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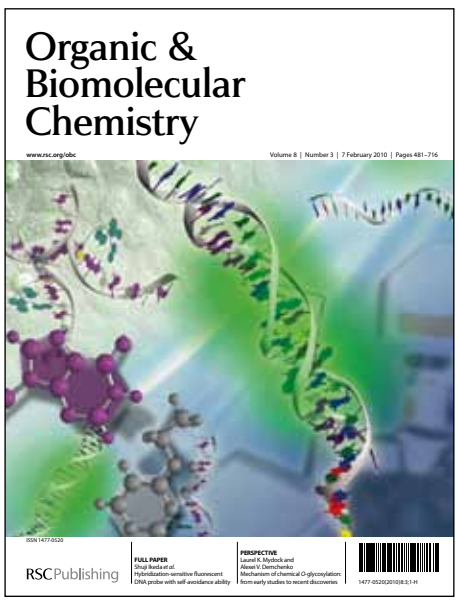

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ARTICLE TYPE

Pd(II)-SDP-Catalyzed enantioselective 5-*exo-dig* cyclization of γ-alkynoic acids: application to the synthesis of functionalized dihydofuran-2(3*H*)-ones containing a chiral quaternary carbon center

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The Pd(II)-SDP-catalyzed first enantioselective intramolecular cyclization of α,α-disubstituted γ-alkynoic acids is described. This 5-*exo-dig* cyclization afforded dihydrofuran-2(3*H*)-ones bearing a chiral quaternary carbon center in excellent yields with enantioselectivities up to 71%. A mechanism involving palladium(II) species is proposed to rationalize the outcome of the reaction.

Introduction

Oxygen-containing heterocyclic compounds and their fused analogs have significant application in biology and medicine. Small-sized oxygen heterocycles, such as furan and its saturated derivatives, are present in a number of natural products and pharmaceutically relevant compounds. In particular, as represented in Fig. 1, the dihydrofuran-2(3*H*)-one scaffold is an essential fragment in numerous biologically important natural products including the tornabeatins **1**,[1] matairesinol **2**[2] and muricatacin **3**.[3] A considerable number of coumarin-attached dihydrofuran-2(3*H*)-ones, exemplified by clauslactones A and B (**4**),[4] and fused dihydrofuran-2(3*H*)-ones[5] such as helenalin **5**, costunolide **6** and alantolactone **7** are widespread in nature. Apart from these compounds, a large number of synthetic and natural dihydrofuran-2(3*H*)-ones have revealed interesting biological activities.[6]

The intramolecular cyclization of alkynes bearing tethered nucleophiles, in the presence of suitable catalytic systems, is an attractive protocol for the synthesis of simple carbo- and heterocyclic compounds, with the nature of the final product being dependent on the nature of the attached nucleophiles.[7] Although a considerable number of strategies have been established for the synthesis of dihydrofuran-2(3*H*)-one derivatives, the most straightforward approach to the construction of their skeleton involves metal-catalyzed[8] intramolecular 5-*exo-dig* cyclizations of γ-alkynoic acids.[9] While palladium catalysts were initially employed to achieve this synthetically important transformation, gold catalysts were also found to be attractive in this regard in recent years.[10,11] Other metal catalysts, including the salts or complexes of rhodium,[12] ruthenium,[13] iridium,[14] molybdenum,[15] tungsten[16] and silver,[17] have also been proved to catalyze the aforementioned transformation effectively. The intermediates obtained through the intramolecular cyclization of alkynoic acids were also employed as starting compounds for subsequent cascade transformations that afford structurally complex compounds in a single operation.[18]

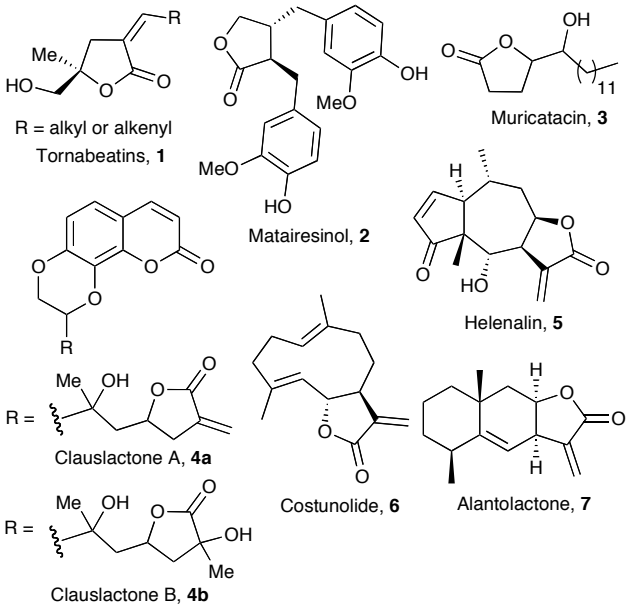

Fig. 1 Representative examples of dihydrofuran-2(3*H*)-one natural products

Results and Discussion

Although a significant number of procedures have been developed for the intramolecular cyclization of γ-alkynoic acids, including the α,α-disubstituted derivatives **8**, to afford the corresponding dihydrofuran-2(3*H*)-one derivatives **9**, the enantioselective version of this useful desymmetrization reaction has not yet been explored. Hence we envisioned developing an enantioselective procedure for this important transformation. Our initial aim was to identify a suitable bulky chiral catalytic system that would induce high enantioselectivity in this desymmetrization process. As discussed previously, palladium catalysts would be the best choice to allow the intramolecular

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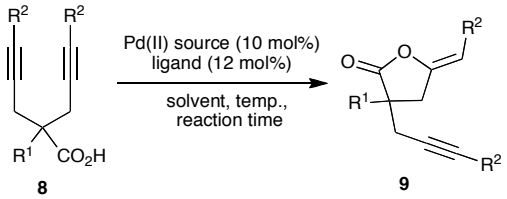
Table 1 Screening of substrates and ligands



8 **9**

Entry	Substrate/ Product	R^1	R^2	Pd source	Solvent	Ligand	Temp (°C)	Time	Yield (Conversion) of **9** (%)	ee of **9** (%)
1	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	Dioxane	(*M,S,S*)-*i*-Pr-SPRIX	25	4 h	88 (100)	*rac*
2	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*M,S,S*)-*i*-Pr-SPRIX	25	4 h	93 (100)	5
3	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(-)-Spartein	25	3 h	92 (100)	*rac*
4	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*S,S*)-*t*-BuBOX	25	3 h	94 (100)	*rac*
5	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	-	25	4 h	89 (100)	*rac*
6	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*S*)-BINAP	25	1 d	86 (100)	19
7	**8a**/**9a**	H	Ph	$Pd(TFA)_2$	DCM	(*S*)-BINAP	25	3 d	71[a]	*rac*
8	**8a**/**9a**	H	Ph	$PdCl_2$	DCM	(*S*)-BINAP	25	3 d	9[a]	-6
9	**8a**/**9a**	H	Ph	$[(\eta 3\text{-}C_3H_5)PdCl]_2$	DCM	(*S*)-BINAP	25	3 d	16[a]	*rac*
10	**8a**/**9a**	H	Ph	$PdCl_2$-(*S*)-BINAP[b]	DCM	-	25	3 d	8[a]	-4
11	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*R*)-SEGPHOS	25	1.5 d	83 (100)	8
12	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*R*)-DIFLUORPHOS	25	1 d	18[a]	13
13	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*R*)-SYNPHOS	25	12 h	83 (100)	*rac*
14	**8a**/**9a**	H	Ph	$Pd(OAc)_2$	DCM	(*S*)-MOP	25	8 h	86 (100)	*rac*
15	**8b**/**9b**	H	Me	$Pd(OAc)_2$	DCM	(*S*)-BINAP	25	5 h	78 (100)	*rac*
16	**8c**//**9c**	CO_2Me	Me	$Pd(OAc)_2$	DCM	(*S*)-BINAP	25	5 h	84 (100)	*rac*
17	**8d**/**9d**	Ph	H	$Pd(OAc)_2$	DCM	(*S*)-BINAP	25	3 h	69 (100)	*rac*
18	**8e**/**9e**[c]	Ph	Ph	$Pd(OAc)_2$	$CHCl_3$	(*S*)-BINAP	25	5 d	84 (90)	33
19	**8e**/**9e**	Ph	Ph	$Pd(OAc)_2$	$CHCl_3$	(*S*)-BINAP	65	1 d	77 (84)	22

[a] The remaining unreacted starting material was recovered. [b]Isolated $PdCl_2$-(*S*)-BINAP complex (10 mol%) was used. [c] Lowering the reaction temperature to 10 or 0 °C reduced the reaction rate without improving the ee.

cyclization smoothly. It is relevant to mention here that Czekelius and co-workers have recently reported a gold-catalyzed enantioselective cyclization of diynamides to pyrrolidines.[19] Unlike our substrates (1,6-diynes), these authors have employed 1,4-diynamides and thus the prochiral carbon is adjacent to the reaction site.

Our first choice of ligands for this enantioselective 5-*exo*-*dig* cyclization was chiral bidentate nitrogen ligands, especially the spiro bis(isoxazoline) ligands (SPRIXs), which have been excellent to achieve a number of enantioselective intramolecular cyclization reactions when combined with suitable palladium salts.[20,21] We started our preliminary studies for the intramolecular cyclization of γ-alkynoic acid **8a** in the presence of *in situ* generated Pd(II)-*i*-Pr-SPRIX complex under mild conditions (Table 1, Fig. 2). The reaction proceeded smoothly in various solvents including dioxane, DCM, $CHCl_3$, MeCN, MeOH, AcOH and toluene to furnish dihydrofuran-2(3*H*)-one **9a** in excellent yields in short reaction times, although as a racemic compound (entries 1 and 2). Palladium complexes of other commercially available chiral bidentate nitrogen ligands (-)-spartein and (*S,S*)-*t*-BuBOX also failed to induce enantioselectivity (entries 3 and 4). We assumed that the Pd(II)-ligand complexes might not be stable in the presence of excess of the coordinating diakyne substrate **8a**. The relatively weakly coordinated ligands might be replaced by the substrate to allow the background reaction to afford the racemic product. To support this assumption we carried out a set of ^{1}H-NMR experiments in which we measured the ^{1}H-NMR spectra of pure *i*-Pr-SPRIX ligand, $Pd(OAc)_2$-*i*-Pr-SPRIX complex and $Pd(OAc)_2$-*i*-Pr-SPRIX complex in the presence of excess of substrate **8a** in $CDCl_3$. After the addition of substrate **8a** to $Pd(OAc)_2$-*i*-Pr-SPRIX complex, only the dissociated free *i*-Pr-SPRIX ligand signals were observed in the ^{1}H-NMR spectra, together with signals of the product **9a**, but no traces of the $Pd(OAc)_2$-*i*-Pr-SPRIX complex were detected in the solution. These experiments confirmed that the chiral Pd(II)-ligand complex is dissociated or decomposed in the presence of the substrate to allow the background reaction. In a separate experiment, it was also confirmed that the reaction proceeded splendidly in the presence of $Pd(OAc)_2$ without any ligand (entry 5).

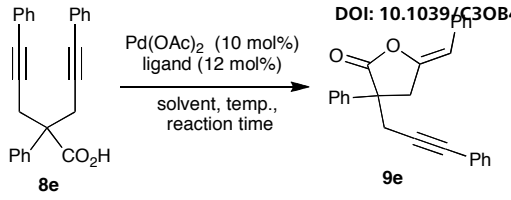
Next, we moved to the relatively strong coordinating chiral bidentate phosphine ligands anticipating that they would form strong complexes with Pd(II) species that would be stable in the presence of the dialkyne substrates. As shown in entry 6, the Pd(II)-(*S*)-BINAP complex afforded product **9a** in high yields with 19% ee. Prompted by this encouraging result, we carried out an extensive optimization study to improve the enantioselectivity by altering various factors including reaction solvents, additives and reaction temperatures (see the Supporting Information for details), but unfortunately we were unable to improve the enantioselectivity significantly. Change of reaction solvents to $CHCl_3$, MeCN, MeOH, dioxane and Et_2O, and addition of one equivalent of additives including K_2CO_3, KOH, Et_3N and AcOH were not effective. The reaction was also carried out at different temperatures (45 °C, 10 °C, 0 °C, -20 °C and -40 °C), however the enantioselectivity was not improved. Utilization of chiral

catalysts derived from the (*S*)-BINAP ligand and a number of palladium(II) species (entries 7 to 9) or the use of isolated $PdCl_2$-(*S*)-BINAP complex as catalyst (entry 10) were not effective in terms of both reactivity and enantioselectivity. Similarly other chiral catalysts obtained by the combination $Pd(OAc)_2$ with chiral bidentate phosphine ligands including (*R*)-SEGPHOS, (*R*)-DIFLUORPHOS and (*R*)-SYNPHOS (entries 11 to 13) or monodentate ligand (*S*)-MOP (entry 14) were unable to provide good enantioselectivity. The substrate **8b** (R^1 = H, R^2 = Me) also furnished the racemic product under similar conditions (entry 15).

Eventually we presumed that the nature of the substrate itself imposed a constraint that prevented high enantioselectivity due to the distance between the reaction site and the prochiral center. For this reason, we introduced another substituent at the α-position of the carboxylic acid group of substrate **8** aiming to improve enantioselectivity because of the added steric hindrance, and also with a view to synthesize dihydrofuran-2(3*H*)-one derivatives **9** bearing a quaternary chiral carbon. Screening of other substrates (**8c** to **8e**, entries 16 to 18) bearing different substituents at R^1 and R^2 positions suggested that the nature of substituents is crucial to allow higher enantioselectivity. As shown in entry 18, the substrate **8e** bearing three phenyl substituents afforded the maximum ee of 33% in chloroform at room temperature. Change of solvents (DCM or MeCN) and the reaction temperatures (10 °C, 0 °C and 65 °C) did not improve the ee value (entries 18 and 19). The geometry of the products across the exocyclic double bond was confirmed as *Z* through NOESY experiments and by comparison with literature data.

After identifying the appropriate substrate for the enantioselective intramolecular cyclization reaction, we made an extensive effort to identify a suitable catalytic system and reaction conditions to afford good enantioselectivity (Table 2, Fig. 2). Based on our previous optimization studies, we understood that the only option left to improve the enantioselectivity was to find out a suitable chiral ligand that would control the enantioselectivity of the cyclization reaction, overcoming the difficulties imposed by the distance between the reaction site and the prochiral carbon. Although it was a challenging task, we screened a wide number of chiral bidentate phosphine ligands combined with palladium(II) acetate, as shown in Table 2 and Fig. 2, for the intramolecular cyclization of substrate **8e** in halogenated solvents. The catalysts derived from $Pd(OAc)_2$ and (*R*)-SEGPHOS, (*R*)-DIFLUORPHOS, (*R*)-SYNPHOS, (*S*)-MOP, (*S*)-Tol-BINAP or (*R*,*R*)-Chiraphos were not effective to improve the enantioselectivity (entries 3-13). Interestingly the $Pd(OAc)_2$/(*R*)-SDP system was found to be efficient to allow good enantioselectivity (entries 14-18). The maximum ee of 60% was achieved in the presence of the $Pd(OAc)_2$/(*R*)-SDP complex in chloroform solvent at room temperature (entry 15). While lowering the reaction temperature slightly improved the ee (up to 64%) the reaction rate was reduced significantly (entries 17 and 18). Other chiral ligands including Josiphos-1, (*S*,*S*)-BenzP*, (*R*,*R*)-QuinoxP*, (*R*,*R*,*S*,*S*)-DuanPhos, (*R*)-BINAPHANE and (*R*)-Tol-SDP were not competent to improve the enantioselectivity (entries 19-24).

Table 2 Optimization of the enantioselective intramolecular cyclization of substrate **8e**



Entry	Solvent	Ligand	Temp (°C)	Time	Yield (Conversion) of **9e** (%)	ee of **9e** (%)
1	$CHCl_3$	(*S*)-BINAP	25	5 d	84 (90)	33
2[a]	$CHCl_3$	(*S*)-BINAP	25	5 d	96 (100)	19
3	DCM	(*R*)-SEGPHOS	25	5 d	91 (100)	15
4	$CHCl_3$	(*R*)-SEGPHOS	25	5 d	43 (49)	5
5	DCM	(*R*)-DIFLUORPHOS	25	5 d	39 (47)	23
6	$CHCl_3$	(*R*)-DIFLUORPHOS	25	5 d	15 (21)	24
7	DCM	(*R*)-SYNPHOS	25	5 d	94 (100)	10
8	$CHCl_3$	(*R*)-SYNPHOS	25	5 d	97 (100)	2
9	DCM	(*S*)-MOP	25	3 h	93 (100)	7
10	DCM	(*S*)-Tol-BINAP	25	12 h	91 (100)	2
11	$CHCl_3$	(*S*)-Tol-BINAP	25	2 d	94 (100)	22
12	DCM	(*R*,*R*)-Chiraphos	25	12 h	95 (100)	6
13	$CHCl_3$	(*R*,*R*)-Chiraphos	25	12 h	96 (100)	6
14	DCM	(*R*)-SDP	25	12 h	98 (100)	43 (42)[b]
15	$CHCl_3$	(*R*)-SDP	25	2 d	96 (100)	60 (58)[b]
16	DCE	(*R*)-SDP	25	1 d	91 (100)	36
17	$CHCl_3$	(*R*)-SDP	10	5 d	71 (75)	63
18	$CHCl_3$	(*R*)-SDP	0	7 d	84 (90)	64
19	$CHCl_3$	Josiphos-1	25	3 d	93 (100)	14
20	$CHCl_3$	(*S*,*S*)-BenzP*	25	5 d	77 (90)	35
21	$CHCl_3$	(*R*,*R*)-QuinoxP*	25	43 h	68 (100)	*rac*
22	$CHCl_3$	(*R*,*R*,*S*,*S*)-DuanPhos	25	43 h	82 (100)	-20
23	$CHCl_3$	(*R*)-BINAPHANE	25	43 h	89 (100)	4
24	$CHCl_3$	(*R*)-Tol-SDP	25	1 d	82 (100)	16

[a] Molecular sieves (3Å) was used as additive. [b] ee values given in parenthesis were obtained from a second run.

The scope and limitations of this protocol were then studied by employing the optimized reaction conditions ($Pd(OAc)_2$/(*R*)-SDP, 25 °C, $CHCl_3$) to the enantioselective intramolecular cyclization of a number of α,α-disubstituted γ-alkynoic acids **8** (Table 3). As shown in entries 1-6, the γ-alkynoic acids bearing substituted aryl groups afforded the corresponding dihydrofuran-2(3*H*)-one derivatives **9** in good to excellent yields with enantioselectivities up to 71%. Surprisingly the alkynoic acid **8j** bearing an electron-withdrawing substituent (*p*-bromo) afforded almost racemic product **9j** (entry 7). The sterically hindered *o*-tolyl substrate **8k** was found to be very slow and gave only 23% of the cyclized product, as a racemic compound, ever after seven days reaction at room temperature (entry 8). The poor reactivity and enantioselectivity are presumably due to the bulky *o*-methyl substituents, which prevent the Pd(II)-SDP complex from approaching the alkyne moiety to trigger the annulation process. At the same time a slow background reaction, catalyzed by traces of free $Pd(OAc)_2$ present in the reaction mixture, produced small amount of the racemic product. In order to extend the scope of the reaction, we synthesized two more γ-alkynoic acids (**8l** and **8m**) bearing different substituents both at α- and terminal positions. While compound **8l** bearing terminal methyl substituents afforded the corresponding cyclized product in 93%

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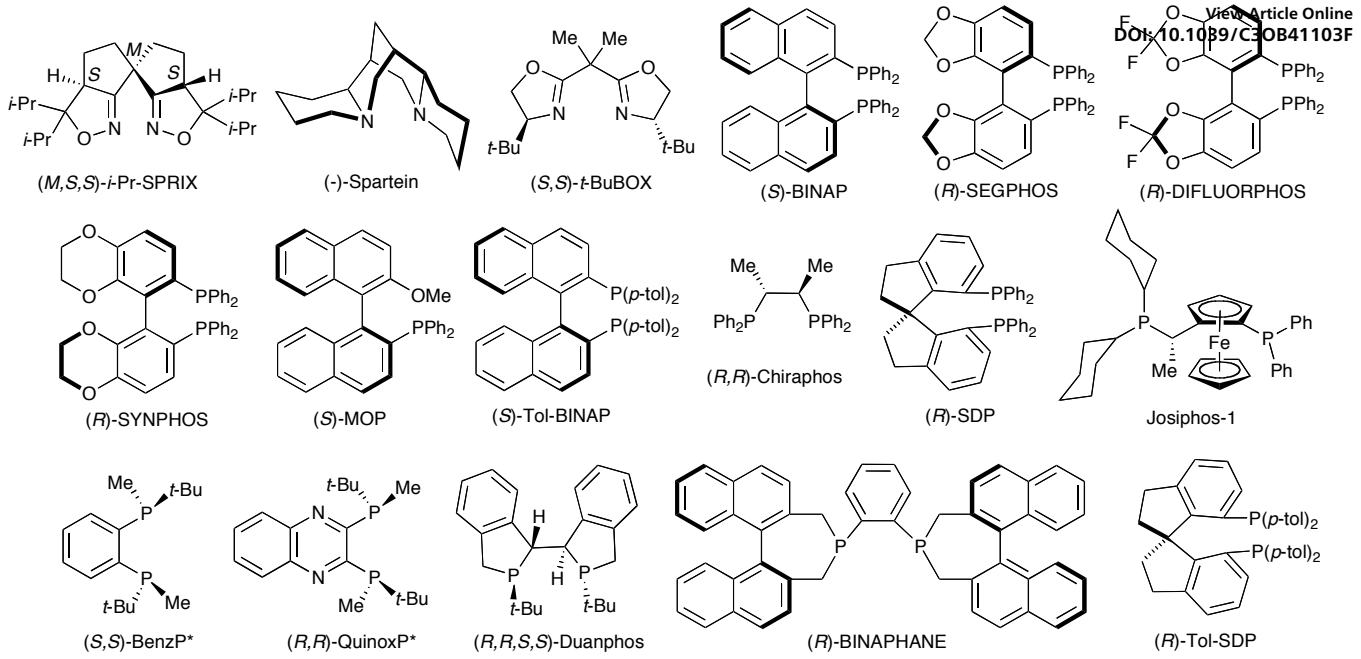


Fig. 2 Chiral ligands used for the reactions shown in tables 1 to 3

yield (32% ee), the α-ester substituted substrate **8m** furnished the product in 92% yield with 15% ee (entries 9 and 10). The enantioselectivity of the product obtained from the terminal unsubstituted alkynoic acid **8d** was also poor, giving 13% ee (93% yield, entry 11). These results demonstrated that both α- and terminal substituents should be aryl, not only in terms of reactivity but also to achieve good enantioselectivity.

A plausible reaction mechanism for the palladium(II)-catalyzed enantioselective cyclization of alkynoic acids **8** is shown in Fig. 3. Initial coordination of the chiral Pd(II)-SDP complex **10** with substrate **8** afforded the cationic palladium intermediate **A** after elimination of a molecule of acetic acid. Subsequent nucleopalladation of the activated species **A** in a 5-*exo-dig* fashion furnished the cyclic intermediate **B** thus controlling the enantioselectivity. Final protonation of the palladium(II) intermediate **B** afforded the dihydrofuran-2(3*H*)-one derivative **9** after releasing the catalyst **10**. Although we are convinced that the proposed mechanism involving Pd(II) species constitutes the best explanation for our findings, an alternative pathway involving Pd(0) and Pd(II) intermediates, where the key steps would be oxidative addition of carboxylic acid to Pd(0), migratory insertion to the alkyne moiety and reductive elimination, cannot be completely ruled out.

Fine-tuning of the SDP ligands, utilization of other nucleophiles as well as detailed mechanistic studies are under investigation in our laboratory.

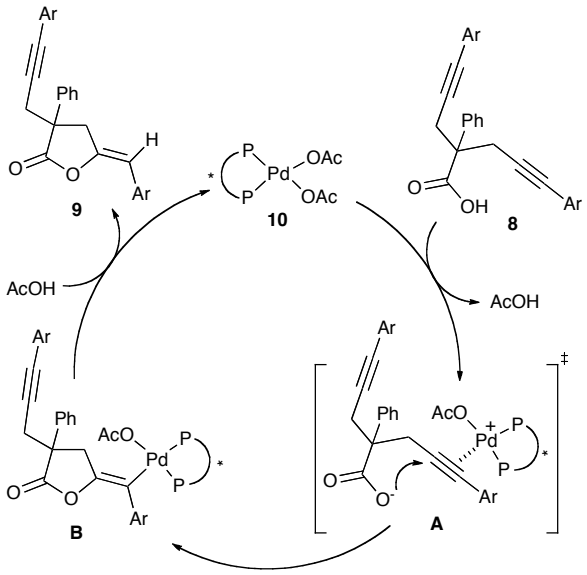


Fig. 3 Plausible reaction mechanism

Conclusions

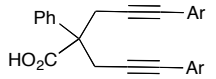
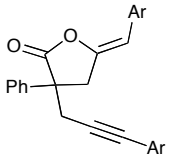
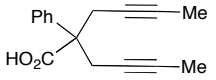
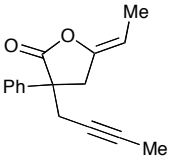
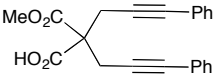
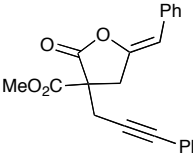
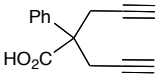
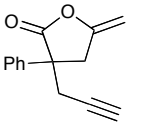
In conclusion, we have developed the first enantioselective 5-*exo-dig* cyclization of α,α-disubstituted-γ-alkynoic acids catalyzed by a chiral Pd(II)-(*R*)-SDP complex under mild conditions. The reaction allowed access to chiral dihydrofuran-2(3*H*)-one derivatives bearing a quaternary carbon center in excellent yields and enantioselectivities up to 71%. A plausible catalytic cycle involving coordination, nucleopalladation and protonation steps is proposed to explain the product formation and enantiocontrol.

Experimental

General Information

Commercially available reagents were used as received without further purification and solvents were purified and dried using standard procedures prior to use. Reactions were monitored by thin layer chromatography, on glass plates coated with silica gel with fluorescent indicator (Merck). Compounds were purified through flash column chromatography on silica gel (Kanto Silica

Table 3 Substrate scope[a]

Entry	Starting compound, **8**	Product, **9** (temp., time, yield, ee)
		
1	**8e**, Ar = Ph	**9e**, 25 °C, 2 d, 96%, 60% ee
2	**8e**, Ar = Ph	**9e**, 0 °C, 7 d, 84%, 64% ee
3	**8f**, Ar = 3-Me-C_6H_4-	**9f**, 25 °C, 20 h, 75%, 60% ee
4	**8g**, Ar = 4-Me-C_6H_4-	**9g**, 25 °C, 2 d, 88%, 60% ee
5	**8h**, Ar = 4-*i*-Pr-C_6H_4-	**9h**, 25 °C, 4 d, 92%, 71% ee
6	**8i**, Ar = 4-OMe-C_6H_4-	**9i**, 25 °C, 1 d, 73%, 60% ee
7	**8j**, Ar = 4-Br-C_6H_4-	**9j**, 25 °C, 1 d, 66%, 8% ee
8	**8k**, Ar = 2-Me-C_6H_4-	**9k**, 25 °C, 7 d, 23%, 0% ee
9	 **8l**	 **9l**, 25 °C, 24 h, 93%, 32% ee
10	 **8m**	 **9m**, 25 °C, 24 h, 92%, 15% ee
11	 **8d**	 **9d**, 25 °C, 24 h, 93%, 13% ee

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), (*R*)-SDP (12 mol%), $CHCl_3$, 25 °C.

Gel 60 (40-100 μm). ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL JMN ECS400 FT-NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). ESI-MS spectra were obtained with JMS-T100LC (JEOL) instrument. Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of hexane and *i*-PrOH or EtOH as eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Melting points were measured on SHIMADZU DSC-60 apparatus.

General procedure for the palladium-catalyzed enantioselective cyclization of alkynoic acids (Tables 1, 2 and 3)

A screw cap tube was charged with palladium salt (0.005 mmol, 10 mol%), suitable chiral ligand (0.006 mmol, 12 mol%) and solvent (0.5 mL). The mixture was stirred at 25 °C under N_2 for 2 h. The corresponding alkynoic acid **8** (0.05 mmol, 1 eq) was added and stirring was continued until complete consumption of the starting material, as indicated by TLC, or the reaction times shown in tables 1, 2 and 3. The reaction mixture was then filtered through a short pad of silica gel and the solvent was evaporated. The residue was purified through short silica column chromatography using hexane/ethyl acetate as eluent to afford the desired dihydrofuran-2(3*H*)-one **9**. The reaction was also carried out in the absence of chiral ligand to obtain the corresponding racemic products.

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(*Z*)-5-Benzylidene-3-(3-phenylprop-2-ynyl)dihydrofuran-2(3*H*)-one (9a).[22] Yield: 86%; yellow solid; mp: 59-62 °C; IR (KBr): ν = 3060, 2919, 2360, 1804, 1732, 1598, 1491, 1442, 1233, 1110, 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.86-2.98 (m, 2H), 3.07-3.17 (m, 2H), 3.21-3.26 (m, 1H), 5.61 (s, 1H), 7.19-7.29 (m, 4H), 7.30-7.38 (m, 4H), 7.55-7.57 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 32.2, 38.5, 83.5, 84.6, 105.3, 122.9, 126.9, 128.3, 128.4, 128.5, 128.6, 131.8, 133.9, 146.7, 175.6; HRMS (ESI): calcd for $C_{20}H_{16}NaO_2$, m/z 311.1048 ([M+Na]$^+$); found, m/z 311.1036.

(*Z*)-3-(But-2-ynyl)-5-ethylidenedihydrofuran-2(3*H*)-one (9b).[11a] Yield: 99%; colorless oil; IR (KBr): ν = 2922, 2861, 1800, 1711, 1440, 1223, 1126 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.66-1.69 (m, 3H), 1.76 (t, *J* = 2.7 Hz, 3H), 2.50-2.62 (m, 2H), 2.77-2.97 (m, 3H), 4.62-4.68 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 3.6, 10.5, 20.3, 30.7, 39.6, 74.4, 78.6, 99.6, 147.0, 176.1; HRMS (ESI): calcd for $C_{10}H_{12}NaO_2$, m/z 187.0735 ([M+Na]$^+$); found, m/z 187.0726.

(*Z*)-Methyl 3-(but-2-ynyl)-5-ethylidene-2-oxotetrahydrofuran-3-carboxylate (9c).[11a] Yield: 84%; colorless oil; IR (KBr): ν = 2926, 2361, 1802, 1744, 1438, 1219, 1135, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.69-1.71 (m, 3H), 1.75 (d, *J* = 1.8 Hz, 3H), 2.77-2.87 (m, 2H), 3.11-3.24 (m, 2H), 3.78 (d, *J* = 1.8 Hz, 3H), 4.67-4.73 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 3.6, 10.6, 24.4, 34.8, 53.6, 54.8, 72.6, 79.9, 100.1, 145.5, 169.2, 172.1; HRMS (ESI): calcd for $C_{12}H_{14}NaO_4$, m/z 245.0790 ([M+Na]$^+$); found, m/z 245.0782.

5-Methylene-3-phenyl-3-(prop-2-ynyl)dihydrofuran-2(3*H*)-one (9d).[11a] Yield: 93%; colorless oil; IR (KBr): ν = 3292, 2357, 1799, 1677, 1261, 1146, 1038 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.09-2.10 (m, 1H), 2.83 (dd, *J* = 16.9, 1.8 Hz, 1H), 2.98 (dd, *J* = 16.9, 1.8 Hz, 1H), 3.28 (d, *J* = 16.0 Hz, 1H), 3.46 (dd, *J* = 16.0, 1.8 Hz, 1H), 4.40 (s, 1H), 4.79 (s, 1H), 7.32-7.44 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.6, 37.9, 52.1, 72.3, 79.1, 89.8, 126.0, 128.3, 129.2, 138.5, 153.1, 175.8; HRMS (ESI): calcd for $C_{14}H_{12}NaO_2$, m/z 235.0735 ([M+Na]$^+$); found, m/z 235.0728.

(*Z*)-5-Benzylidene-3-phenyl-3-(3-phenylprop-2-ynyl)dihydrofuran-2(3*H*)-one (9e). Yield: 96%; colorless solid; mp: 113-115 °C; $[\alpha]_D^{23}$ = +11.9 (*c* = 1.1, $CHCl_3$); IR (KBr): ν = 3069, 3022, 2360, 1802, 1691, 1597, 1493, 1442, 1317, 1227, 1178, 1108, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.09 (dd, *J* = 16.9, 1.8 Hz, 1H), 3.23 (dd, *J* = 16.9, 1.8 Hz, 1H), 3.47 (d, *J* = 16.5 Hz, 1H), 3.72 (d, *J* = 16.5 Hz, 1H), 5.63 (s, 1H), 7.18-7.26 (m, 4H), 7.28-7.34 (m, 5H), 7.37-7.42 (m, 2H), 7.52-7.57 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 30.0, 39.6, 51.4, 84.3, 84.4, 105.5, 122.8, 126.1, 127.0, 128.31, 128.34, 128.36, 128.5, 128.6, 129.2, 131.8, 133.9, 138.8, 145.8, 176.0; HRMS (ESI): calcd for $C_{26}H_{20}NaO_2$, m/z 387.1361 ([M+Na]$^+$); found,

m/z 387.1353. Enantiomeric excess: 60%, determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 9/1, flow rate: 1.5 mL/min, 254 nm): major enantiomer: t_R =17.7 min, minor enantiomer: t_R = 11.4 min.

(*E*)-5-(3-Methylbenzylidene)-3-phenyl-3-(3-*m*-tolylprop-2-ynyl)dihydrofuran-2(3*H*)-one (9f). Yield: 75%; pale yellow solid; mp: 111-112 °C; $[\alpha]_D^{22}$ = +3.4 (*c* = 0.7, $CHCl_3$); IR (KBr): ν = 3033, 2927, 2360, 1798, 1697, 1504, 1445, 1357, 1189, 1106, 1013 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 2.33 (s, 3H), 3.07 (d, *J* = 16.5 Hz, 1H), 3.22 (d, *J* = 16.9 Hz, 1H), 3.44 (dd, *J* = 16.0, 0.9 Hz, 1H), 3.72 (dd, *J* = 16.0, 1.8 Hz, 1H), 5.60 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.30-7.34 (m, 1H), 7.36-7.41 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.50-7.53 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.6, 30.0, 39.5, 51.5, 83.7, 84.5, 105.4, 119.7, 126.1, 128.2, 128.5, 129.08, 129.10, 129.3, 131.0, 131.7, 136.7, 138.4, 138.9, 145.1, 176.1; HRMS (ESI): calcd for $C_{28}H_{24}NaO_2$, m/z 415.1674 ($[M+Na]^+$); found, m/z 415.1664. Enantiomeric excess: 60%, determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 9/1, flow rate: 1 mL/min, 254 nm): major enantiomer: t_R = 59.3 min, minor enantiomer: t_R = 19.2 min.

(*E*)-5-(4-Methylbenzylidene)-3-phenyl-3-(3-*p*-tolylprop-2-ynyl)dihydrofuran-2(3*H*)-one (9g). Yield: 88%; pale yellow oil; $[\alpha]_D^{22}$ = +8.9 (*c* = 0.9, $CHCl_3$); IR (KBr): ν = 3033, 2921, 2360, 1799, 1689, 1598, 1490, 1442, 1319, 1259, 1189, 1113, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 2.33 (s, 3H), 3.07 (d, *J* = 16.5 Hz, 1H), 3.22 (d, *J* = 16.9 Hz, 1H), 3.44 (dd, *J* = 16.0, 0.9 Hz, 1H), 3.72 (dd, *J* = 16.0, 1.8 Hz, 1H), 5.60 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.30-7.34 (m, 1H), 7.36-7.41 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.50-7.53 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.6, 30.0, 39.5, 51.5, 83.7, 84.5, 105.4, 119.7, 126.1, 128.2, 128.5, 129.08, 129.10, 129.3, 131.0, 131.7, 136.7, 138.4, 138.9, 145.1, 176.1; HRMS (ESI): calcd for $C_{28}H_{24}NaO_2$, m/z 415.1674 ($[M+Na]^+$); found, m/z 415.1664. Enantiomeric excess: 60%, determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 9/1, flow rate: 1 mL/min, 254 nm): major enantiomer: t_R = 59.3 min, minor enantiomer: t_R = 19.2 min.

(*E*)-5-(4-Isopropylbenzylidene)-3-(3-(4-isopropylphenyl)prop-2-ynyl)-3-phenyldihydrofuran-2(3*H*)-one (9h). Yield: 92%; colorless solid; mp: 98-100 °C; $[\alpha]_D^{23}$ = -1.2 (*c* = 1.0, $CHCl_3$); IR (KBr): ν = 3050, 2958, 2358, 1795, 1690, 1501, 1450, 1319, 1248, 1181, 1116, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.9 Hz, 6H), 1.24 (d, *J* = 6.9 Hz, 6H), 2.80-2.93 (m, 2H), 3.07 (d, *J* = 16.9 Hz, 1H), 3.21 (d, *J* = 16.9 Hz, 1H), 3.43 (d, *J* = 16.5 Hz, 1H), 3.71 (dd, *J* = 16.0, 1.8 Hz, 1H), 5.61 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.24-7.26 (m, 2H), 7.29-7.33 (m, 1H), 7.38 (t, *J* = 8.2 Hz, 2H), 7.48-7.52 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.1, 29.9, 34.0, 34.2, 39.5, 51.5, 83.6, 84.5, 105.4, 120.2, 126.2, 126.5, 126.6, 128.2, 128.6, 129.1, 131.5, 131.9, 138.9, 145.2, 147.8, 149.4, 176.1; HRMS (ESI): calcd for $C_{32}H_{32}NaO_2$, m/z 471.2300 ($[M+Na]^+$); found, m/z 471.2289. Enantiomeric excess: 71%, determined by HPLC (Chiralpak AS, *n*-hexane/*i*-PrOH = 99/1, flow rate: 0.5 mL/min, 254 nm): major enantiomer: t_R = 17.8 min, minor enantiomer: t_R = 13.5 min.

(*E*)-5-(4-Methoxybenzylidene)-3-(3-(4-methoxyphenyl)prop-2-ynyl)-3-phenyldihydrofuran-2(3*H*)-one (9i). Yield: 73%; pale yellow solid; mp: 97-99 °C; $[\alpha]_D^{22}$ = -0.7 (*c* = 0.9, $CHCl_3$); IR (KBr): ν = 2959, 2839, 2359, 1793, 1688, 1604, 1505, 1451, 1293, 1254, 1181, 1118, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.05 (d, *J* = 16.9 Hz, 1H), 3.20 (d, *J* = 16.9 Hz, 1H), 3.42 (d, *J* = 16.0 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 5.57 (s, 1H), 6.75 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 7.24-7.26 (m, 2H), 7.29-7.33 (m, 1H), 7.36-7.41 (m, 2H), 7.48-7.52 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 30.0, 39.5, 51.6, 55.4, 82.9, 84.2, 104.9, 113.9, 113.95, 114.0, 115.0, 126.2, 126.7, 128.2, 129.1, 129.9, 133.3, 139.0, 144.2, 158.5, 159.6, 176.2; HRMS (ESI): calcd for $C_{28}H_{24}NaO_4$, m/z 447.1572 ($[M+Na]^+$); found, m/z 447.1562. Enantiomeric excess: 60%, determined by HPLC (Chiralpak AS, *n*-hexane/EtOH = 9/1, flow rate: 1.0 mL/min, 254 nm): major enantiomer: t_R = 25.0 min, minor enantiomer: t_R = 12.7 min.

(*E*)-5-(4-Bromobenzylidene)-3-(3-(4-bromophenyl)prop-2-ynyl)-3-phenyldihydrofuran-2(3*H*)-one (9j). Yield: 66%; colorless solid; mp: 199-200 °C; $[\alpha]_D^{23}$ = -1.3 (*c* = 1.0, $CHCl_3$); IR (KBr): ν = 3072, 2360, 1813, 1685, 1486, 1259, 1177, 1104, 1001 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.06 (d, *J* = 16.9 Hz, 1H), 3.21 (d, *J* = 16.9 Hz, 1H), 3.46 (d, *J* = 16.5 Hz, 1H), 3.66 (dd, *J* = 16.5, 1.8 Hz, 1H), 5.57 (s, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.32-7.37 (m, 3H), 7.38-7.44 (m, 6H), 7.49-7.52 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 30.2, 39.7, 51.3, 83.5, 85.5, 104.4, 120.8, 121.7, 122.7, 126.1, 128.5, 129.3, 130.1, 131.6, 131.7, 132.8, 133.3, 138.6, 146.4, 175.7; HRMS (ESI): calcd for $C_{26}H_{18}Br_2NaO_2$, m/z 542.9571 ($[M+Na]^+$); found, m/z 542.9557. Enantiomeric excess: 8%, determined by HPLC (Chiralpak IE, *n*-hexane/*i*-PrOH = 9/1, flow rate: 1.0 mL/min, 254 nm): major enantiomer: t_R = 10.8 min, minor enantiomer: t_R = 13.3 min.

(*E*)-5-(2-Methylbenzylidene)-3-phenyl-3-(3-*o*-tolylprop-2-ynyl)dihydrofuran-2(3*H*)-one (9k). Yield: 23%; yellow oil; IR (KBr): ν = 3466, 3061, 2922, 2360, 1797, 1689, 1601, 1490, 1453, 1203, 1115 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.31 (s, 3H), 3.16 (d, *J* = 16.9 Hz, 1H), 3.29 (d, *J* = 16.5 Hz, 1H), 3.50 (dd, *J* = 16.5, 1.4 Hz, 1H), 3.78 (dd, *J* = 16.0, 1.8 Hz, 1H), 5.77 (s, 1H), 7.07-7.20 (m, 6H), 7.31-7.35 (m, 2H), 7.38-7.42 (m, 2H), 7.52-7.55 (m, 2H), 7.75 (d, *J* = 7.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.8, 30.0, 39.6, 51.6, 83.2, 88.3, 102.8, 122.7, 125.6, 126.12, 126.14, 127.1, 128.3, 128.4, 129.2, 129.3, 129.5, 130.1, 132.2, 132.3, 135.3, 138.8, 140.4, 145.9, 176.1; HRMS (ESI): calcd for $C_{28}H_{24}NaO_2$, m/z 415.1674 ($[M+Na]^+$); found, m/z 415.1660.

(*Z*)-3-(But-2-ynyl)-5-ethylidene-3-phenyldihydrofuran-2(3*H*)-one (9l). Yield: 93%; colorless oil; $[\alpha]_D^{23}$ = +12.4 (*c* = 0.5, $CHCl_3$); IR (KBr): ν = 3468, 2923, 2360, 1792, 1495, 1443, 1222, 1137, 1038 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.67-1.69 (m, 3H), 1.77 (t, *J* = 2.7 Hz, 3H), 2.69-2.75 (m, 1H), 2.88-2.94 (m, 1H), 3.13-3.18 (m, 1H), 3.39-3.45 (m, 1H), 4.65-4.71 (m, 1H), 7.28-7.32 (m, 1H), 7.34-7.38 (m, 2H), 7.41-7.44 (m, 2H); ^{13}C-

NMR (100 MHz, $CDCl_3$): δ = 3.7, 10.5, 29.1, 37.8, 52.3, 74.0, 79.6, 99.8, 126.1, 128.0, 129.0, 139.3, 146.0, 176.4; HRMS (ESI): calcd for $C_{16}H_{16}NaO_2$, m/z 263.1048 ($[M+Na]^+$); found, m/z 263.1039. Enantiomeric excess: 32%, determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 9/1, flow rate: 0.5 mL/min, 254 nm): major enantiomer: t_R = 9.9 min, minor enantiomer: t_R = 13.9 min.

(*Z*)-Methyl 5-benzylidene-2-oxo-3-(3-phenylprop-2-ynyl)tetrahydrofuran-3-carboxylate (9m).[11a] Yield: 92%; pale yellow oil; $[\alpha]_D^{23}$ = +15.7 (*c* = 0.7, $CHCl_3$); IR (KBr): ν = 3059, 2955, 2360, 1805, 1745, 1697, 1599, 1490, 1440, 1246, 1115, 1031cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.15 (d, *J* = 16.9 Hz, 1H), 3.21 (d, *J* = 16.9 Hz, 1H), 3.45 (dd, *J* = 16.9, 1.8 Hz, 1H), 3.54 (dd, *J* = 16.9, 1.8 Hz, 1H), 3.83 (s, 3H), 5.64 (s, 1H), 7.18-7.25 (m, 4H), 7.29-7.35 (m, 4H), 7.55 (d, *J* = 7.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.2, 36.4, 53.8, 53.9, 82.7, 84.6, 105.8, 122.5, 127.1, 128.3, 128.5, 128.6, 128.6, 131.9, 133.6, 145.1, 168.8, 171.9; HRMS (ESI): calcd for $C_{22}H_{18}NaO_4$, m/z 369.1103 ($[M+Na]^+$); found, m/z 369.1093. Enantiomeric excess: 15%, determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 9/1, flow rate: 1.5 mL/min, 254 nm): major enantiomer: t_R = 19.2 min, minor enantiomer: t_R = 11.9 min.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedueres, characterization data, ^{1}H, ^{13}C-NMR spectra and HPLC data of final compounds. See DOI: 10.1039/b000000x/

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