Efficient Synthesis of Naphtho[1,2-*e*][1,3]oxazine Derivatives via a Chemoselective Reaction with the Aid of Low-Valent Titanium Reagent

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A series of new naphtho[1,2-*e*][1,3]oxazine derivatives such as *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chloride, 1-aryl-2-benzyl-1,2- dihydronaphtho[1,2-*e*][1,3]oxazine-3-one, and *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*] [1,3]oxazine-2(3*H*)-carbaldehyde were selectively synthesized via a chemoselective reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines and triphosgene or triethyl orthoformate, respectively, induced by different low-valent titanium systems. This method has the advantages of short reaction time (15 min), convenient manipulation, and high chemoselectivity.

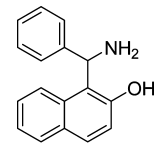
Introduction

Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis.[1] Many other functional groups can also be coupled.[2] Recently, we have reported some intermolecular[3] and intramolecular[4] reductive coupling reactions induced by low-valent titanium reagents.

N-substituted-3,4-dihydro-2*H*-1,3-oxazines condensed with aromatic rings have various pharmacological activities.[5] In particular, their antifungal and antitumoral properties have been reported by Urbanski et al.[6−9]

Aromatic oxazines were first synthesized in 1944 by Holly and Cope through Mannich reactions from phenols, formaldehyde, and amines.[10] From the 1950s to the 1960s, many benzoxazines and naphthoxazines were synthesized by Burke and co-workers.[11−19] However, these methods suffer from some disadvantages such as unsatisfactory yields and long-reaction time. Therefore, the development of more efficient methods for preparing this kind of compounds with improved yields is highly desired.

The Betti reaction is a convenient method to prepare α-aminobenzyl naphthol derivatives. Earlier, this three-component modified Mannich reaction with 2-naphthol, benzaldehyde, and ammonia resulted in 1,3-diphenylnaphthoxazine, which upon subsequent hydrolysis, gave the desired 1-α-aminobenzyl-2-naphthol (Betti base **I**).[20] This reaction can be extended by using substituted benzaldehyde or formaldehyde instead of benzaldehyde,[21] and 1-naphthol instead of 2-naphthol.[22] Although Betti's classical procedure for the preparation of Betti base was published more than a century ago, the possibilities of the application of this versatile synthon in the ring-closure reactions to give naphthalene-condensed heterocyclic derivatives have not been thoroughly investigated. The new publications that have appeared on this topic only focus on the reactions of **I** with aldehydes, phosgene, and oxocarboxylic acids.[23] In recent years, our interest has focused on the synthesis of heterocyclic compounds using a low-valent titanium reagent. We have previously reported the synthesis of quinazolines[24] and pyrroles.[25] As our earlier works goes, herein, we report a novel and convenient protocol for the synthesis of naphtho[1,2-*e*][1,3]oxazine derivatives via the chemoselective reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]-oxazines and triphosgene or triethyl orthoformate, respectively, induced by different low-valent titanium systems.

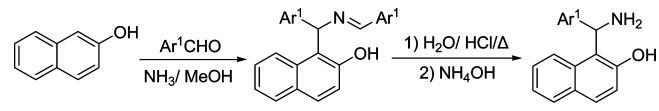


I

Results and Discussion

Betti's classical procedure, a Mannich-type aminoalkylation reaction of 2-naphthol, was applied to prepare the starting materials. Condensation of 2-naphthol (**1**) and aromatic aldehyde in the presence of ammonia, and subsequent acidic hydrolysis, gave amino naphthols (**3**) in good yields (Scheme 1).

Scheme 1. Synthesis of Amino Naphthols



1 **2** **3**

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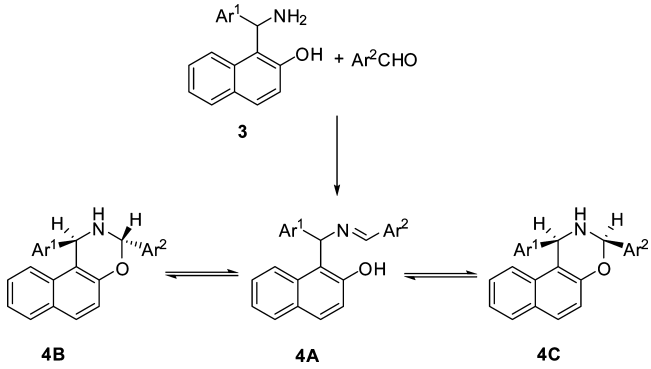
Scheme 2. Synthesis of Starting Materials



Condensations of amino naphthols (**3**) with equivalent amounts of another aromatic aldehyde resulted in imine (**4**), later showed[21a,26] to be in solution equilibrium with two diastereomeric *trans*- and *cis*-oxazine structures (**4B** and **4C**), formed by tautomeric *N*,*O*-proton transfer (Scheme 2).

In a preliminary study, 1,3-bis(4-bromophenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3] oxazine (**4a**) was used to define the reaction conditions for this reaction (Scheme 3).

The low-valent titanium reagent was usually prepared by reduction of $TiCl_4$ with metals such as Zn, Sm, Mg, Fe, and Al et al. The choice of an appropriate low-valent titanium system is of crucial importance not only for the successful synthesis but also for the effective control of chemoselective reaction. To choose the optimum low-valent titanium system, the reaction of 1,3-bis(4-bromophenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (**4a**) (1 mmol) with equimolar triphosgene induced by different low-valent titanium systems was examined at refluxing temperature using tetrahydrofuran (THF) as solvent (Scheme 3).

The results of the screening of low-valent titanium systems are presented in Table 1. It was observed that both naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chloride (**5a**) and naphtho[1,2-*e*][1,3]oxazine-3-one (**6a**) could be obtained when the reaction was induced by $TiCl_4$/Zn system. However, when the reaction was induced by $TiCl_4$/Mg, $TiCl_4$/Fe, or $TiCl_4$/Al systems, respectively, the product **5a** was generated without byproducts, whereas when $TiCl_4$/Sm system was used as low-valent reagent, only naphtho[1,2-*e*][1,3]oxazine-3-one (**6a**) was obtained (Table 1). When $TiCl_4$/Sm/Et_3N and $TiCl_4$/Mg/Et_3N (pH = 7) (Table 1, entry 6, 7) were used, none of the desired products **5a** and **6a** were obtained. It is worth noting that the reaction could be controlled to exclusively yield **5a** or **6a** by varying low-valent titanium system.

Under the conditions described above, the scopes of these chemoselective reactions were examined using various easily available starting materials (Table 2). A series of *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chloride (**5**) was obtained by the reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines and triphosgene induced by $TiCl_4$/Mg. Another series of 1-aryl-2-benzyl-1,2-dihydro naphtho[1,2-*e*][1,3]oxazine-3-one (**6**) was obtained by using the same reaction induced by $TiCl_4$/Sm.

To expand the scope of this method, the replacement of triphosgene with triethyl orthoformate was examined (Scheme 4).

As a preliminary study, 3-bis(4-bromophenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (**4a**) was used to define the reaction conditions for this reaction. Low-valent titanium system and the ratio of substrate and low-valent titanium reagent were screened in a model reaction. The results of extensive low-valent titanium system screening and optimization are shown in Table 3. Among the screened systems, $TiCl_4$/Fe was the system of choice, since via this low-valent system, the reaction proceeded smoothly and afforded the desired products in good yield. To further optimize the reaction condition, the same reaction was carried out via $TiCl_4$/Fe at temperatures ranging from room temperature (r.t.) to reflux. The yield of product **7a** was increased, and the reaction time was shortened as the temperature was increased (Table 3, entries 2, 5−7). Therefore, the refluxing temperature was chosen as the reaction temperature. Furthermore, we were surprised to find that only equiv of $TiCl_4$ and Fe system gave the best yield of product **7a** (Table 3, entry 8).

The use of these optimal experimental conditions [$TiCl_4$/Fe, 1:3 (the ratio of substrates and $TiCl_4$/Fe), reflux] to the reactions of different 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines afforded good yields of naphtho[1,2-*e*][1,3]oxazine- 2(3*H*)-carbaldehyde (Table 4).

As shown in Tables 2 and 4, we were pleased to find that the method was applicable to a broad substrate scope on substituted imines **4**. It can be seen that this protocol can be applied not only to Ar^1 and Ar^2 with weak electron-withdrawing groups (such as halide groups) but also to Ar^1 and Ar^2 with electron-donating groups (such as alkyl groups) under the same conditions. However, when Ar^1 and Ar^2 were with strong electron-withdrawing groups (such as trifluoromethyl), the desired products **5**, **6**, and **7** were not obtained.

We propose a possible mechanism to explain the chemoselectivity. When the $TiCl_4$/Mg system was used, $TiCl_4$ is reduced by Mg dust to give low-valent titanium species, which catalyzed the reaction of ring-closed tautomer **4B** and triphosgene to give products **5** (Scheme 5). When the $TiCl_4$/Sm system was used, $TiCl_4$ is reduced by Sm to give low-valent titanium species and Sm^{2+}. In the initial step, the open tautomer **4A** was reduced by Sm^{2+} and low-valent titanium to aminophenol intermediate **8**. Then the products **6** were obtained by the reaction of **8** and triphosgene catalyzed by low-valent titanium species (Scheme 5).

All the products were characterized by NMR, IR, and HRMS spectra. The structures of compounds **5c**, **6i**, and **7b** were further confirmed by X-ray diffraction analysis. The molecular structures of the products **5c**, **6i**, and **7b** are shown in Figures 1, 2, and 3, respectively.

Conclusion

In summary, series of *trans*-1,3-diary-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl chlorides, 1-aryl-2-benzyl-1*H*-naphtho[1,2-*e*][1,3]oxazine-3-ones, and *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbaldehydes were synthesized by the chemoselective reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphtha [1,2-*e*][1,3] oxazines and triphosgene or triethyl orthoformate induced by different low-valent titanium systems. This method has the advantages of short

Scheme 3. Chemoselective Synthesis of Naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl Chloride and Naphtho[1,2-*e*][1,3]oxazine-3-one

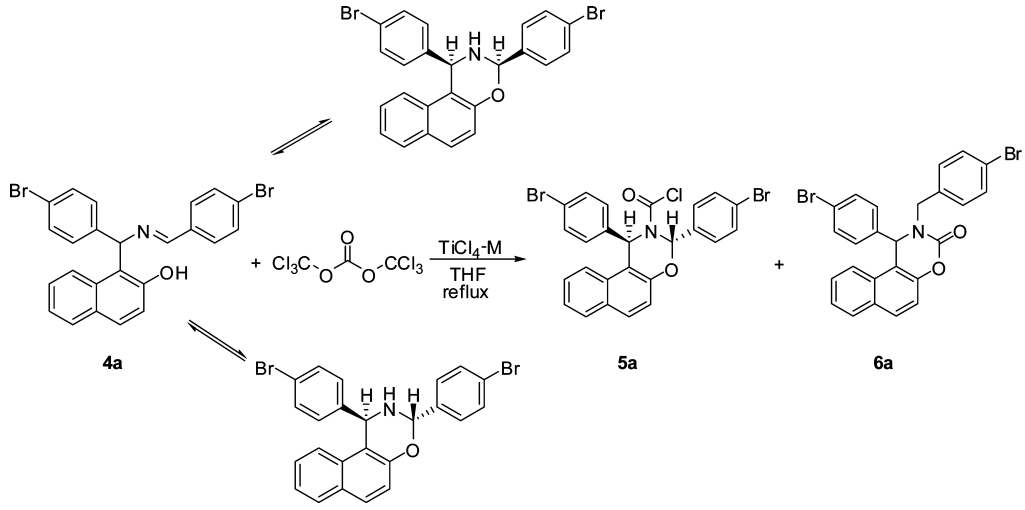


Table 1. Optimization of Chemoselectivity Conditions in the Synthesis of Compouds **5a** and **6a**

				yield(%)	
entry	M	ratio[a]	temperature (°C)	**5a**	**6a**
1	$TiCl_4$/Sm	1:2	reflux	trace	65
2	$TiCl_4$/Zn	1:2	reflux	8	59
3	$TiCl_4$/Fe	1:2	reflux	57	trace
4	$TiCl_4$/Mg	1:2	reflux	87	trace
5	$TiCl_4$/Al	1:2	reflux	45	trace
6	$TiCl_4$/Sm/Et_3N	1:2	reflux	0	0
7	$TiCl_4$/Mg/Et_3N	1:2	reflux	0	0

[a] Ratio of $TiCl_4$ and M.

reaction time, high chemoselectivity, accessible materials, and convenient manipulation.

Experimental Section

General Information. THF was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr with absorptions in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR were determined on Varian Inova-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from internal standard TMS. HRMS data were obtained using a time-of-flight mass spectrometry (TOF-MS) instrument. X-ray diffractions were recorded on a Siemens P4 or Simart-1000 diffractometer.

Typical Procedure for Preparation of *trans*-1,3-diaryl-1*H*-naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbonyl Chloride (5). $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of magnesium powder (0.14 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t., and a solution of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines (**4**, 1 mmol) and triphosgene (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 15 min under N_2. After this period, the thin-layer chromatography (TLC) analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product **5** was purified by recrystallization from acetone. Compound **5a:** mp 178−180 °C. IR (KBr) *ν*: 1740, 1627, 1588, 1518, 1487, 1398, 1369, 1327, 1265, 1239, 1199, 1154, 1074, 1041, 1013, 969, 918, 883, 834, 817, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (*δ*, ppm): 6.85 (s, 1H, CH), 7.15−7.20 (m, 3H, CH+ ArH), 7.36−7.51 (m, 9H, ArH), 7.73 (d, $J = 8.8$ Hz, 2H, ArH), 7.78 (d, $J = 8.0$ Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 54.39, 79.28, 114.57, 117.22, 117.97, 118.09, 118.64, 119.99, 120.47, 122.81, 123.17, 123.47, 124.26, 124.62, 125.51, 126.12, 126.61, 127.27, 127.44, 134.45, 142.77. HRMS: *m/z* [M^+] calcd for $C_{25}H_{16}{}^{79}Br_2{}^{35}ClNO_2$: 554.9236, found 554.9247.

Typical Procedure for Preparation of 1-Aryl-2-benzyl-1,2-dihydronaphtha [1,2-*e*][1,3]oxazine-3-one (6). $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.9 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t., and a solution of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines (**4**, 1 mmol) and triphosgene (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 15 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product **6** was purified by recrystallization from acetone. Compound **6a:** mp 221−222 °C. IR (KBr) *ν*: 1721, 1634, 1590, 1517, 1486, 1403, 1359, 1237, 1211, 1188, 1105, 1070, 1010, 951, 805, 772, 741 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (*δ*, ppm): 4.29 (d, $J = 15.6$ Hz, 1H, CH), 4.80 (d, $J = 15.6$ Hz, 1H, CH), 6.31 (s, 1H, CH), 7.26 (d, *J*

Table 2. Synthesis of Compounds **5** and **6** Induced by Low-Valent Titanium

Entry	Product	Ar^1	Ar^2	Yield (%)	Mp (°C)
1	**5a***	4-BrC_6H_4	4-BrC_6H_4	87	178-180
2	**5b***	C_6H_5	C_6H_5	72	171-173
3	**5c***	4-ClC_6H_4	4-ClC_6H_4	63	199-200
4	**5d***	4-$CH_3C_6H_4$	4-BrC_6H_4	70	130-232
5	**5e***	4-FC_6H_4	4-FC_6H_4	74	158-160
6	**5f***	4-FC_6H_4	4-ClC_6H_4	90	178-179
7	**5g***	4-FC_6H_4	3,4-$Cl_2C_6H_3$	85	200-201
8	**5h***	4-ClC_6H_4	4-FC_6H_4	64	185-186
9	**5i***	4-ClC_6H_4	4-$CH_3C_6H_4$	67	182-184
10	**5j***	4-ClC_6H_4	4-BrC_6H_4	66	190-192
11	**5k***	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	0	
12	**6a****	4-BrC_6H_4	4-BrC_6H_4	65	221-222
13	**6b****	4-ClC_6H_4	4-ClC_6H_4	71	196-197
14	**6c****	4-ClC_6H_4	4-FC_6H_4	75	198-200
15	**6d****	4-ClC_6H_4	2-Thienyl	72	165-167
16	**6e****	4-ClC_6H_4	4-BrC_6H_4	83	194-196
17	**6f****	4-BrC_6H_4	4-$CH_3C_6H_4$	77	206-208
18	**6g****	4-BrC_6H_4	4-ClC_6H_4	86	228-229
19	**6h****	4-BrC_6H_4	4-FC_6H_4	80	218-219
20	**6i****	4-ClC_6H_4	4-$CH_3C_6H_4$	68	170-172
21	**6j****	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	0	

* In the preparation of compounds **5**, the low-valent titanium ($TiCl_4$/Mg) system was used. ** In the preparation of compounds **6**, the low-valent titanium ($TiCl_4$/Sm) system was used.

Scheme 4. Synthesis of Naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbaldehyde

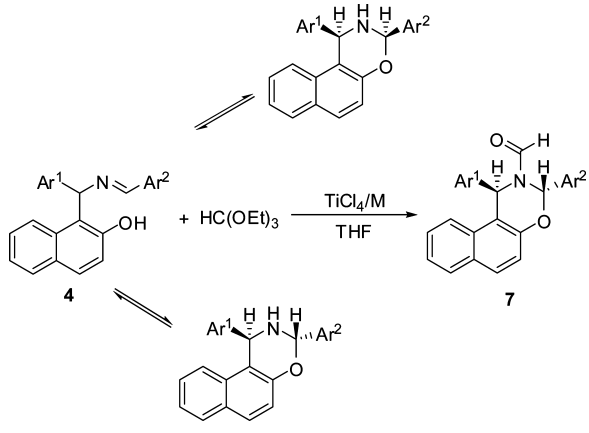


Table 3. Optimization of Low-valent System, Ratio, and Temperature in the Synthesis of **7a**

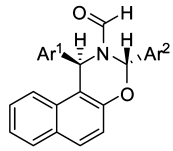
entry	M	ratio[a]	temperature(°C)	yield(%)	time(min)
1	Zn	1:2	reflux	27	15
2	Fe	1:2	reflux	89	15
3	Al	1:2	reflux	75	15
4	Mg	1:2	reflux	32	15
5	Fe	1:2	r.t.	58	120
6	Fe	1:2	40	86	120
7	Fe	1:2	60	78	15
8	Fe	1:1	reflux	95	15
9	Fe	1:3	reflux	90	15
10	Fe	1:4	reflux	88	15
11	Fe/Et_3N	1:2	reflux	0	120

[a] Ratio of $TiCl_4$ and M.

= 8.4 Hz, 2H, ArH), 7.44−7.55 (m, 9H, ArH), 7.88 (d, J = 8.4 Hz, 1H, ArH), 7.97 (d, J = 8.0 Hz, 1H, ArH), 8.03 (d, J = 8.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 50.35, 59.14, 115.24, 117.36, 121.15, 122.50, 123.36, 126.06, 128.35, 128.91, 129.47, 130.36, 130.39, 131.19, 131.34, 132.01, 132.77, 136.56, 140.19, 147.13, 150.39. HRMS: m/z [M^+] calcd for $C_{25}H_{17}{}^{79}Br_2NO_2$: 520.9626, found 520.9638.

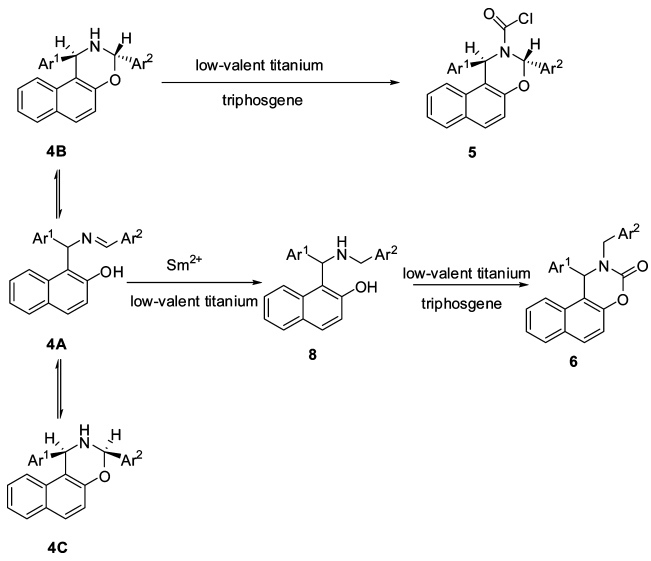
Typical Procedure for Preparation of Naphtho[1,2-*e*][1,3]oxazine-2(3*H*)-carbaldehyde (7). $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of iron powder (0.17 g, 3 mmol) in freshly

Table 4. Synthesis of Naphtho[1,2-e][1,3]oxazine-2(3*H*)-carbaldehyde[a]

Entry	Products	Ar^1	Ar^2	Yield (%)	Mp (°C)
1		4-BrC_6H_4	4-BrC_6H_4	95	238-240
2		4-ClC_6H_4	4-ClC_6H_4	96	216-218
3		4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	96	217-218
4		4-FC_6H_4	4-FC_6H_4	91	186-187
5		C_6H_5	C_6H_5	88	152-154
6		3,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	78	229-231
7	**7a-7m**	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	85	162-164
8		4-$CH_3C_6H_4$	4-FC_6H_4	76	178-180
9		4-$CH_3C_6H_4$	4-BrC_6H_4	87	233-235
10		4-ClC_6H_4	4-$OCH_3C_6H_4$	81	179-181
11		4-ClC_6H_4	4-$CH_3C_6H_4$	86	176-178
12		2-Thienyl	2-Thienyl	65	159-161
13		4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	0	

[a] In the preparation of compounds **7**, the low-valent titanium ($TiCl_4$/Fe) system was used.

Scheme 5. Possible Mechanism to Explain the Chemoselectivity



distilled anhydrous THF (10 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t., and a solution of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines (**4**, 1 mmol) and triethyl orthoformate (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 15 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product **7** was purified by recrystallization from acetone. Compound **7a:** mp 238−240

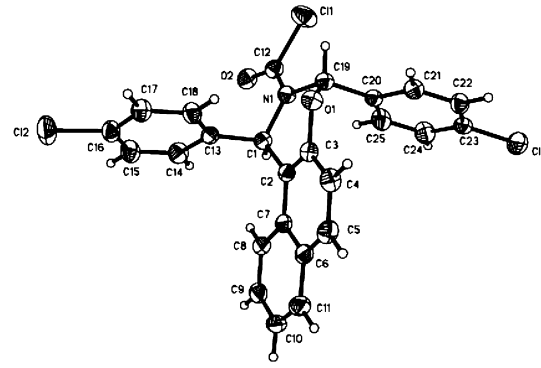


Figure 1. Molecular structure of **5c**.

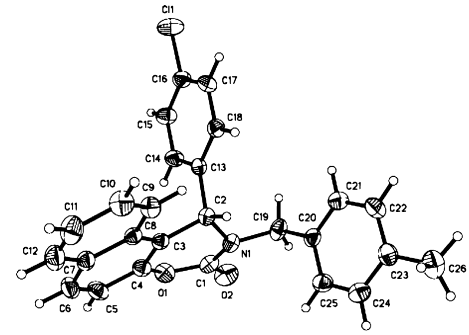


Figure 2. Molecular structure of **6i**.

°C. IR (KBr) ν: 1681, 1624, 1599, 1515, 1487, 1432, 1344, 1327, 1232, 1141, 1070, 1009, 820, 790, 769, 740 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 6.39 (s, 1H, CH), 7.11 (s, 1H, CH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.37 (d, J = 9.2 Hz, 1H, ArH), 7.43−7.54 (m, 6H, ArH), 7.62 (d, J = 8.0 Hz, 2H, ArH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.97−8.02 (m, 3H, ArH + CHO). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 51.04, 81.17, 104.98, 112.76, 122.27, 123.46, 123.84, 126.03, 128.07, 129.47, 130.09, 130.96, 131.01, 131.25,

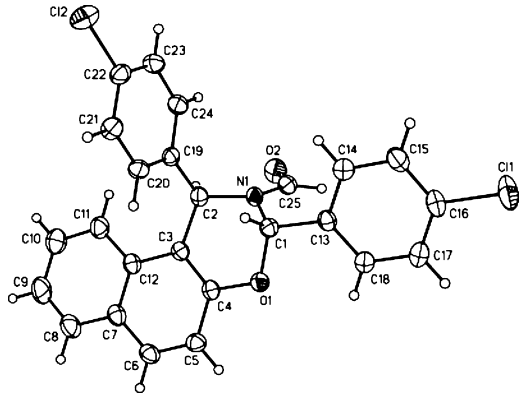


Figure 3. Molecular structure of **7b**.

131.36, 132.17, 132.53, 132.69, 140.51, 151.79, 160.68. HRMS: *m/z* [M^+] Calcd for $C_{25}H_{17}{}^{79}Br_2NO_2$: 520.9626, found 520.9628.

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Supporting Information Available. Detailed descriptions of experimental procedures and spectroscopic and analytical data are available for compounds **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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