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C_3-Symmetric Cinchonine-Squaramide-Catalyzed Asymmetric Chlorolactonization of Styrene-Type Carboxylic Acids with 1,3-Dichloro-5,5-dimethylhydantoin: An Efficient Method to Chiral Isochroman-1-ones

Xin Han,[a] Chune Dong,[a] and Hai-Bing Zhou[a,*]

[a] Key Laboratory of Combinatorial Biosynthesis and Drug Discovery (Wuhan University), Ministry of Education, Wuhan University School of Pharmaceutical Sciences, Donghu Road 185#, Wuhan, People's Republic of China
Fax: (+86)-27-6875-9850; e-mail: zhouhb@whu.edu.cn

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Abstract: A more practical and efficient catalytic asymmetric chlorolactonization of styrene-type carboxylic acids with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) using C_3-symmetric cinchonine-squaramide (CSCS) as organocatalyst has been developed. A series of chiral chloro-substituted isochroman-1-ones was obtained in excellent yields (up to 95%) and enantioselectivities (up to 99% *ee*), whwereby the results for chloro-substituted isochroman-1-ones are the best ever achieved. The catalyst can be recovered and reused for six cycles. Moreover, the chlorolactonization product **3b** was further transformed to optically active bicyclic isochroman-1-one derivatives in high yield without losing the enantioselectivity. Furthermore, compounds **3e** and **2n** proved to be highly potent inhibitors of the HIV-1 in TZM-bl cells.

Keywords: asymmetric chlorolactonization; C_3-symmetrical cinchonine-squaramides; carboxylic acids; isochroman-1-ones

Introduction

Halolactonization is one of the most important reactions in organic chemistry due to the fact that the resulting halogenated lactones are among the most versatile building blocks in organic synthesis.[1,2] Over the years, the reaction has been applied in the context of various heterocyclic syntheses, and it continues to be a significant focus of research.[3,4] Given its importance, asymmetric halolactonization has been actively pursued since Bartlett and co-workers described the first stereoselective iodolactonization,[5] in particular, bromolactonization and iodolactonization have become well established in recent years (Figure 1).[6,7] The rapid development has still continued, and a number of newly structured organocatalysts such as thiocarbamate, urea, trisimidazoline etc. have been developed by several other groups.[8–10] For example, in 2010, Tang and co-workers reported a highly enantioselective bromolactonization of conjugated (*Z*)-enynes governed by a cinchonidine-based urea organocatalyst.[11] In the same year, Veitch and Jacobsen disclosed an aminourea-mediated asymmetric iodolactonization of alkenoic acids that proceeds in high yields and excellent *ee*s.[12] More recently, Hansen's group discovered a novel organocatalytic asymmetric iodolactonization that afforded chiral iodolactones in up to 96% *ee* value in the presence of NIS.[13] At the same time, Martin and co-workers reported that 5-*exo* and 6-*endo* bromolactones could be obtained by the asymmetric bromolactonization of alkenecarboxylic acids with TBCO and BINOL ligand.[14] Despite a wealth of accomplishments in asymmetric bromolactonization and iodolactonazition, reports on chlorolactonizations remain scarce, mainly because of the low reactivity of the chlorinating agent. Only a few examples of asymmetric chlorolactonization have been described so far. Borhan and co-workers reported the first dimeric *Cinchona* alkaloid derivative $(DHQD)_2PHAL$-catalyzed enantioselective chlorolactonizations of alkenoic acids.[15] However, regarding this type of asymmetric chlorolactonization reaction, there are still some limitations. For instance, the reaction conditions are not practical, the catalyst is non-recyclable, and the substrate scopes are rather limited and lack generality. Furthermore, to the best of our

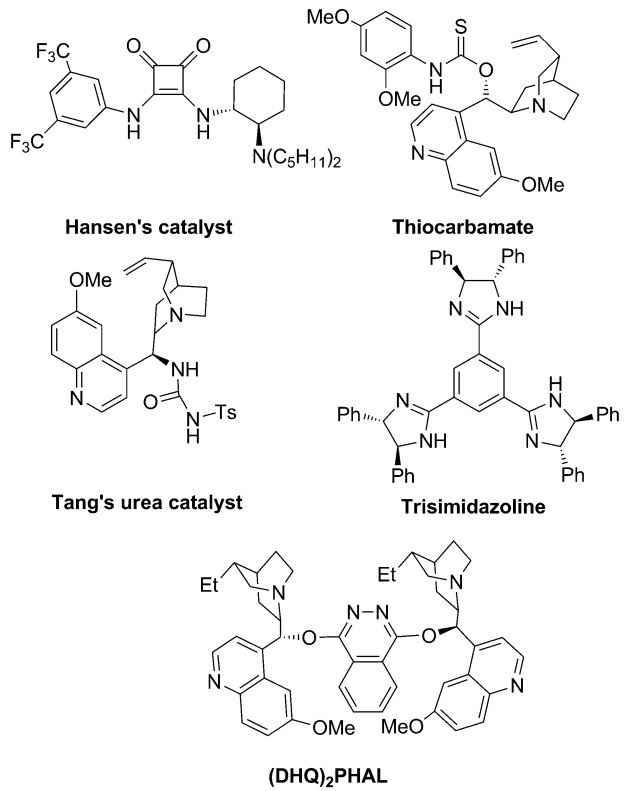


Figure 1. Representative chiral organic catalysts in asymmetric halolactonization.

knowledge, there is no report on the enantioselective chlorolactonization of styrene-type carboxylic acids. Therefore, the development of more practical, recyclable, highly efficient organocatalysts for enantioselective chlorolactonization of styrene-type carboxylic acids is highly desirable.

For some time, we have been interested in the development of novel C_3-symmetric chiral squaramide organocatalysts and their applications in a series of asymmetric transformations.[16] Building on our previous success with the C_3-symmetric chiral cinchonine-squaramide (CSCS), we discovered that application of this readily available C_3-symmetric cinchonine-squaramide in the asymmetric chlorolactonization of styrene-type carboxylic acids results in a drastic improvement in enantioselectivity.

Herein, we report the first, highly efficient, recyclable C_3-symmetric cinchonine-squaramide-catalyzed asymmetric chlorolactonization of styrene-type carboxylic acids affording the corresponding isochroman derivatives in up to 99% *ee* and excellent yields, which are potential bioactive substances with anti-HIV activity.[17] Furthermore, this methodology was extended to the synthesis of enantiomerically pure fully substituted isochroman-1-one derivatives.

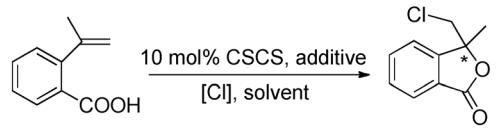
Results and Discussion

Using 2-(prop-1-en-2-yl)benzoic acid **1a** as model substrate, we began to screen conditions for the asymmetric chlorolactonization of **1a**. The results are summarized in Table 1. To our surprise, the reaction proceeded smoothly to give the racemic product **2a** in 95% yield in the presence of 10 mol% CSCS (entry 1). In order to achieve the optically active product, various additives were screened in toluene with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the chloro source at −78 °C in the presence of 10 mol% CSCS; $NsNH_2$ was the best providing the desired product in 51% *ee* (entries 2–9). Increasing the amount of $NsNH_2$ to 5 equivalents resulted in 64% *ee* (entry 13). With 5 equiv. of $NsNH_2$ as the additive, various solvents and chloro sources such as NCS (*N*-chlorosuccinimide), TCCA (trichloroisocyanuric acid), DCDPH (1,3-dichloro-5,5-diphenylhydantoin), NCP (*N*-chlorophthalimide) and DCDHH (1,3-dichlorohydantoin), have also been examined for this reaction (Table 1, entries 15–25), the use of chloroform was determined to be the most appropriate solvent and DCDMH gave the highest *ee* value for this study. No further improvement was observed by increasing the catalyst loading to 20 mol% (Table 1, entry 28). Much to our delight, 83% *ee* was obtained when the reaction was run in $CHCl_3$ at −60 °C for 16 h in the presence of 5 equivalents of additive $NsNH_2$ and 10 mol% of CSCS (entry 21).

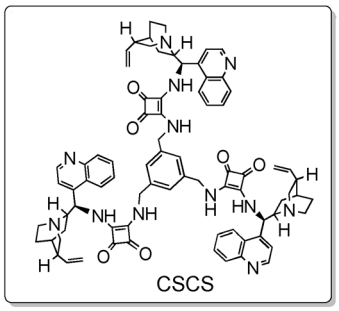
With the optimized reaction conditions in hand, CSCS was employed in the asymmetric chlorolactonization of a series of carboxylic acids bearing different substituent groups; the results are summarized in Table 2. In general, the desired products were formed in excellent yields (entries 1–14, Table 2). As might be expected, the nature of the substrates plays an important role in this reaction. As can be seen in Table 2, carboxylic acids with terminal alkenes favored the 5-*exo* products; while, carboxylic acids with internal alkenes preferentially provided more 6-*endo* products. For instance, when R^2 was hydrogen, the products returned with high 5-*exo* selectivity (up to 99:1) (entries 1, 8, 10–12, 14). A 3:1 ratio of the 6-*endo*/5-*exo* (**3**:**2**) mixture was obtained in excellent enantioselectivity (up to 99% *ee* for the major isomer) for the R^2 as a methyl group (entry 2). Further investigation indicated that, for carboxylic acids with internal alkenes, the presence of electron-rich or electron-deficient R^1 groups on the aryl ring has little effect on the enantioselectivity (entries 3–5). However, for terminal alkenes, a better *ee* was obtained when changing R^1 to an electron-deficient group (entries 10 *vs.* 12). In comparison, when R^2 was an ethyl group, the desired product was obtained with good 6-*endo* selectivity but poorer enantioselectivity (entry 13). Finally, we were delighted to find that when NBS (*N*-bromosuccini-

mide) was used as halo source, the corresponding bromolactonization product was also obtained in excellent yield and enantioselectivity (entry 15).

Table 1. Screening conditions for the enantioselective chlorolactonization of carboxylic acid **1a**.[a]



1a **2a**



Entry	Additive (equiv.)	Solvent	Yield [%][b]	*ee* [%][c]
1	–	toluene	95	0
2	$TsNH_2$ (0.5)	toluene	94	3
3	$NsNH_2$ (0.5)	toluene	95	51
4	4-methylbenzoic acid (0.5)	toluene	93	5
5	phenylhydrazine (0.5)	toluene	97	8
6	*ortho*-toluenesulfonamide (0.5)	toluene	91	17
7	hydroxypyrrolidine-2,5-dione (0.5)	toluene	93	17
8	4-sulfamoylbenzoic acid (0.5)	toluene	92	7
9[k]	$NsNH_2$ (0.5)	toluene	90	37
10	$NsNH_2$ (2.5)	toluene	94	40
11	$NsNH_2$ (1)	toluene	95	51
12	$NsNH_2$ (2)	toluene	90	62
13	$NsNH_2$ (5)	toluene	92	64
14	$NsNH_2$ (7.5)	toluene	93	47
15	$NsNH_2$ (10)	toluene	91	57
16	$NsNH_2$ (5)	toluene	92	NR[d]
17	$NsNH_2$ (5)	toluene	92	17[e]
18	$NsNH_2$ (5)	$CHCl_3$	91	65[f]
19	$NsNH_2$ (5)	$CHCl_3$	92	36[g]
20	$NsNH_2$ (5)	DCM	95	45
21	$NsNH_2$ (5)	$CHCl_3$	95	83
22	$NsNH_2$ (5)	C_2H_5Br	90	24
23	$NsNH_2$ (5)	AcOEt	94	3
24	$NsNH_2$ (5)	DCE	95	5
25	$NsNH_2$ (5)	$CHCl_3$/toluene (1:1)	94	66
26	$NsNH_2$ (5)	$CHCl_3$	95	61[h]
27	$NsNH_2$ (5)	$CHCl_3$	95	65[i]
28	$NsNH_2$ (5)	$CHCl_3$	90	80[j]

To determine the recycling ability of our C_3-symmetric catalyst in this type of reaction, CSCS was recovered after the catalytic process and was reused in the asymmetric chololactonization of **1b** with DCDMH under the optimized reaction conditions. As illustrated in Table 3, catalyst CSCS can be recovered in high yields (90–93%) and be reused without significant loss of activity. It is gratifying our CSCS catalyst maintained its catalytic activity even after six cycles (94–99% *ee*s).

Lactone derivatives are notable because of their extensive bioactivities, including anti-tumor promoting, anti-platelet aggregation and so on.[18] Even so, reports on potent anti-HIV agents based on the chiral lactone skeleton are rare. Therefore, our compounds were evaluated for anti-HIV activity by using an HIV-1_{IIIB}/TZM-bl indicator cell culture system as previously described,[19] and the results are summarized in Table 4. Following a TZM-bl cell assay, we were surprised to see that **3e** and **2n** showed excellent anti-HIV-1 activity on HIV-1 strains with an EC_{50} value as low as 15 μM (Table 4). This work opens new prospects on the design and synthesis of highly efficient anti-HIV agents. Further investigations to clarify the structure–activity relationships (SARs) of these compounds, which are currently underway, will be reported in due course.

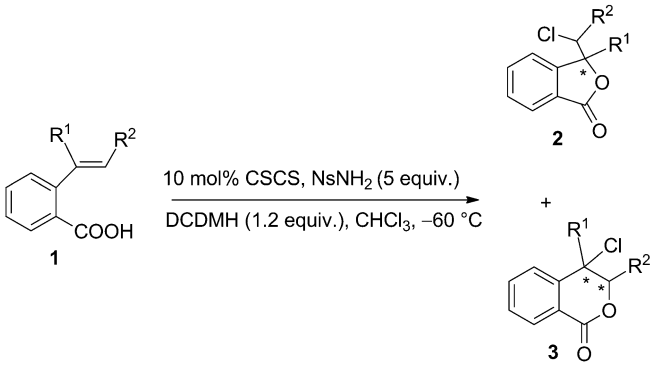
Furthermore, in order to expand the utility of this reaction protocol, the chlorolactonization product **3b** was treated with alkynes in the presence of $Pd(PPh_3)Cl_2$/CuI to provide fully substituted isochroman-1-ones **4a–d** in 92–95% yields and 98–99% *ee*s, which have potential activity in the inhibition of various bacteria and fungi species (Scheme 1).[20]

Conclusions

In conclusion, we have developed the first highly enantioselective chlorolactonization of styrene-type

[a] *Reaction conditions:* 0.1 mmol of **1a**, 0.5 mmol of additive, indicated amount of catalyst in 2.0 mL of appropriate solvent for 30 min at room temperature and then 0.12 mmol of DCDMH was added at low temperature for 16 h.
[b] Isolated yield.
[c] The *ee* values were determined by HPLC analysis using a Chiralpac AD-H column.
[d] NCS or NCP was used in the reaction, no *ee* was observed.
[e] TCCA was used.
[f] DCDPH was used.
[g] DCDHH was used.
[h] When the C_3-symmetric cinchonidine-squaramide was used, the opposite configuration was observed.
[i] 5 mol% CSCS were used.
[j] 20 mol% CSCS were used.
[k] 96 h.

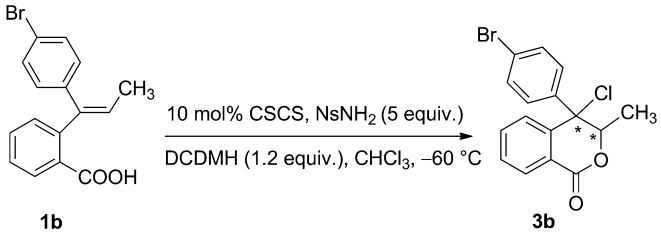
Table 2. Asymmetric chlorolactonization of **1** with DCDMH.[a]



Entry	R^1	R^2	Yield [%][b] (**2**:**3**)	*ee* [%][c]
1	Me	H, **1a**	93 (>99:1)	83
2	4-BrC_6H_4	Me, **1b**	92 (1:3)	99
3	H	Me, **1c**	94 (1:99)	95
4	4-FC_6H_4	Me, **1d**	93 (1:2)	92
5	4-ClC_6H_4	Me, **1e**	93 (1:3)	90
6	Me	Me, **1f**	92 (99:1)	84
7	4-IC_6H_4	Me, **1g**	93 (1:4)	83
8	4-ClC_6H_4	H, **1h**	93 (99:1)	82
9	Ph	Me, **1i**	92 (1:99)	80
10	4-FC_6H_4	H, **1j**	92 (99:1)	77
11	H	H, **1k**	95 (99:1)	67
12	4-MeC_6H_4	H, **1l**	92 (99:1)	62
13	4-BrC_6H_4	Et, **1m**	90 (1:5)	33
14	Ph	H, **1n**	92 (99:1)	57
15[d]	4-BrC_6H_4	Me, **1b**	93 (1:4)	92

[a] Unless otherwise noted, the reactions were carried out with 0.1 mmol of **1**, 0.5 mmol of $NsNH_2$, 0.12 mmol of DCDMH, 0.01 mmol of CSCS in 2.0 mL of $CHCl_3$ at −60 °C for 16 h.
[b] Isolated yield of **2** and **3**.
[c] Tha *ee* values were determined by HPLC analysis using a chiralpac OD-H, AD-H or AS-H column.
[d] NBS as the halo source.

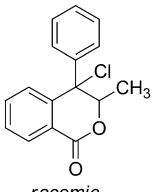
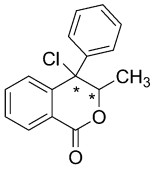
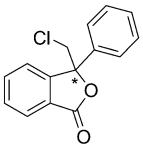
Table 3. Catalyst recovery.[a]



Cycle	Recovery rate [%]	Yield [%][b]	*ee* [%][c]
0	91	93	99
1	92	93	98
2	90	92	99
3	93	92	99
4	90	90	98
5	90	91	94

[a] All reactions were carried out with 0.6 mmol **1b**, 0.72 mmol DCDMH in 5 mL of $CHCl_3$ in the presence of 10 mol% CSCS for 16 h.
[b] Isolated yield.
[c] *ee* values were determined by HPLC analysis using a chiralpac OD-H column.

Table 4. Anti-HIV activity of **3e** and **2n** in TZM-bl cells.[a]

Compounds	 *racemic*	 **3e**	 **2n**
EC_{50} (μM)	NA[b]	29.33	15.46

[a] EC_{50}: effective concentration (μM) for 50% inhibition of HIV-1 (HIV-1_{IIIB} strain) as evaluated with the luciferase activity in TZM-bl cells.
[b] NA: no activity.

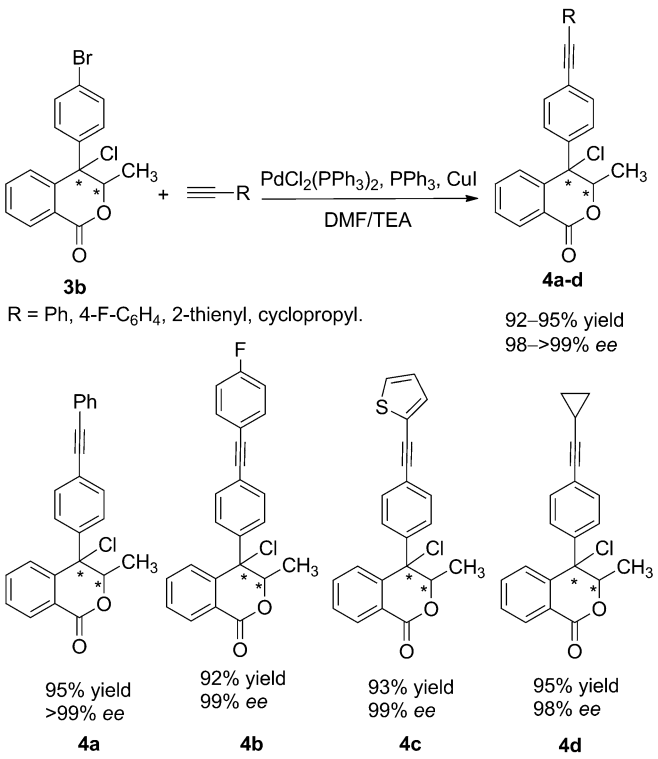
carboxylic acids catalyzed by recoverable C_3-symmetric cinchonine-squaramide (CSCS) providing the isochroman derivatives in up to 99% *ee*. The chlorolactonization product was further transformed to optically active bicyclic isochroman-1-one derivatives in high yield without loss of the enantioselectivity. Furthermore, compounds **3e** and **2n** proved to be highly potent inhibitors of the HIV-1 in TZM-bl cells. This work not only expands the application of chiral C_3-symmetric catalysts in asymmetric chlorolactonization, but also opens new prospects for the design and synthesis of highly specific anti-HIV agents.

Experimental Section

Unless otherwise noted, reagents and materials were obtained from commercial suppliers and were used without further purification. All solvents were purified according to reported procedures. Reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were performed using 230–400 mesh silica gel. Carboxylic acids **1** were prepared according to the literature procedure.[21]

Typical Procedure for the Enantioselective Chlorolactonization of Carboxylic Acids

A solution of 2-(prop-1-en-2-yl)benzoic acid **1a** (32.4 mg, 0.2 mmol), CSCS (25.6 mg, 0.02 mmol) and additive $NsNH_2$ (204 mg, 1 mmol) in dry $CHCl_3$ (1 mL) was stirred for 30 min at room temperature and then the resulting solution was cooled to −60 °C, DCDMH (47.3 mg, 0.24 mmol) was then added in one portion to the solution and the reaction mixture was stirred at −60 °C for 16 h. Upon completion, the solvent was removed and the residue was purified by



Scheme 1. Application of the methodology.

SiO_2 column chromatography (petroleum ether/AcOEt = 4:1) to give **2a** as colorless solid.

Anti-HIV-1 Activity Assays

The inhibitory activity of the experimental compounds on primary HIV-1 replication was determined as previously described.[19]

General Procedure for the Synthesis of Isochroman-1-ones 4

Under an argon atmosphere, a mixture of **3b** (35.2 mg, 0.1 mmol), $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol, 5%), PPh_3 (7.9 mg, 0.03 mmol, 30%), CuI (2 mg, 0.01 mmol, 10%), and acetylene (0.16 mmol) in 1 mL DMF and 1.5 mL TEA as mixed solvent was heated to 80 °C for 24 h. The solvent was removed and the residue was purified by flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (8:1) to afford the product **4**.

4a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (t, $J = 7.1$ Hz, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.74 (t, $J = 7.7$ Hz, 1H), 7.57 (q, $J = 8.6$ Hz, 5H), 7.52 (dd, $J = 6.5$, 3.0 Hz, 2H), 7.41–7.31 (m, 3H), 4.86 (q, $J = 6.7$ Hz, 1H), 1.46 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.19$, 149.89, 137.99, 134.44, 132.10, 131.67, 129.91, 129.74, 128.99, 128.59, 128.42, 126.20, 126.02, 125.90, 125.36, 125.20, 124.04, 122.86, 122.73, 90.70, 90.11, 88.37, 60.98, 19.81: HR-MS (ESI): m/z = 373.0996, calcd. for $C_{24}H_{17}ClO_2$ $[M]^+$: 373.0995. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:2-propanol, 1.0 mL min^{-1}, 220 nm); $t_{major} = 15.357$ min, $t_{minor} = 19.527$ min; >99% *ee*; $[\alpha]_D^{20}$: +95.1 ($c = 0.84$, $CHCl_3$).

4b: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 7.5$ Hz, 1H), 7.74 (t, $J = 6.6$ Hz, 1H), 7.58 (t, $J = 7.2$ Hz, 3H), 7.55–7.48 (m, 3H), 7.38 (t, $J = 9.3$ Hz, 1H), 7.05 (t, $J = 8.6$ Hz, 2H), 4.90–4.78 (m, 1H), 1.46 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 167.87$, 161.59 (d, $^1J_{C,F} = 248.0$ Hz), 147.83, 136.31, 133.32, 132.57, 132.49, 130.73, 129.09, 125.32, 124.95, 122.74, 122.38, 114.68 (d, $^2J_{C,F} = 22.0$ Hz), 108.95, 89.25, 88.47, 87.10, 59.96, 18.62; HR-MS (ESI): $m/z = 391.0900$, calcd. for $C_{24}H_{16}ClFO_2$ $[M]^+$: 391.0901. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:2-propanol, 1.0 mL min^{-1}, 220 nm); $t_{major} = 13.470$ min, t_{minor} = 17.100 min; >99% *ee*; $[\alpha]_D^{20}$: +90.1 ($c = 0.74$, $CHCl_3$).

4c: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (t, $J = 6.5$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 7.63–7.46 (m, 5H), 7.44–7.32 (m, 2H), 7.31–7.26 (m, 1H), 4.90–4.80 (m, 1H), 1.46 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.36$, 149.99, 134.43, 134.29, 132.10, 131.85, 129.74, 128.97, 128.80, 127.14, 125.91, 125.40, 125.21, 122.80, 122.72, 92.02, 90.31, 90.07, 61.18, 19.83; HR-MS (ESI): $m/z = 379.0553$, calcd. for $C_{22}H_{15}ClSO_2$ $[M]^+$: 379.0559. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:2-propanol, 1.0 mL min^{-1}, 220 nm); $t_{major} = 9.282$ min, $t_{minor} = 12.197$ min; >99% *ee*; $[\alpha]_D^{20}$: +79.1 ($c = 0.87$, $CHCl_3$).

4d: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 7.6$ Hz, 1H), 7.74 (dd, $J = 13.3$, 7.5 Hz, 2H), 7.57 (d, $J = 7.3$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 4.83 (q, J = 6.7 Hz, 1H), 1.44 (d, $J = 6.7$ Hz, 3H), 0.94–0.81 (m, 3H), 0.81–0.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.78$, 148.65, 136.12, 134.08, 131.64, 129.87, 126.29, 126.11, 125.64, 124.51, 123.31, 94.78, 90.21, 74.77, 60.88, 19.49, 8.52; HR-MS (ESI): $m/z = 337.0999$, calcd. for $C_{21}H_{17}ClO_2$ $[M]^+$: 337.0995. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:2-propanol, 1.0 mL min^{-1}, 220 nm); $t_{major} = 9.405$ min, $t_{minor} = 10.222$ min; 98% *ee*; $[\alpha]_D^{20}$: +71.1 ($c = 0.83$, $CHCl_3$).

Acknowledgements

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