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Enantioselective Palladium-Catalyzed Ring-Opening Reaction of Azabenzonorbornadienes with Methyl 2-Iodobenzoate: An Efficient Access to *cis*-Dihydrobenzo[*c*]phenanthridinones

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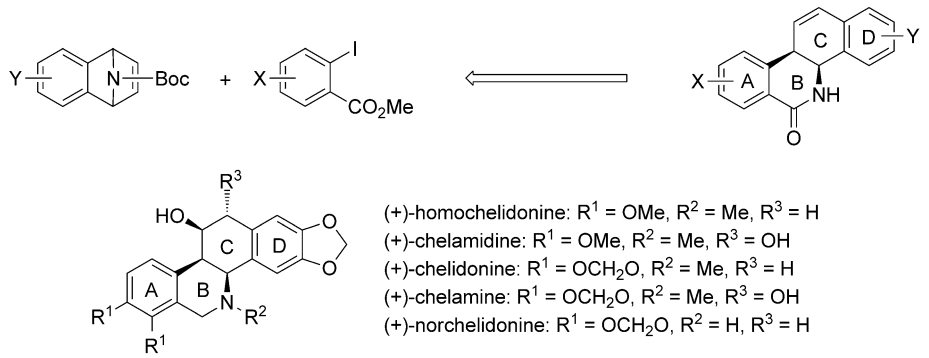
Abstract: The palladium-catalyzed asymmetric ring-opening (ARO) reaction of azabenzonorbornadienes with iodobenzoate derivatives was realized by using chiral spirophosphine ligands with zinc powder as a reducing reagent. Various enantiomerically enriched *cis*-dihydrobenzo[*c*]phenanthridinones, the core structure of numerous chiral natural products, were prepared by the ARO reaction and tandem amidation from easily obtained starting materials with favorable enantioselectivity (up to 86% *ee*) under mild reaction conditions. The present palladium-catalyzed ARO reaction avoids the direct use of organometallic reagents, enables tandem cyclization, and thus improves synthetic efficiency. The formal total synthesis of a chiral natural product, (+)-chelidonine, was accomplished with the ARO reaction as a key step, which demonstrates the potential synthetic applications of the present methodology.

Keywords: asymmetric ring-opening reaction; chiral spiro ligands; *cis*-dihydrophenanthridinones; palladium catalysis

Transition metal-catalyzed asymmetric ring-opening (ARO) reactions of oxa- and azabicyclic alkenes provide efficient methods to access versatile chiral alcohols or amines with multiple chiral centers from easily accessible starting materials.[1] As such, organic synthesis using this reaction has attracted intense research interest. Over the last few decades, the ARO reactions of oxabicyclic alkenes have been extensively studied and good to excellent enantioselectivities have been obtained for diverse substrates.[2] However, although the ring-opening reactions of azabicyclic alkenes with various carbon nucleophiles provide efficient methods for biologically important nitrogen-containing compounds, the asymmetric versions of these reactions are rarely reported.[3] To date, only few ARO of azabicyclic alkenes with organozinc reagents,[3a–c] organoboronic acids,[3d,e] and silylacetylenes[3f,g] as carbon nucleophiles have been reported. The direct utilization of easily accessible organic halides instead of organometallic reagents for better functional group tolerance in the non-asymmetric ring-opening reactions of azabicyclic alkenes has been realized.[4] As well, the concise synthesis of benzo[*c*]-phenanthridines through palladium-catalyzed ring-opening coupling of azabicyclic alkenes with *o*-iodobenzoates followed by tandem cyclization has been achieved.[5] Although the reaction creates a potentially excellent method for the synthesis of chiral amines with multiple chiral centers, the transition metal-catalyzed ARO reaction of azabicyclic alkenes with organic halides remains unknown. Herein, we report for the first time the ARO reactions of azabicyclic alkenes with iodobenzoate derivatives or phenyl triflate catalyzed by palladium complexes of chiral spiro phosphine ligands. Through tandem cyclization, various chiral *cis*-dihydrobenzo[*c*]phenanthridinones, which are the core of a series of chiral natural products (Scheme 1),[6] have been prepared from easily available starting materials with good enantioselectivity (up to 86% *ee*).

We have evaluated the palladium-catalyzed ARO reaction of azabicyclic alkene **1a** and commercially available methyl 2-iodobenzoate **2a** with zinc powder

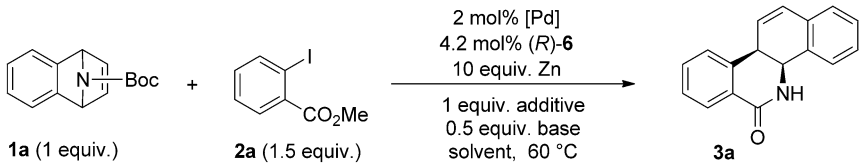


Scheme 1. New strategy for the synthesis of chiral *cis*-dihydrobenzo[*c*]phenanthridinones via ARO reaction and selected natural products with *cis*-dihydro benzo[*c*]phenanthridinone as a core structure.

as a reducing agent, Et_3N as a base, and $ZnCl_2$ as a Lewis acid additive (Table 1). Chiral palladium catalysts were generated *in situ* from $Pd(MeCN)_2Cl_2$ and chiral ligands. A number of chiral monodentate phosphorus ligands (**4**–**6**) developed in our laboratory[7] were evaluated (entries 1–10). The tested ligands produced the desired *cis*-dihydrobenzo[*c*]phenanthridinone **3a** with moderate to good yields. Phosphite (*R*)-**4** exhibited moderate yield with low enantioselectivity (entry 1). Phosphoramidite (*R*)-**5a** generated a good yield and 60% *ee* (entry 2). Compared with those of **5a**, the results obtained after changing the amine moieties of ligand **5** were inferior (entries 3–7). Electron-rich phosphine (*R*)-**6a**[8] gave the best yield and enantioselectivity (82% yield, 72% *ee*; entry 8). Additional substituents on the *P*-phenyl of ligand **6** exhibited negative impacts on both yield and enantioselectivity (entries 9 and 10). Two widely used bidentate ligands, namely **7** and **8**, were also tested in this reaction. Both produced extremely low enantioselectivity or yield (entries 11 and 12).

Other parameters of this reaction were optimized using ligand (*R*)-**6a** (Table 2). The tested Pd(II) salts, such as $Pd(MeCN)_2Cl_2$, $PdCl_2$, $Pd(OAc)_2$, and

Table 2. Palladium-catalyzed ARO reaction of azabenzonorbornadienes with methyl 2-iodobenzoate: optimization of reaction conditions.[a]

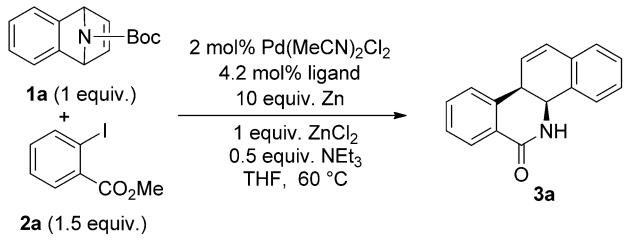


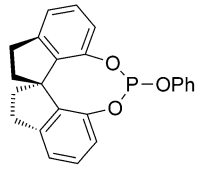
Entry	[Pd]	Base	Additive	Solvent	Yield [%]	*ee* [%]
1	$Pd(MeCN)_2Cl_2$	Et_3N	$ZnCl_2$	THF	82	72
2	$PdCl_2$	Et_3N	$ZnCl_2$	THF	80	72
3	$Pd(OAc)_2$	Et_3N	$ZnCl_2$	THF	72	63
4	$Pd(acac)_2$	Et_3N	$ZnCl_2$	THF	63	68
5	$Pd(dba)_2$	Et_3N	$ZnCl_2$	THF	–[b]	–[b]
6	$Pd(MeCN)_2Cl_2$	DIPEA	$ZnCl_2$	THF	35	47
7	$Pd(MeCN)_2Cl_2$	DABCO	$ZnCl_2$	THF	81	60
8	$Pd(MeCN)_2Cl_2$	*n*-$BuNH_2$	$ZnCl_2$	THF	–[b]	–[b]
9	$Pd(MeCN)_2Cl_2$	pyrrolidine	$ZnCl_2$	THF	–[b]	–[b]
10	$Pd(MeCN)_2Cl_2$	Et_3N	ZnI_2	THF	73	81
11	$Pd(MeCN)_2Cl_2$	Et_3N	I_2	THF	85	81
12	$Pd(MeCN)_2Cl_2$	Et_3N	ICl	THF	70	80
13	$Pd(MeCN)_2Cl_2$	Et_3N	I_2	MeCN	23	82
14	$Pd(MeCN)_2Cl_2$	Et_3N	I_2	acetone	36	80
15	$Pd(MeCN)_2Cl_2$	Et_3N	I_2	EtOAc	51	81

[a] *Reaction conditions:* **1a**/**2a**/[Pd]/(*R*)-**6a**/Zn/additive/base = 0.5:0.75:0.01:0.021:5:0.5:0.25 (mmol), in 4 mL of solvent at 60 °C, reaction time = 24 h; analysis is identical to that shown in Table 1.

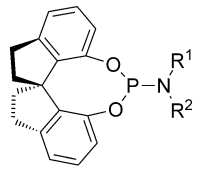
[b] No desired product.

Table 1. Palladium-catalyzed ARO reaction of azabenzonorbornadienes with methyl 2-iodobenzoate: ligand evaluation.[a]

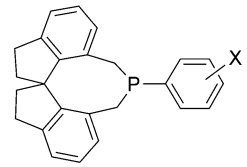




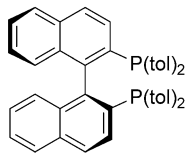
(*R*)-**4**



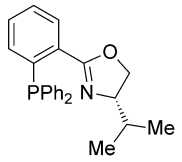
(*R*)-**5a** $R^1 = R^2$ = Me
(*R,R,R*)-**5b** $R^1 = R^2$ = (*R*)-CHMePh
(*R,S,S*)-**5c** $R^1 = R^2$ = (*S*)-CHMePh
(*R*)-**5d** $R^1 = R^2$ = 3,5-$Me_2C_6H_3$
(*R*)-**5e** $R^1 = R^2$ = 4-ClC_6H_4
(*R*)-**5f** R^1 = Me, R^2 = Ph



(*R*)-**6a** X = H
(*S*)-**6b** X = 2-PhC_6H_4
(*R*)-**6c** X = 4-MeO-3,5-(*t*-Bu)$_2C_6H_2$



(*S*)-**7**



(*S*)-**8**

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	(*R*)-**4**	46	28
2	(*R*)-**5a**	81	60
3	(*R,R,R*)-**5b**	38	18
4	(*R,S,S*)-**5c**	52	67
5	(*R*)-**5d**	62	60
6	(*R*)-**5e**	61	45
7	(*R*)-**5f**	67	56
8	(*R*)-**6a**	82	72
9	(*S*)-**6b**	38	47
10	(*R*)-**6c**	62	46
11[d]	(*S*)-**7**	72	7
12[d]	(*S*)-**8**	17	31

[a] *Reaction conditions:* **1a**/**2a**/$Pd(MeCN)_2Cl_2$/ligand/Zn/$ZnCl_2$/Et_3N = 0.5:0.75:0.01:0.021:5:0.5:0.25 (mmol), in 4 mL of THF at 60 °C, reaction time = 24 h.
[b] Isolated yields.
[c] Determined by chiral HPLC with a Chiralcel OD-H column.
[d] Using 2 mol% of ligand.

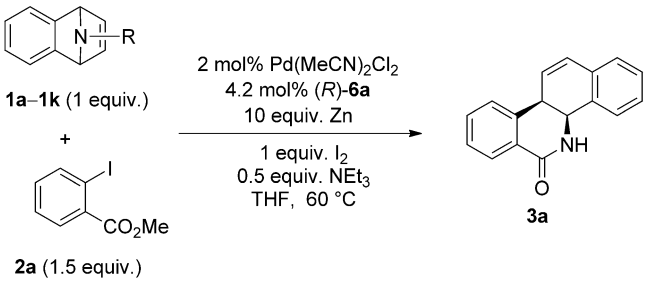
$Pd(acac)_2$, were observed to be suitable precursors for the ARO reaction and produced almost identical yields and enantioselectivities (entries 1–4). By contrast, the Pd(0) precursor $Pd(dba)_2$ failed to develop the desired product under the standard reaction conditions (entry 5). Various bases were also evaluated in this reaction (entries 6–9). Besides Et_3N, other tertiary amines, including *N*,*N*-diisopropylethylamine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane (DABCO), promoted the ARO reaction but with lower yields and enantioselectivities (entries 6 and 7). Secondary amines, such as *n*-$BuNH_2$ and pyrrolidine did not produce the desired product (entries 8 and 9). When ZnI_2 was used as additive instead of $ZnCl_2$, the enantioselectivity improved significantly to 81% *ee* (entry 10). Addition of I_2 or ICl, which can *in situ* generate ZnI_2 through reaction with zinc powder, produced an enantioselectivity that was essentially identical to that obtained with ZnI_2 (entries 11 and 12). When I_2 was used as an additive, a better yield was obtained (entry 11). Other solvents, including acetonitrile, acetone, and ethyl acetate, essentially yielded the same level of enantioselectivity as that produced by THF but with lower yields (entries 13–15). On the other hand, no desired product was obtained when *N*,*N*-dimethylformamide, dimethyl sulfoxide, chloroform, or toluene was used as a solvent (data not shown).

The protecting groups of substrate **1** were evaluated in the ARO reaction (Table 3). The nature of the protecting groups strongly influenced the yield and enantioselectivity of the reaction. Azabenzonorbornadienes with carbamates (**1a–1g**) or benzoyl (**1h**) as protecting groups exhibited good yields and enantioselectivity (entries 1–8). Among these, **1c** (N–$COOCHMe_2$) demonstrated the best results (88% yield, 86% ee; entry 3). Azabenzonorbornadienes with different sulfonyl protecting groups (**1i–1k**) were also tested, but none produced the desired product (entries 9–11).

Under our optimized reaction conditions, various substituted methyl 2-iodobenzoates (**2a–2k**) were tested in the palladium-catalyzed ARO reaction with azabenzonorbornadiene **1c** (Table 4). In most cases, good enantioselectivities were obtained. In general, 5-substituted substrates **2** exhibited good yields (70–82%) and enantioselectivities (79–85% *ee*; entries 4, 6, and 9–11). Substrate **2b** with a 3-fluoro and substrate **2g** with a 4-trifluoromethyl substituent yielded products with significantly decreased enantioselectivity (entries 2 and 7). When the model reaction was scaled up to 4 mmol scale, the desired product **3a** was obtained with 64% yield and 86% *ee*. The optical purity of **3a** could be improved to 96% *ee* through recrystallization form ether with 53% yield.

Similar to 2-iodobenzoates, methyl 2-(trifluoromethylsulfonyloxy)benzoate (**2l**) is a suitable substrate

Table 3. Palladium-catalyzed ARO reaction of azabenzonorbornadienes with methyl 2-iodobenzoate: evaluation of protecting groups.[a]



1a R = $COOCMe_3$
1b R = $COOCH_2CCl_3$
1c R = $COOCHMe_2$
1d R = $COOCH_2Ph$
1e R = COOMe
1f R = $COOCH_2CHMe_2$
1g R = COOPh
1h R = COPh
1i R = Ts
1j R = Mes
1k R = Tf

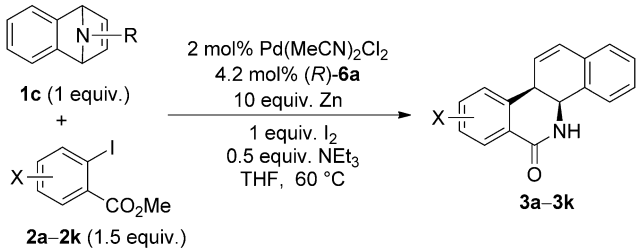
Entry	Azabicycle	Yield [%]	*ee* [%]
1	**1a**	85	81
2	**1b**	78	75
3	**1c**	88	86
4	**1d**	68	82
5	**1e**	59	81
6	**1f**	70	85
7	**1g**	63	86
8	**1h**	63	70
9	**1i**	–[b]	–[b]
10	**1j**	–[b]	–[b]
11	**1k**	–[b]	–[b]

[a] Reaction conditions and analysis are identical to those in Table 2, entry 11.
[b] No desired product.

for the palladium-catalyzed ARO reaction (Scheme 2). Under standard reaction conditions, the desired *cis*-dihydrobenzo[*c*]phenanthridinone **3a** was obtained with 82% yield and 86% *ee*.

The formal synthesis of (+)-chelidonine was accomplished with the palladium-catalyzed ARO reaction as a key step, which further demonstrates the potential synthetic applications of the present reaction (Scheme 3). The palladium-catalyzed ARO reaction of asymmetric ring opening with azabenzonorbornadiene **1l** and methyl 2-iodobenzoate **2m** gave *cis*-dihydrobenzo[*c*]phenanthridinone **3l** with 88% yield and

Table 4. Palladium-catalyzed asymmetric ring opening of **1c** with substituted methyl 2-iodobenzoates.[a]



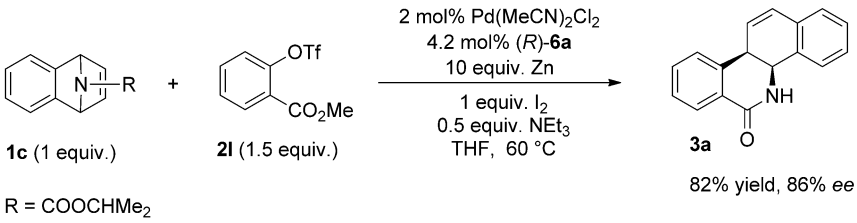
R = $COOCHMe_2$

Entry	X	Substrate	Products	Yield [%]	*ee* [%]
1	H	**2a**	**3a**	88	86
2	3-F	**2b**	**3b**	47	15
3	4-F	**2c**	**3c**	52	78
4	5-F	**2d**	**3d**	80	85
5	4-Cl	**2e**	**3e**	67	76
6	5-Cl	**2f**	**3f**	70	79
7	4-CF_3	**2g**	**3g**	64	45
8	3-Me	**2h**	**3h**	88	79
9	5-Me	**2i**	**3i**	75	82
10	5-OMe	**2j**	**3j**	82	81
11	5-OCF_3	**2k**	**3k**	78	80

[a] Reaction conditions and analysis are identical to those in Table 2, entry 11.

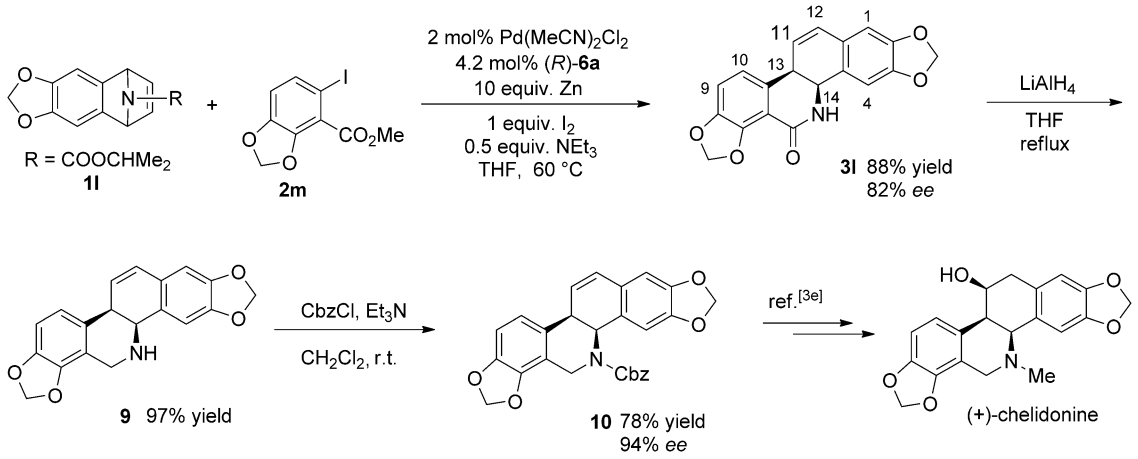
82% *ee*. Thereby, the core structure of (+)-chelidonine which features a fused ring system with two conjunctive chiral centers was constructed in one step. After reduction of *cis*-dihydrobenzo[*c*]phenanthridinone **3l** with $LiAlH_4$ and a subsequent protection step, the known intermediate **10**[3e] was obtained with 76% yield (over two steps). The optical purity of compound **10** was improved to 94% *ee* during the purification. According to the literature,[3e] the total synthesis of (+)-chelidonine could be achieved beginning with intermediate **10** through three steps with 63% overall yield. The absolute configuration of **3l** was assigned as (13*R*,14*S*) by comparing its optical rotation with that of the same compound reported by Lautens.[3e]

In conclusion, the palladium-catalyzed ARO of azabenzonorbornadienes with iodobenzoate derivatives was realized. This reaction is efficient and provides



R = $COOCHMe_2$

Scheme 2. Palladium-catalyzed ARO reaction of azabenzonorbornadiene with methyl 2-(trifluoromethylsulfonyloxy)benzoate.



Scheme 3. Formal synthesis of (+)-chelidonine.

a practical access to optically active *cis*-dihydrobenzo[*c*]phenanthridinones in good yields and enantioselectivities under mild reaction conditions. The electron-rich chiral spirophosphine ligand (*R*)-**6a** and I_2 additive were key factors in attaining good reactivity and enantioselectivity. The new methodology uses easily available organic halides instead of organometallic reagents and remarkably improves the efficiency of the construction of fused ring systems with multiple chiral centers. The formal total synthesis of a chiral natural product (+)-chelidonine was accomplished with the ARO reaction as a key step. Further investigations on the detailed reaction mechanism and testing of the biological and pharmaceutical activities of hexahydrobenzo[*c*]phenanthridine alkaloids with *cis*-fused B/C rings are in progress in our laboratory.

Experimental Section

Typical Procedure for the Palladium-Catalyzed ARO Reaction

To a flame-dried round-bottom flask, $Pd(MeCN)_2Cl_2$ (2.6 mg, 0.01 mmol, 2 mol%), (*R*)-**6a** (7.4 mg, 0.021 mmol, 4.2 mol%) and 4 mL THF were introduced under an argon atmosphere and stirred for 1 hour at room temperature. Azabenzonorbornadiene **1c** (114.5 mg, 0.5 mmol), methyl 2-iodobenzoate **2a** (196.5 mg, 0.75 mmol), Zn (327 mg, 5 mmol), I_2 (127 mg, 0.5 mmol), and NEt_3 (25 mg, 0.25 mmol) were then introduced into the resultant mixture and heated at 60 °C with stirring. The reaction was monitored by TLC until the full consumption of **1c**. The reaction mixture was then diluted with CH_2Cl_2, filtered through celite, and washed with CH_2Cl_2 several times. The combined organic solution was condensed in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1, v/v) to afford the desired product **3a** as a white solid; mp 175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J = 7.7, 1.1 Hz, 1H, Ar-H), 7.53 (td, J = 7.5, 1.4 Hz, 1H, Ar-H), 7.39 (td, J = 7.6, 1.0 Hz, 1H, Ar-H), 7.36–7.24 (m, 4H, Ar-H), 7.16 (d, J = 7.2 Hz, 1H, Ar-H), 6.58 (dd, J = 9.6, 2.7 Hz, 1H, CH), 5.89–5.67 (m, 2H, CH & NH), 4.87 (d, J = 5.7 Hz, 1H, CH), 3.87–3.84 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.03, 139.57, 132.96, 132.64, 131.91, 129.25, 128.58, 128.31, 127.95, 127.61, 127.58, 127.25, 127.08, 127.06, 52.18, 38.63. IR: ν = 767, 1091, 1398, 1465, 1658 cm^{-1}; HR-MS: m/z = 248.1074, calcd. for $C_{17}H_{13}NO$ $[M+H]^+$: 248.1070; *ee* = 86%; HPLC (Chiralpack OD-H, isopropyl alcohol/hexane = 15:85, flow rate 0.9 mL min^{-1}, λ = 220 nm): t_R = 13.6 min (minor), t_R = 20.3 min (major)]; $[\alpha]_D^{25}$: +2.7 (*c* 1.0 in chloroform).

Acknowledgements

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