.92 (dd, J = 8.9 and 17.5 Hz, 1H), 2.63 (dd, J = 8.9 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.0, 139.2, 138.2, 128.7, 93.0, 73.7, 40.7, 35.5; HRMS calcd for ($C_{10}H_9IO_2$) 287.9647, found 287.9617.

(*R*)-4-(4-Methoxyphenyl)dihydrofuran-2(3*H*)-one (17g). 79% yield (152 mg). Obtained as a white solid after flash chromatography: mp 93−94 °C; $[\alpha]_D^{20}$ = −48 (c = 0.81, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.15 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 4.63 (dd, J = 8.1 and 8.9 Hz, 1H), 4.22 (t, J = 8.5 Hz, 1H), 3.8 (s, 3H), 3.74 (qn, J = 8.5 Hz, 1H), 2.89 (dd, J = 8.7 and 17.4 Hz, 1H), 2.63 (dd, J = 9.2 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.5, 159.0, 131.2, 127.7, 114.4, 74.2, 55.3, 40.4, 35.8. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[14c]

(*R*)-4-(2-Methoxyphenyl)dihydrofuran-2(3*H*)-one (17h). 72% yield (138 mg). Obtained as pale yellow oil after flash chromatography: $[\alpha]_D^{20}$ = −48 (c = 1.24, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.27 (td, J = 1.5 and 8.2 Hz, 1H), 7.13 (dd, J = 0.9 and 7.6 Hz, 1H), 6.93 (td, J = 0.5 and 7.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.64 (dd, J = 8.5 and 8.7 Hz, 1H), 4.27 (dd, J = 7.4 and 8.7 Hz, 1H), 3.95 (qn, J = 8.3 Hz, 1H), 3.83 (s, 3H), 2.82 (dd, J = 9.1 and 17.5 Hz, 1H), 2.75 (dd, J = 8.4 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 177.1, 157.1, 128.6, 127.4, 120.6, 110.6, 72.8, 55.1, 36.5, 33.7. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[25]

(*R*)-4-(3,4-Dimethoxyphenyl)dihydrofuran-2(3*H*)-one (17i). 58% yield (129 mg). Obtained as a yellow solid after flash chromatography: mp 95−96 °C; $[\alpha]_D^{20}$ = −11 (c = 0.14, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 6.86 (d, J = 8.2 Hz, 1H), 6.79 (dd, J = 1.8 and 8.2 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 4.65 (dd, J = 8.3 and 8.6 Hz, 1H), 4.25 (dd, J = 8.3 and 8.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.74 (qn, J = 8.5 Hz, 1H), 2.91 (dd, J = 8.6 and 17.4 Hz, 1H), 2.65 (dd, J = 9.1 and 17.4 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.4, 149.3, 148.4, 131.8, 118.6, 111.5, 109.8, 74.1, 55.8, 55.8, 40.7, 35.7. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[16]

(*R*)-4-(3,4,5-Trimethoxyphenyl)dihydrofuran-2(3*H*)-one (17j). 50% yield (126 mg). Obtained as a white solid after flash chromatography: mp 106−107 °C; $[\alpha]_D^{20}$ = 9 (c = 1.48, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 6.43 (s, 2H), 4.65 (dd, J = 8 and 8.9 Hz, 1H), 4.28 (dd, J = 7.2 and 8.9 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.72 (qn, J = 8.5 Hz, 1H), 2.93 (dd, J = 8.7 and 17.4 Hz, 1H), 2.66 (dd, J = 8.5 and 17.4 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.3, 153.7, 137.5, 135.3, 103.7, 74.1, 60.9, 56.2, 41.4, 35.8; HRMS calcd for ($C_{13}H_{16}O_5$) 252.0998, found 252.1011.

(*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)dihydrofuran-2(3*H*)-one (17k). 50% yield (126 mg). Obtained as a white solid after flash chromatography: mp 93−94 °C; $[\alpha]_D^{20}$ = −44 (c = 1.07, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 6.79 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 6.68 (dd, J = 1.5 and 7.9 Hz, 1H), 5.97 (s, 2H), 4.62 (dd, J = 8.3 and 8.6 Hz, 1H), 4.21 (dd, J = 8.2 and 8.9 Hz, 1H), 3.71 (qn, J = 8.4 Hz, 1H), 2.89 (dd, J = 8.7 and 17.5 Hz, 1H), 2.61 (dd, J = 9.2 and 17.4 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.3, 148.3, 147.1, 133.1, 119.9, 108.7, 106.9, 101.3, 74.1,40.9, 35.9; HRMS calcd for ($C_{11}H_{10}O_4$) 206.0579, found 206.0580.

(*R*)-4-(3-(Cyclopentyloxy)-4-methoxyphenyl) dihydrofuran-2(3*H*)-one (17l). 61% yield (169 mg). Obtained as a pale yellow oil after flash chromatography: $[\alpha]_D^{20}$ = −26 (c = 0.6, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 6.84 (d, J = 8.1 Hz, 1H), 6.76 (dd, J = 2.2 and 8.2 Hz, 1H), 6.73 (d, J = 2 Hz, 1H), 4.77 (m, 1H), 4.63 (dd, J = 8 and 8.9 Hz, 1H), 4.23 (dd, J = 8 and 8.9 Hz, 1H), 3.83 (s, 3H), 3.71 (qn, J = 8.3 Hz, 1H), 2.90 (dd, J = 8.7 and 17.4 Hz, 1H), 2.63 (dd, J = 8.9 and 17.4 Hz, 1H), 1.87 (m, 6H), 1.62 (m, 2H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.5, 149.6, 148.1, 131.8, 118.7, 113.6, 112.3, 80.6, 74.2, 56.1, 40.7, 35.9, 32.8, 24.0. Enantiomeric ratio was estimated from its optical rotation when compared to the value reported in the literature. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[26]

(*R*)-4-(4-Phenoxyphenyl)dihydrofuran-2(3*H*)-one (17m). 87% yield (221 mg). Obtained as a yellow solid after flash chromatography: mp 108−109 °C; $[\alpha]_D^{20}$ = −30 (c = 0.76, $CHCl_3$).^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.33 (m, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H) 6.99 (m, 4H), 4.63 (dd, J = 8 and 8.9 Hz, 1H), 4.23 (t, J = 8.1 and 8.8 Hz, 1H), 3.76 (qn, J = 8.5 Hz, 1H), 2.90 (dd, J = 8.6 and 17.4 Hz, 1H), 2.63 (dd, J = 9.1 and 17.4 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 176.3, 156.7, 156.7, 133.9, 129.7, 128.0, 123.4,

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119.1, 118.9, 74.0, 40.4, 35.7; HRMS calcd for ($C_{16}H_{14}O_3$) 254.0943, found 254.0959.

(*R*)-4-(3-Trifluoromethylphenyl)dihydrofuran-2(3*H*)-one (17n). 74% yield (170 mg). Obtained as a pale yellow oil after flash chromatography: $[\alpha]_D^{20} = -26$ (c = 1.38, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.56 (d, J = 13.4 Hz, 1H), 7.51 (m, 2H), 7.48 (d, J = 7.6 Hz, 1H), 4.71 (dd, J = 7.9 and 9.1 Hz, 1H), 4.29 (dd, J = 7.8 and 9.2 Hz, 1H), 3.90 (qn, J = 8.2 Hz, 1H), 2.98 (dd, J = 8.8 and 17.4 Hz, 1H), 2.65 (dd, J = 8.8 and 17.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 175.7, 140.5, 131.3 (q, J = 32 Hz), 130.0, 129.6, 124.4 (q, J = 3.7 Hz), 123.8 (q, J = 271 Hz), 123.6 (q, J = 3.7 Hz), 73.4, 40.7, 35.4; HRMS calcd for ($C_{11}H_9O_2F_3$) 230.0555, found 230.0566.

Synthesis of the Aryl Pyrrolidine 23. To a 250 mL round-bottom flask equipped with a magnetic stirring bar were added *O*-methyl lactol **16a** [1.29 g, obtained from the Heck–Matsuda reaction of 6.2 mmol of diol (*Z*)-**1**], acetonitrile (100 mL) and HCl 1 mol·L^{-1} (50 mL). The resulting green solution was stirred at 25 °C for 2 h. Next, acetonitrile was evaporated in vacuo, and the resulting suspension was transferred to a separatory funnel, followed by washing with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to furnish a dark blue solid. This crude mixture of diastereomeric lactols **24** was used in the next step without further purification.

Lactol Reduction. To a 500 mL round-bottom flask equipped with a magnetic stirring bar was added the crude product obtained above dissolved in methanol (100 mL), and the resulting solution was cooled at 0 °C. Sodium borohydride (1.38 g) was then added in three equal portions within 3 min intervals, and the reaction was left stirring at 0 °C for 30 min. Next, 20 g of silica gel were added, and the volatiles were evaporated in vacuo. The resulting slurry was placed on top of a chromatographic column (10 × 4 cm) containing silica gel and eluted with EtOAc:MeOH = 95:5 (500 mL). The collected fractions were combined and evaporated under reduced pressure to furnish diol **25** as yellow oil.

*Mesylation of Diol **25**.* In a 100 mL round-bottom flask equipped with a magnetic stirring bar, the crude diol **25** was dissolved in anhydrous dichloromethane (60 mL), followed by addition of triethylamine (2.52 mL), DMAP (179 mg), and methanesulfonyl chloride (MsCl) (1.43 mL). The reaction mixture was stirred at 25 °C for 12 h. Next, the reaction was diluted with dichloromethane (100 mL) and washed with saturated NH_4Cl (3 × 100 mL) and brine (1 × 100 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered through a plug of silica gel, and evaporated to furnish dimesylate **26** as colorless oil.

*Nucleophilic Substitution of the Dimesylate **26**.* The dimesylate **26** was suspended in anhydrous THF (240 mL) in a 500 mL round-bottom flask followed by addition of K_2CO_3 (1.69 g, 12.22 mmol), and 2-(4-methoxyphenyl)-ethylamine (**27**) (1.84 g, 12.17 mmol). The reaction mixture was placed in an oil bath (stabilized at 120 °C) and stirred for 20 h. Next, the reaction was cooled to room temperature, and the volatiles were evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (DCM:MeOH 9:1) to furnish 960 mg of aryl pyrrolidine **23** as a pale yellow oil (50% overall yield over 5 steps).

(*R*)-3-(4-Chlorophenyl)-1-(4-methoxyphenethyl)pyrrolidine (23). Data: $[\alpha]_D^{20} = 14$ (c = 1.0, $CHCl_3$; ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 7.24 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H), 3.33 (m, 1H), 3.05 (t, J = 8.5 Hz, 1H), 2.84 (q, J = 7.8 Hz, 1H), 2.70 (m, 5H), 2.53 (dd, J = 7.7 and 1.3 Hz, 1H), 2.36 (m, 1H), 1.82 (m, 1H); ^{13}C NMR $CDCl_3$, 125 MHz, δ (ppm) 157.9, 144.1, 132.4, 131.7, 129.5, 128.6, 128.4, 113.8, 62.2, 58.4, 55.2, 54.6, 42.8, 34.7, 33.2; HRMS calcd for ($C_{19}H_{23}ClNO$) 316.1468, found 316.1443.

Synthesis of Chiral β-Aryl Aldehydes. *Enantioselective Heck–Matsuda Reaction.* To a 15 mL pressure tube equipped with a magnetic stirring bar were added in this order: $Pd(TFA)_2$ (16.6 mg, 0.05 equiv, 0.05 mmol), (*R*)-BOX-**14** (35.2 mg, 0.11 equiv, 0.11 mmol) and methanol (3.7 mL). The flask was sealed, and the reaction mixture was then immersed in a previously heated oil bath (60 °C) for 5 min. Next, the sealed flask was removed from the oil bath, and the following were added to it, in this order: $ZnCO_3$ (62.7 mg, 0.5 equiv, 0.5 mmol), the allylic alcohol **4** or **30** (1 equiv, 1 mmol) and the corresponding aryldiazonium salt (2 equiv, 2 mmol). After the addition, the flask was sealed again, immersed once again in the oil bath at 60 °C and kept under vigorous stirring for 20 min (during this time the suspension turned homogeneous). The reaction was then cooled to room temperature, transferred to a 100 mL round-bottom flask, and evaporated under reduced pressure. The product was then extracted from the residue by successive washings with a mixture of hexanes:ethyl acetate (1:1) in small portions (6 × 50 mL). The residue was discarded, and the combined organic phases were filtered through a short plug of silica gel (2.5 × 3 cm). The filtrate was concentrated in vacuo to provide a clean oily residue corresponding to an inseparable mixture of dimethyl acetals **31** and **32** (single spot on TLC). This mixture was used in the next step without further purification.

Hydrolysis of the Dimethylacetals. To a 25 mL round-bottom flask equipped with a magnetic stirring bar was added the dimethyl acetals isolated above dissolved in acetonitrile (5 mL). Next, HCl 1 mol L^{-1} (2.5 mL) was added, and the reaction was stirred at 25 °C for 90 min. After this time, the acetonitrile was evaporated, and the residue was transferred to a separatory funnel using 40 mL of ethyl acetate and washed with brine (3 × 20 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and rotoevaporated. The crude residue was then purified by column chromatography over silica gel (EtOAc:Hexanes = 3:97) to furnish the corresponding β-aryl aldehydes **33** as colorless oils. Most α-aryl aldehydes **34** decomposed during chromatography. Only aryl aldehydes **34a** and **34e** could be obtained in pure form.

(*S*)-3-(4-Chlorophenyl)butanal (33c). 49% (89 mg). Obtained as a pale yellow oil after flash chromatography: $[\alpha]_D^{20} = 48$ (c = 1.3, $CHCl_3$); ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 9.69 (t, J = 1.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.34 (sx, J = 7 Hz, 1H), 2.73 (ddd, J = 1.6, 6.9, and 16.9 Hz, 1H), 2.63 (ddd, J = 1.9, 7.5, and 16.9 Hz, 1H), 1.28 (d, J = 7 Hz, 1H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 201.1, 143.9, 132.1, 128.7, 128.1, 51.6, 33.6, 22.0. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[27]

(*S*)-2-(4-Chlorophenyl)butanal (34c). 15% (27 mg). Obtained as a colorless oil after flash chromatography: $[\alpha]_D^{20} = 65$ (c = 0.91, $CHCl_3$); ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 9.65 (d, J = 1.9 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 3.39 (m, 1H), 2.10 (hp, J = 7.2 Hz, 1H), 1.72 (hp, J = 7.4 Hz, 1H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 200.3, 134.8, 133.5, 130.1, 129.1, 60.1, 22.9, 11.6; HRMS calcd for ($C_{10}H_{11}ClO$) 182.0498, found 182.0507.

(*S*)-3-(4-Methylphenyl)butanal (33d). 37% (60 mg). Obtained as a colorless oil after flash chromatography: $[\alpha]_D^{20} = 35$ (c = 0.93, $CHCl_3$); ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 9.70 (t, J = 2 Hz, 1H), 7.12 (s, 4H), 3.33 (sx, J = 7.1 Hz, 1H), 2.73 (ddd, J = 2, 7, and 16.6 Hz, 1H), 2.63 (ddd, J = 2.2, 7.6, and 16.4 Hz, 1H), 2.32 (s, 3H), 1.30 (d, J = 6.9 Hz, 1H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 202.0, 142.4, 136.1, 129.3, 126.6, 51.8, 33.9, 22.3, 21.0. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[21a]

(*S*)-2-(4-Methylphenyl)butanal (34d). 5% (8 mg). Obtained as a colorless oil after flash chromatography: $[\alpha]_D^{20} = 58$ (c = 0.85, $CHCl_3$); ^{1}H NMR $CDCl_3$, 500 MHz, δ (ppm) 9.65 (d, J = 2.11 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 3.37 (m, 1H), 2.35 (s, 3H), 2.10 (hp, J = 7.2 Hz, 1H), 1.74 (hp, J = 7.5 Hz, 1H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 201.0, 137.2, 133.1, 129.7, 128.7, 60.4, 22.8, 21.0, 11.7; HRMS calcd for ($C_{11}H_{14}O$) 162.1045, found 162.1074.

(*S*)-3-(4-Chlorophenyl)pentanal (33e). 42% (83 mg). Obtained as a colorless oil after flash chromatography: $[\alpha]_D^{20} = 10$ (c = 1.1, $CHCl_3$); ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 9.65 (t, J = 1.8 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 3.07 (qn, J = 7.5 Hz, 1H), 2.69 (m, 2H), 1.64 (m, 2H), 0.79 (t, J = 7.5 Hz, 1H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 201.4, 142.2, 132.1, 128.8, 128.7, 50.1, 41.0, 29.3, 11.7. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[21b]

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(*S*)-2-(4-Chlorophenyl)butanoic acid (35). To a 10 mL round-bottom flask equipped with a magnetic stirring bar was added aldehyde **34a** (20 mg, 0.11 mmol, *er* 78:22) dissolved in a mixture of acetone:water = 3:1 (2 mL). The reaction mixture was cooled in an ice bath and stirred over 5 min, followed by addition of 0.12 mL of the Jones solution. The mixture was cooled at 0 °C for 30 min and then left at rt for 90 min. Next, isopropanol was added (1 mL) to the reaction resulting in the formation of a green suspension, which was stirred for 10 min. The volatiles were then removed in vacuo, and the resulting suspension was transferred to a separatory funnel. To the suspension was added 10 mL of ethyl acetate (turning it homogeneous), and then the mixture was washed with brine (3 × 5 mL). The organic phases were combined, dried over Na_2SO_4, filtered and rotoevaporated. The crude acid **35** was obtained as a viscous yellow oil (20 mg, 92% yield): $[\alpha]_D^{20} = 43$ (c = 1.0, $CHCl_3$); ^{1}H NMR $CDCl_3$, 250 MHz, δ (ppm) 7.31 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 3.44 (t, J = 7.8 Hz, 1H), 2.07 (hp, J = 6.8 Hz, 1H), 1.79 (hp, J = 7.3 Hz, 1H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR $CDCl_3$, 62.5 MHz, δ (ppm) 179.8, 136.7, 133.3, 129.4, 128.8, 52.6, 26.3, 12.0. The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[22]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization studies and copies of ^{1}H and ^{13}C NMR spectra for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: roque@iqm.unicamp.br.

Notes

The authors declare no competing financial interest.

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