JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

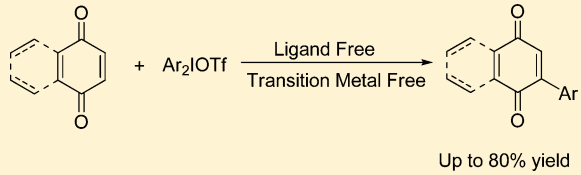
Transition Metal-Free Direct C−H Functionalization of Quinones and Naphthoquinones with Diaryliodonium Salts: Synthesis of Aryl Naphthoquinones as β-Secretase Inhibitors

Dawei Wang,* Bingyang Ge, Liang Li, Jie Shan, and Yuqiang Ding*

The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu, China

Supporting Information

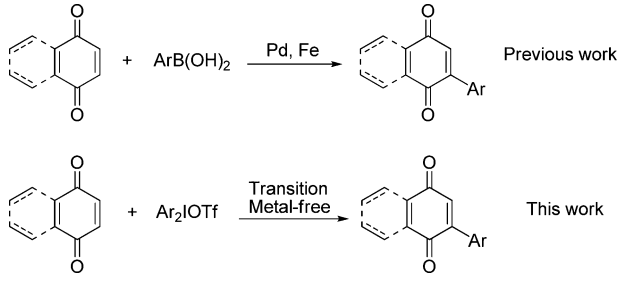
ABSTRACT: A novel ligand-free, transition metal-free direct C−H functionalization of quinones with diaryliodonium salts has been developed for the first time. The transformation was promoted only through the use of a base and gave aryl quinone derivatives in moderate to good yields. This methodology provided an effective and easy way to synthesize β-secretase inhibitors. The radical trapping experiments showed that this progress was the radical mechanism.



INTRODUCTION

Quinone derivatives are important and common building blocks, and convenient precursors for many biological compounds, including pharmaceuticals, medicine, etc.[1] They are distributed in many practical compounds and show some biological activities.[2] Interestingly, aryl-substituted quinones were used as anticancer compounds, antibiotics, pigments, and dyes because of their special properties.[3] Over the years, several methods have been used for the synthesis of aryl-substituted quinones. For example, diazonium salts are used as the common method to synthesize quinone derivatives,[4] but they pose a great danger because they are unstable and explosive. Very recently, arylboronic acids have been shown to be efficient, mild reagents for the reaction of quinones to arylquinones (Scheme 1).[5] In 2009, Molina et al. reported the first coupling of quinones with arylboronic acids by using a palladium catalyst.[5a] Later, Baran described the iron-catalyzed direct functionalization of a variety of quinones with several boronic acids in moderate to good yields.[5c] Zhang and Yu reported FeS-catalyzed direct arylation with arylboronic acids through an aryl radical transfer pathway.[5d] Singh,[5e] Demchuk,[5b] Komeyama,[5f] and Maiti[5g] also reported their results in this area.[6] However, most of aryl acids commercially available are expensive, and catalysts are also needed in this transformation, which greatly limited their application with aryl acids as starting materials. Therefore, the search for an effective synthetic method for quinone derivatives is still a scientific and important issue.

Scheme 1. Transition Metal-Free C−H Functionalization of Quinones with Diaryliodonium Salts



Diaryliodonium salts have attracted considerable attention in modern organic chemistry, particularly with regard to transition metal-catalyzed cross-couplings through α-arylation reaction and C−H activation, over the past decade.[7] Recently, scientists have attempted to use diaryliodonium salts as coupling reagents in the field of metal-free chemistry.[8] On the basis of the advantages of the easy synthesis and high reactivity of diaryliodonium salts, herein, we present the first ligand-free, transition metal-free direct arylation of quinones with diaryliodonium salts in moderate to good yields.

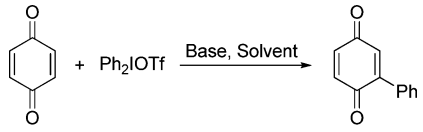
RESULTS AND DISCUSSION

On the basis of our ongoing efforts and the development of a new methodology,[9] the simple quinone and diphenyliodonium salt were selected as model substrates to try the reaction. The reaction mixture was set up in toluene at room temperature. However, none of the desired product was checked. When Na_2CO_3 was added to the reaction mixture, it was found that the desired product was separated in 21% yield. Next, the screened solvents were tested, whereby a strong solvent-dependent phenomenon was observed. CH_2Cl_2, THF, and DMF led to a very low reactivity, but DCE was found to be the optimal solvent. As in the previously reported cases, the reaction did not work well when organic alkali or a weak base NaOAc was applied. The desired product was attained in good yield when NaOH was used, and the reaction reached completion within 12 h (Table 1).

Received: June 5, 2014
Published: August 29, 2014

   dx.doi.org/10.1021/jo501467v | J. Org. Chem. 2014, 79, 8607−8613

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a

entry	base	solvent	yield (%)[b]
1	none	toluene	<5
2	K_2CO_3	toluene	21
3	K_2CO_3	benzene	11
4	K_2CO_3	CH_2Cl_2	<5
5	K_2CO_3	THF	<5
6	K_2CO_3	DMF	<5
7	K_2CO_3	dioxane	<5
8	K_2CO_3	DCE	47
9	$KHCO_3$	DCE	31
10	KOH	DCE	56
11	*t*BuOK	DCE	53
12	NaOH	DCE	70
13	Na_2CO_3	DCE	42
14	Cs_2CO_3	DCE	58
15	NaOAc	DCE	34

[a]Conditions: **1a** (2.0 mmol, 1.0 equiv), **2a** (1.5 equiv), base (1.5 equiv), 8 mL of solvent, 12 h, reflux. [b]Isolated yields based on **1a**.

Given this new method, representative diaryliodonium salts were prepared to investigate the scope of the reaction substrate. The results are summarized in Table 2. Generally, all the quinones were converted completely to produce the corresponding aryl-substituted quinones. Moderate to good isolated yields were obtained regardless of steric hindrance of substituent groups. For the diaryliodonium salts with an electron-withdrawing group, the desired product was separated in low yield (Table 2, entry 11). It should be noted that the highest yield (80%) was obtained in the case of di(*p*-methoxyaryl)iodonium salts (Table 2, entry 6).

The coupling reactions of naphthoquinone with diaryliodonium salts were also explored under the optimized conditions (Table 3). In most cases, the reaction proceeded well and the corresponding products were separated in good to excellent yields. Both ortho-substituted and meta-substituted diaryliodonium salts were suitable for this transformation. Compared to the reported methods, this methodology provides a very easy method for the synthesis of aryl quinones, although moderate yields were realized in most cases. After all, transition metal-free and easy reaction conditions are good complements to other methods (Figure 1).

The coupling of quinones with diaryliodonium salts provides an easy method for the synthesis of aryl-substituted quinones; however, another aryl group was formed as a byproduct, which is a huge waste, especially for a very valuable aryl component. Next, we investigated unsymmetric diaryliodonium salts to solve this problem. As shown in Table 4, both benzoquinone and naphthoquinone were suitable for this transformation. However, the ratio of the two corresponding products was not good. In most cases, poor chemoselectivity of two products was found. In general, the ratio of the two corresponding products with naphthoquinones as subtrates is slightly higher than that with benzoquinones. The best result was obtained with a 1:2.2 ratio, when diaryliodonium salts have a strong electron-donating group (Table 4, entry 6). Although the ratio is not good, after all, this provides an alternative strategy to use an unsymmetric iodonium where one arene (less valuable) does not transfer.

Additionally, this reaction of transition metal-free direct arylation of quinones with diphenyliodonium salts provides an efficient route for the synthesis of aryl-substituted quinone derivatives, which are effective inhibitors of β-secretase (BACE1).[10] It is widely believed that halting the production of β-amyloid peptide through the inhibition of BACE1 is an attractive therapeutic modality for the treatment of Alzheimer's disease (AD).[11] Bermejo-Bescós et al. showed that several arylquinones and their derivatives are effective inhibitors of β-secretase (Scheme 2).[6]

Given the methodology mentioned above, 2-phenylnaphthalene-1,4-dione (**A**) was synthesized only from naphthoquinones while producing a 71% yield. For another inhibitor of BACE1, 2-(4-hydroxyphenyl)naphthalene-1,4-dione (**B**) was synthesized under the conditions of BBr_3 to remove methyl group protection in two total steps (Scheme 3).

To evaluate the applicability of this new method to a gram scale synthesis, we performed the direct C−H functionalization of 2.0 g of naphthoquinone with diphenyliodonium salt. Full conversion was achieved, and a pure inhibitor (**A**) of BACE1 was obtained in 72% yield (Scheme 4).

To unambiguously elucidate this transformation, a preliminary mechanism study was conducted. According to the literature, diaryliodonium salts are easy to turn into aryl radicals via decomposition, and a radical mechanism has been proposed in reactions involving high-valence iodonium salts.[12] Here, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to this reaction mixture as a radical scavenger (Scheme 5). Therefore, the reaction mixture of quinone and diphenyliodonium triflate was set up under 1.0 equiv of TEMPO, and the result showed that nearly no product (<5%) was detected even after a prolonged reaction time under the optimized conditions. These experiments indicated that radical intermediates were involved in this reaction, which are consistent with the literature.[13]

In conclusion, a novel method for ligand-free, transition metal-free direct arylation of quinones with diaryliodonium salts has been developed. This reaction provides an easy, convenient method with respect to aryl-substituted quinones. Two inhibitors of BACE1, **A** and **B**, were easily synthesized with this methodology. The radical trapping experiments showed that this progress was the aryl radical mechanism.

EXPERIMENTAL SECTION

General Procedure for the Reaction of Quinones and Diaryliodonium Salts. A mixture of 1,4-quinone (**1a**) (216.0 mg, 2.0 mmol), diphenyliodonium salt (**2a**) (1290.0 mg, 3.0 mmol), and NaOH (120 mg, 1.5 equiv) in DCE (2.0 mL) was stirred at reflux for 12 h. Upon completion of the reaction, the mixture was evaporated to give the residue, which was then purified by column chromatography on silica gel (1:10 ethyl acetate/petroleum ether) to provide the corresponding product as a pale yellow solid (257.9 mg, 70%).

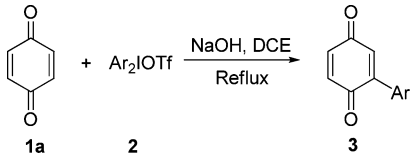
2-Phenyl[1,4]benzoquinone (3a). Faint yellow solid. Mp: 115−117 °C. Known compound:[5c] 257.9 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.42 (m, 5H), 6.84−6.90 (m, 3H).

2-*p*-Tolyl[1,4]benzoquinone (3b). Orange solid. Mp: 137−138 °C. Known compound:[5c] 257.7 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.88−6.77 (m, 3H), 2.40 (s, 3H).

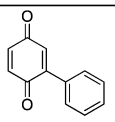
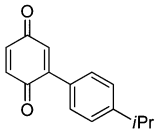
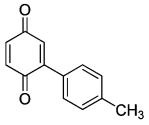
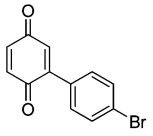
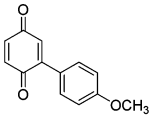
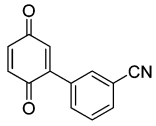
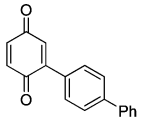
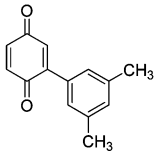
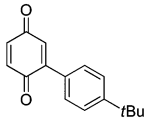
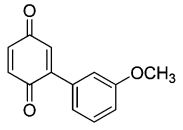
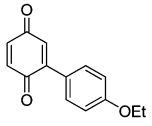
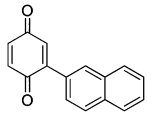
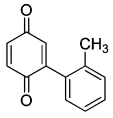
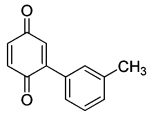
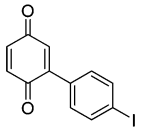
2-(4-Methoxyphenyl)[1,4]benzoquinone (3c). Yellow solid. Mp: 106−108 °C. Known compound:[5c] 342.3 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.88−6.77 (m, 3H), 3.86 (s, 3H).

dx.doi.org/10.1021/jo501467v | J. Org. Chem. 2014, 79, 8607−8613

Table 2. Substrate Expansion of Quinones[a]



1a 2 3

Entry	Ar	Product	Yield[%][b]	Entry	Ar	Product	Yield[%][b]
1	C_6H_5		70(**3a**)	9	*p*-*i*Pr-C_6H_4		71(**3i**)
2	*p*-CH_3-C_6H_4		65(**3b**)	10	*p*-Br-C_6H_4		22(**3j**)
3	*p*-OCH_3-C_6H_4		80(**3c**)	11	*m*-CN-C_6H_4		11(**3k**)
4	*p*-C_6H_5-C_6H_4		71(**3d**)	12	3,5-di-CH_3-C_6H_3		74(**3l**)
5	*p*-*t*Bu-C_6H_4		63(**3e**)	13	*m*-OCH_3-C_6H_4		70(**3m**)
6	*p*-OEt-C_6H_4		62(**3f**)	14	2-naphthyl		60(**3n**)
7	*o*-CH_3-C_6H_4		65(**3g**)	15	*m*-CH_3-C_6H_4		62(**3o**)
8	*p*-I-C_6H_4		38(**3h**)				

[a]Conditions: **1a** (2.0 mmol, 1.0 equiv), **2** (1.5 equiv), NaOH (1.5 equiv), 8 mL of solvent, 12 h, reflux. [b]Isolated yields based on **1a**.

2-Biphenyl-4-yl[1,4]benzoquinone (3d). Faint yellow solid. Mp: 199−200 °C. Known compound:[14a] 369.1 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73−7.55 (m, 6H), 7.47 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 6.88 (m, 3H).

2-(4-*tert*-Butylphenyl)[1,4]benzoquinone (3e). Orange solid. Mp: 73−75 °C. Known compound:[5c] 302.8 mg, 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 6.88−6.79 (m, 3H), 1.35 (s, 9H).

2-(4-Ethoxyphenyl)[1,4]benzoquinone (3f). Yellow solid. Mp: 104−106 °C. Known compound:[14b] 282.9 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.87−6.77 (m, 3H), 4.08 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H).

2-*o*-Tolyl[1,4]benzoquinone (3g). Yellow oil. Known compound:[5c] 269.2 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dt, J = 11.6, 4.5 Hz, 1H), 7.29−7.21 (m, 2H), 7.10 (d, J = 7.2 Hz, 1H), 6.82 (m, 3H), 2.18 (s, 3H).

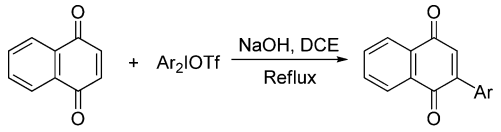
2-(4-Iodophenyl)[1,4]benzoquinone (3h). Light yellow solid. Mp: 133−135 °C. Known compound:[5c] 235.8 mg, 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.91−6.80 (m, 3H).

2-(4-Isopropylphenyl)[1,4]benzoquinone (3i). Yellow solid. Mp: 47−50 °C. Known compound:[15h] 320.8 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.90−6.78 (m, 3H), 2.95 (dt, J = 13.8, 6.9 Hz, 1H), (d, J = 8.3 Hz, 6H), 1.28 (d, J = 6.9 Hz, 6H).

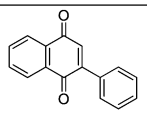
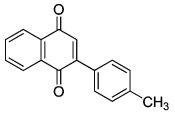
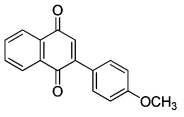
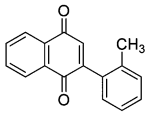
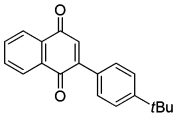
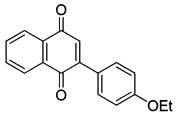
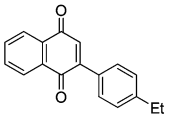
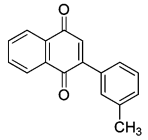
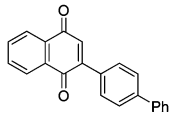
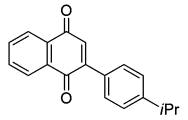
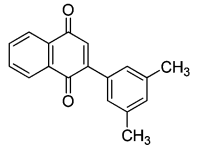
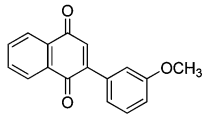
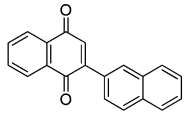
2-(4-Bromophenyl)[1,4]benzoquinone (3j). Orange solid. Mp: 101−102 °C. Known compound:[4] 114.4 mg, 22%. ^{1}H NMR (400 MHz,

dx.doi.org/10.1021/jo501467v | J. Org. Chem. 2014, 79, 8607−8613

Table 3. Substrate Expansion of Naphthoquinones[a]



4a 2 5

Entry	Ar	Product	Yield[%][b]
1	C_6H_5		71(**5a**)
2	*p*-CH_3-C_6H_4		66(**5b**)
3	*p*-OCH_3-C_6H_4		77(**5c**)
4	*o*-CH_3-C_6H_4		61(**5d**)
5	*p*-*t*Bu-C_6H_4		68(**5e**)
6	*p*-OEt-C_6H_4		65(**5f**)
7	*p*-Et-C_6H_4		74(**5g**)
8	*m*-CH_3-C_6H_4		58(**5h**)
9	*p*-C_6H_5-C_6H_4		75(**5i**)
10	*p*-*i*Pr-C_6H_4		76(**5j**)
11	3,5-di-CH_3-C_6H_3		70(**5k**)
12	*m*-OCH_3-C_6H_4		74(**5l**)
13	2-naphthyl		65(**5m**)

[a]Conditions: **4a** (2.0 mmol, 1.0 equiv), **2** (1.5 equiv), NaOH (1.5 equiv), 8.0 mL of solvent, 12 h, reflux. [b]Isolated yields based on **4a**.

Conditions (including Catalyst)	Yield	Ref
$ArB(OH)_2$ $Pd(OAc)_2$ (5%), $K_2S_2O_8$ (4 eq)	low-excellent	**5a**
$ArB(OH)_2$ $AgNO_3$ (20%), $Cu(BF_4)_2$ (20%)	moderate- excellent	**5c**
$ArB(OH)_2$ $Fe(NO_3)_3$ (20%), $K_2S_2O_8$ (4 eq)	good-excellent	**5g**
$ArB(OH)_2$ $Fe(acac)_2$ (20%), $K_2S_2O_8$ (3 eq)	low-good	**5e**
$ArB(OH)_2$ FeS (50%), $K_2S_2O_8$ (3 eq)	good-excellent	**5d**
Ar_2IOTf (only), No cat., No oxidant	moderate-good	**This work**

Figure 1. Comparison with main methods in the literature.

$CDCl_3$): δ 7.57 (d, 2H, J = 8.7 Hz), 7.35 (d, 2H, J = 8.7 Hz), 6.88−6.81 (m, 3H).

3-(3,6-Dioxocyclohexa-1,4-dienyl)benzonitrile (3k). Pale yellow solid. Unstable compound and mp characterization failed. Known compound:[5c] 45.8 mg, 11%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 6.93−6.88 (m, 3H).

2-(3,5-Dimethylphenyl)[1,4]benzoquinone (3l). Pale yellow solid. Mp: 101−102 °C. Known compound:[5f] 313.9 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (1H, s), 7.08 (2H, s), 6.80−6.87 (3H, m), 2.36 (6H, s).

2-(3-Methoxyphenyl)[1,4]benzoquinone (3m). Yellow solid. Mp: 113−114 °C. Known compound:[15g] 299.6 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.32 (m, 1H), 7.05 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 6.5 Hz, 2H), 6.88−6.79 (m, 3H), 3.84 (s, 3H).

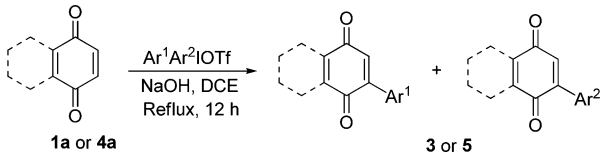
2-Naphthalen-2-yl[1,4]benzoquinone (3n). Pale yellow solid. Mp: 173−174 °C. Known compound:[5d] 280.6 mg, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.95−7.84 (m, 3H), 7.60−7.50 (m, 3H), 6.91 (m, 3H).

2-*m*-Tolylcyclohexa-2,5-diene-1,4-dione (3o). Yellow solid. Mp: 76−78 °C. Known compound:[5c] 245.1 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.24 (m, 4H), 6.90−6.78 (m, 3H), 2.41 (s, 3H).

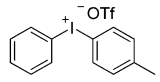
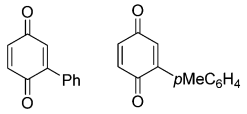
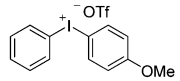
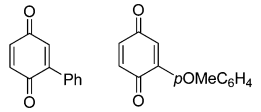
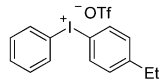
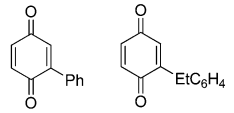
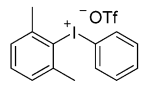
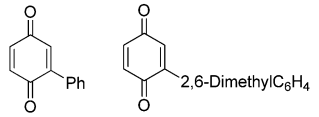
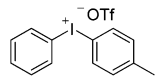
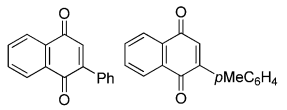
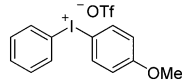
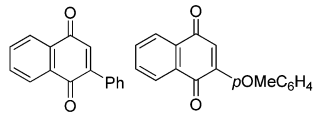
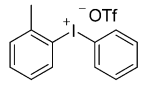
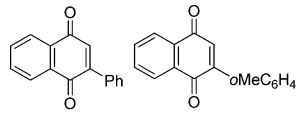
2-Phenyl[1,4]naphthoquinone (5a). Faint yellow solid. Mp: 115−117 °C. Known compound:[5a] 332.3 mg, 71%. ^{1}H NMR (400

dx.doi.org/10.1021/jo501467v | J. Org. Chem. 2014, 79, 8607−8613

Table 4. Substrate Expansion of Unsymmetric Diaryliodonium Salts[a]

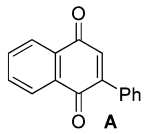


1a or 4a — 3 or 5

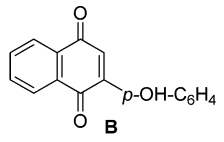
Entry	Ar^1Ar^2IOTf	Products	Ratio[b]	Yield[%][c]
1			1:1.2	73
2			2:3	76
3			1:1.2	64
4			1:1.3	56
5			1:1.9	80
6			1:2.2	79
7			1:2	75

[a]Conditions: **1a** or **4a** (0.5 mmol, 1.0 equiv), Ar^1Ar^2IOTf (1.5 equiv), NaOH (1.5 equiv), 2 mL of DCE, 12 h, reflux. [b]Determined by ^1H NMR. [c]Isolated yields based on **1a** or **4a**.

Scheme 2. Two Selected Inhibitors of BACE1



Anti-BACE1, Ic_{50} (uM): 9.33



Anti-BACE1, Ic_{50} (uM): 8.22

MHz, $CDCl_3$): δ 8.22−8.17 (m, 1H), 8.16−8.10 (m, 1H), 7.82−7.74 (m, 2H), 7.61−7.56 (m, 2H), 7.51−7.46 (m, 3H), 7.09 (s, 1H).

2-*p*-Tolyl[1,4]naphthoquinone (5b). Orange solid. Mp: 103−104 °C. Known compound:[15f] 327.9 mg, 66%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (m, 1H), 8.12 (m, 1H), 7.80−7.75 (m, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 2.42 (s, 3H).

2-(4-Methoxyphenyl)[1,4]naphthoquinone (5c). Yellow solid. Mp: 132−133 °C. Known compound:[15b] 407.0 mg, 77%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 1H), 8.10 (m, 1H), 7.79−7.72 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.04 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H).

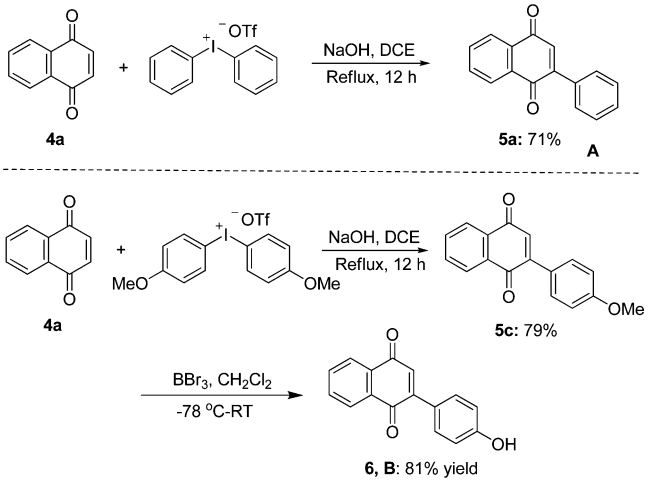
2-*o*-Tolyl[1,4]naphthoquinone (5d). Pale yellow oil. Known compound:[15c] 302.9 mg, 61%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 9.4, 6.3 Hz, 2H), 7.84−7.74 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.28 (dd, *J* = 10.2, 5.9 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 2.23 (s, 3H).

2-(4-*tert*-Butylphenyl)[1,4]naphthoquinone (5e). Faint yellow oil. New compound: 394.8 mg, 68%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (m, 1H), 8.12 (m, 1H), 7.77 (m, 2H), 7.52 (dd, *J* = 17.4, 8.4 Hz, 4H), 7.08 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.1 (s), 184.5 (s), 153.5 (s), 147.9 (s), 134.6 (s), 133.7 (s), 133.76 (s), 132.5 (s), 132.1 (s), 130.5 (s), 129.2 (s), 127.0 (s), 125.9 (s), 125.5 (s), 34.8 (s), 31.2 (s). HRMS: calcd for $C_{20}H_{19}O_2$ $[M + H]^+$ 291.1385, found 291.1382.

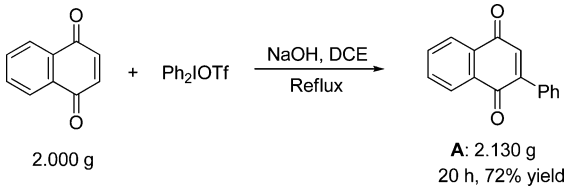
2-(4-Ethoxyphenyl)[1,4]naphthoquinone (5f). Yellow solid. Mp: 115−117 °C. New compound: 361.6 mg, 65%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 1H), 8.14- 8.08 (m, 1H), 7.80−7.73 (m, 2H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.05 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.45 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.21 (s), 184.86 (s), 160.77 (s), 147.45 (s), 133.73 (s), 133.71 (s),

dx.doi.org/10.1021/jo501467v | J. Org. Chem. 2014, 79, 8607−8613

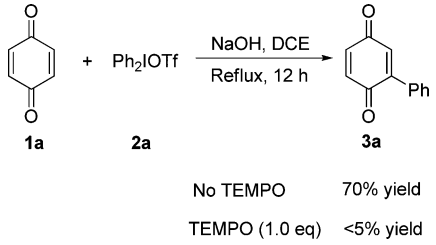
Scheme 3. Synthesis of BACE1 Inhibitors A and B



Scheme 4. Direct C−H Functionalization of Naphthoquinone to Synthesis of BACE1 Inhibitor A on a Gram Scale



Scheme 5. Mechanism of the Verification Test



133.62 (s), 132.63 (s), 132.17 (s), 131.09 (s), 127.01 (s), 125.88 (s), 125.50 (s), 114.56 (s), 63.65 (s), 14.76 (s). HRMS: calcd for $C_{18}H_{15}O_3$ $[M + H]^+$ 279.1021, found 279.1019.

2-(4-Ethylphenyl)[1,4]naphthoquinone (5g). Orange solid. Mp: 67−68 °C. Known compound:[15d] 387.9 mg, 74% (yellow solid, 99.6 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (m, 1H), 8.12 (m, 1H), 7.80−7.75 (m, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.07 (s, 1H), 2.72 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H).

2-*m*-Tolyl[1,4]naphthoquinone (5h). Yellow solid. Mp: 117−119 °C. Known compound:[15a] 288.2 mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22−8.16 (m, 1H), 8.16−8.08 (m, 1H), 7.82−7.74 (m, 2H), 7.41−7.27 (m, 4H), 7.07 (s, 1H), 2.43 (s, 3H).

2-Biphenyl-4-yl[1,4]naphthoquinone (5i). Yellow solid. Mp: 174−175 °C. Known compound:[15e] 465.2 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.19 (m, 1H), 8.16−8.12 (m, 1H), 7.81−7.78 (m, 2H), 7.73−7.64 (m, 6H), 7.48 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.14 (s, 1H).

2-(4-Isopropylphenyl)[1,4]naphthoquinone (5j). Light yellow oil. New compound: 419.4 mg, 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20−8.16 (m, 1H), 8.14−8.09 (m, 1H), 7.79−7.75 (m, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.07 (s, 1H), 2.97 (dt, J = 13.8, 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.2 (s), 184.6 (s), 151.3 (s), 148.0 (s), 134.6 (s), 133.8 (s), 133.8 (s), 132.6 (s), 132.1 (s), 130.9 (s), 129.5 (s), 127.1 (s), 126.7 (s), 125.9 (s), 34.1 (s), 23.8 (s). HRMS: calcd for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1229, found 277.1227.

2-(3,5-Dimethylphenyl)[1,4]naphthoquinone (5k). Yellow solid. Mp: 122−125 °C. New compound: 366.8 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, J = 10.0, 5.0 Hz, 1H), 8.11 (dd, J = 5.9, 3.1 Hz, 1H), 7.80−7.73 (m, 2H), 7.17 (s, 2H), 7.11 (s, 1H), 7.04 (s, 1H), 2.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.2 (s), 184.6 (s), 148.5 (s), 138.1 (s), 135.0 (s), 133.8 (s), 133.8 (s), 133.4 (s), 132.6 (s), 132.1 (s), 131.8 (s), 127.2 (s), 127.0 (s), 125.9 (s), 21.3 (s). HRMS: calcd for $C_{18}H_{15}O_2$ $[M + H]^+$ 263.1072, found 263.1075.

2-(3-Methoxyphenyl)[1,4]naphthoquinone (5l). Pale yellow solid. Mp: 98−99 °C. Known compound:[15f] 390.6 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21−8.15 (m, 1H), 8.14−8.07 (m, 1H), 7.81−7.74 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.11 (s, 1H), 7.08 (s, 1H), 7.02 (dd, J = 8.3, 2.4 Hz, 1H), 3.86 (s, 3H).

[2,2′]Binaphthalenyl-1,4-dione (5m). Light yellow solid. Mp: 169−171 °C. Known compound:[15c] 369.1 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.20 (m, 1H), 8.15 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.90−7.87 (m, 1H), 7.82−7.77 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.57−7.54 (m, 2H), 7.21 (s, 1H).

2-(4-Hydroxyphenyl)[1,4]naphthoquinone (6) (B). Substrate **5c** (0.5 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to −78 °C, and 1 mL of BBr_3 (1.0 M in CH_2Cl_2) was added dropwise while the mixture was being stirred under a nitrogen atmosphere. After addition, the reaction mixture was stirred at −78 °C for 1 h, warmed to rt, and stirred overnight. The reaction was terminated by careful dropwise addition of water. The layers were separated; the organic phase was washed with H_2O, and the combined aqueous layers were evaporated to dryness. The residue was purified by column chromatography on silica gel to provide the corresponding product (101 mg, 81%). Orange solid. Mp: 171−174 °C. Known compound.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.07 (m, 1H), 8.05−8.01 (m, 1H), 7.73−7.65 (m, 2H), 7.49−7.41 (m, 2H), 6.96 (s, 1H), 6.90−6.82 (m, 2H), 5.69 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and ^{1}H NMR data for **3a−p** and **5a−m**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wangdw@jiangnan.edu.cn.
*E-mail: yding@jiangnan.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (21401080 and 21371080), the Natural Science Foundation of Jiangsu Province (BK20130125), the 333 Talent Project of Jiangsu Province (BRA2012165), and MOE & SAFEA for the 111 Project (B13025).

■ REFERENCES

(1) (a) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499. (b) Liu, J.-K. *Chem. Rev.* **2006**, *106*, 2209. (c) Babula, P.; Mikelova, R.; Kizek, R.; Havel, L.; Sladky, Z. *Ceska Slov. Farm.* **2006**, *55*, 151. (d) Koyama, J. *Recent Pat. Anti-Infect. Drug Discovery* **2006**, *1*, 113. (e) Babula, P.; Adam, V.; Havel, L.; Kizek, R. *Ceska Slov. Farm.* **2007**, *56*, 114. (f) Verma, R. P. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 489. (g) Bishop, K. J. M.; Klajn, R.; Grzybowski, B. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5348.

(2) (a) Miller, R. F.; Huang, S. *J. Antibiot.* **1995**, *48*, 520. (b) Zhang, B.; Salituro, G.; Szalkowski, D.; Li, Z.; Zhang, Y.; Royo, I.; Viella, D.; Diez, M. T.; Pelaez, F.; Ruby, C.; Kendall, R. L.; Mao, X.; Griffin, P.; Calaycay, J.; Zierath, J. R.; Heck, J. V.; Smith, R. G.; Möller, D. E. *Science* **1999**, *284*,

974. (c) Fotso, S.; Maskey, R. P.; Grün-Wollny, I.; Schulz, K.-P.; Munk, M.; Laatsch, H. *J. Antibiot.* **2003**, *56*, 931. (d) Coleman, R. S.; Felpin, F.-X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 7309. (e) Nikolovska-Coleska, Z.; Xu, L.; Hu, Z.; Tomita, Y.; Li, P.; Roller, P. P.; Wang, R.; Fang, X.; Guo, R.; Zhang, M.; Lippman, M. E.; Yang, D.; Wang, S. *J. Med. Chem.* **2004**, *47*, 2430. (f) Viault, G.; Grée, D.; Das, S.; Yadav, J. S.; Grée, R. *Eur. J. Org. Chem.* **2011**, *7*, 1233.

(3) Bechtold, T. In *Handbook of Natural Colorants*; Bechtold, T., Mussak, R., Eds.; Wiley: New York, 2009; p 151.

(4) Honraedt, A.; Callonnec, F. L.; Grognec, E. L.; Fernandez, V.; Felpin, F.-X. *J. Org. Chem.* **2013**, *78*, 4604.

(5) (a) Molina, M. T.; Navarro, C.; Moreno, A.; Csaky, A. G. *Org. Lett.* **2009**, *11*, 4938. (b) Demchuk, O. M.; Pietrusiewicz, K. M. *Synlett* **2009**, *7*, 1149. (c) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Bel, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292. (d) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2012**, *48*, 11769. (e) Singh, P. P.; Aithagani, S. K.; Yadav, M.; Singh, V. P.; Vishwakarma, R. A. *J. Org. Chem.* **2013**, *78*, 2639. (f) Komeyama, K.; Kashihara, T.; Takaki, K. *Tetrahedron Lett.* **2013**, *54*, 1084. (g) Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* **2013**, 5251.

(6) Ortega, A.; Rincón, Á.; Jiménez-Aliaga, K. L.; Bermejo-Bescós, P.; Martín-Aragón, S.; Molina, M. T.; Csákÿ, A. G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2183.

(7) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299−5358. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Xiao, Z.-C.; Xia, C.-F. *Youji Huaxue* **2013**, *33*, 2119.

(8) For some reviews and papers, see: (a) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5799. (b) Peng, J.; Chen, C.; Wang, Y.; Lou, Z.-B.; Li, M.; Xi, C.-J.; Chen, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7574. (c) Guo, J.; Dong, S.-X.; Zhang, Y.-L.; Kuang, Y.-L.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10245. (d) Ho, J. S.; Misal Castro, L. C.; Aihara, Y.; Tobisu, M.; Chatani, N. *Asian J. Org. Chem.* **2014**, *3*, 48. (e) Su, X.; Chen, C.; Wang, Y.; Chen, J.-J.; Lou, Z.-B.; Li, M. *Chem. Commun.* **2013**, *49*, 6752. (f) Hu, R.-B.; Zhang, H.; Zhang, X.-Y.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 2193. (g) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (h) Xu, Q.-L.; Gao, H.-Y.; Yousufuddin, M.; Ess, D. H.; Kurti, L. *J. Am. Chem. Soc.* **2013**, *135*, 14048. (i) Lv, T.-Y.; Wang, Z.; You, J.-S.; Lan, J.-B.; Gao, G. *J. Org. Chem.* **2013**, *78*, 5723. (j) Wagner, A. M.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 2263. (k) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188. (l) Gigant, N.; Boissarie, L. C.; Belhomme, M. C.; Poisson, T.; Pannecoucke, X.; Gillaizeau, I. *Org. Lett.* **2013**, *15*, 278. (m) Guo, F.-L.; Han, J.-W.; Mao, S.; Li, J.; Geng, X.; Yu, J.-J.; Wang, L.-M. *RSC Adv.* **2013**, *3*, 6267. (n) Bhong, B. Y.; Shelke, A. V.; Karade, N. N. *Tetrahedron Lett.* **2013**, *54*, 739. (o) Cullen, S. C.; Shekhar, S.; Nere, N. K. *J. Org. Chem.* **2013**, *78*, 12194. (p) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088. (q) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. P.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

(9) For selected recent papers from our group, see: (a) Yang, W.; Wang, D.; Song, Q.; Zhang, S.; Wang, Q.; Ding, Y. *Organometallics* **2013**, *32*, 4130. (b) Li, L.; Wu, F.; Zhang, S.; Wang, D.; Ding, Y.; Zhu, Z. *Dalton Trans.* **2013**, *42*, 4539. (c) Liu, X.; Zhang, S.; Ding, Y. *Dalton Trans.* **2012**, *41*, 5897. (d) Zhang, S.; Ding, Y. *Organometallics* **2011**, *30*, 633. (e) Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218. (f) Yang, W.; Zhang, S.; Ding, Y.; Shi, L.; Song, Q. *Chem. Commun.* **2011**, *47*, 5310. (g) Yang, W.; Fu, H.; Song, Q.; Zhang, M.; Ding, Y. *Organometallics* **2011**, *30*, 77.

(10) Hadden, M. K.; Hill, S. A.; Davenport, J.; Matts, R. L.; Blagg, B. S. *Bioorg. Med. Chem.* **2009**, *17*, 634.

(11) (a) Citron, M. *Neuroscience* **2004**, *5*, 677. (b) Findeis, M. A. *Pharmacol. Ther.* **2007**, *116*, 266.

(12) (a) Lubinkowski, J. J.; Arrieche, C. G.; McEwen, W. E. *J. Org. Chem.* **1980**, *45*, 2076. (b) Dektar, J. L.; Hacker, N. P. *J. Org. Chem.* **1990**, *55*, 639. (c) Chen, D.; Takai, K.; Ochiai, M. *Tetrahedron Lett.* **1997**, *38*, 8211.

(13) (a) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (b) Wen, J.; Zhang, R.-Y.; Chen, S.-Y.; Zhang, J.; Yu, X.-Q. *J. Org. Chem.* **2012**, *77*, 766. (c) Castro, S.; Fernández, J. J.; Vicente, R.; Fananás, F. J.; Rodríguez, F. *Chem. Commun.* **2012**, *48*, 9089.

(14) (a) Kvalnes, D. E. *J. Am. Chem. Soc.* **1934**, *56*, 2478. (b) Aihara, J.; Kushibiki, G.; Matsunaga, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3584.

(15) (a) Zhang, S.; Song, F.; Zhao, D.; You, J. *Chem. Commun.* **2013**, *49*, 4558. (b) Wang, X.; Ye, Y.; Ji, G.; Xu, Y.; Zhang, S.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 3730. (c) Sidhu, G. S.; Pardhasaradhi, M.; Babu, M. H. *Indian J. Chem.* **1976**, *14*, 218. (d) Guenther, R. H.; Szewczyk, J. R. PCT Int. Appl. WO 2011113060, 2011. (e) Shcherban, A. I. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1979**, *22*, 290. (f) Rao, M. L. N.; Giri, S. *RSC Adv.* **2012**, *2*, 12739. (g) Liu, Y.; Zhang, S.; Wang, G. *Desalination* **2013**, *316*, 127. (h) Walensky, L. D.; Stewart, M. L.; Cohen, N. PCT Int. Appl. WO 2011094708, 2011.