JOC The Journal of Organic Chemistry

Note

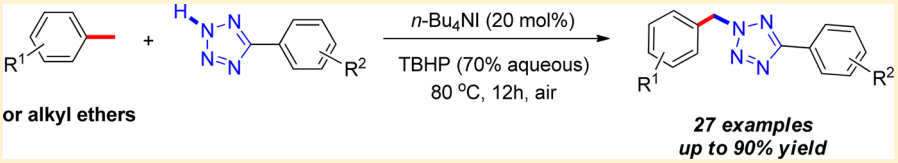
pubs.acs.org/joc

Transition-Metal-Free Direct Alkylation of Aryl Tetrazoles via Intermolecular Oxidative C−N Formation

Liang Wang,* Kaiqiang Zhu, Qun Chen, and Mingyang He*

School of Petrochemical Engineering and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou, 213164, P. R. China

Supporting Information



ABSTRACT: A transition-metal-free synthetic approach for constructing alkylated aryl tetrazoles has been developed using *n*-Bu_4NI as the catalyst and *t*-BuOOH as the oxidant. It involves the direct C−N bond formation through sp^3 C−H activation. A wide range of benzylic C−H substrates (or alkyl ethers) and aryl tetrazoles undergo this reaction smoothly to deliver the corresponding products in good yields.

Tetrazoles are of great importance due to their wide applications in organic chemistry,[1] medicinal chemistry,[2] and material science.[3] For example, biphenyl tetrazoles are key intermediates for preparation of sartan drugs, and 2-arylcarbapenems are useful antibiotics.[4] Recently, tetrazoles were also utilized as directing groups in C−H activation reactions. Seki reported an efficient Ru(III)-catalyzed synthesis of angiotensin II receptor blockers (ARBs) using tetrazole as the directing group (Scheme 1, (a)).[5a] Ackermann and co-workers also disclosed highly efficient Ru(II)-catalyzed direct *ortho*-arylations of aryl tetrazoles.[5b] Inspired by their work, we developed a rhodium-catalyzed direct *ortho* C−H olefination reaction of aryl tetrazoles (Scheme 1, (b)).[5c]

Despite the utilities of the tetrazole moiety, reaction for preparation of alkylated tetrazoles has a limited scope. Generally, they were synthesized by S_N2 reaction between an alkyl halide and a tetrazole. For example, Aridoss and Laali reported a base-promoted the synthesis of alkylated tetrazoles in refluxing acetonitrile (Scheme 1, (c)).[6] The major drawbacks associated with this procedure were the expensive alkyl halides, moderate yields as well as the formation of isomeric dialkylated mixtures.

Recently, the cross-dehydrogenative coupling (CDC) reaction has arisen as an excellent synthetic method to construct more complex compounds.[7] The CDC strategy is very powerful with high atomic economy since no prefunctionalization or preactivation of starting materials is required. Among the reported procedures, the metal-free *n*-Bu_4NI/TBHP system turns out to be the focus of current interest,[8] and some excellent protocols for C−O,[9] C−N,[10] and C−S[11] bond formation have been developed. However, the C−N bond formation catalyzed by *n*-Bu_4NI via sp^3 C−H activation has not been fully explored, especially for the synthesis or functionalization of *N*-containing heterocycles.

Meanwhile, hydrocarbons such as methylarenes are the most cheap and readily available raw materials for chemical industries. Therefore, the direct formation of C−C and C−X bonds via C−H activation of methylarenes is of great importance and is also a big challenge currently. As a part of our continuous interest in the functionalization of tetrazoles,[5c] herein, we report a metal-free alkylation of aryl tetrazoles with benzylic C−H substrates or alkyl ethers by using *n*-Bu_4NI as catalyst and *t*-BuOOH as oxidant (Scheme 1, (d)).

Initially, toluene **1a** and 5-phenyl-2*H*-tetrazole **2a** were chosen as the model substrates to optimize the reaction conditions (Table 1). A 29% yield of product **3aa** was obtained using *n*-Bu_4NI (0.2 equiv) as catalyst and TBHP (3 equiv) as oxidant in ethyl acetate. Replacing TBHP by other oxidants such as H_2O_2, DTBP, $K_2S_2O_8$, or O_2 resulted in the failure of the reaction (Table 1, entries 2−5). Reactions in other solvents, including *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,2-dichloroethane (DCE), and acetonitrile, gave the desired product **3aa** in much lower yields. Encouragingly, a 67% yield of **3aa** was obtained under solvent-free conditions. Increasing the amount of toluene improved the yield notably, and the highest yield was obtained in 1 mL of toluene (ca. 30 equiv) (Table 1, entries 10−12). In addition, no product was observed in the absence of either *n*-Bu_4NI or TBHP (Table 1, entries 13 and 14). Increasing the amount of TBHP to 5 equiv led to a decreased yield. Other catalysts, such as *n*-Bu_4NBr, *n*-Bu_4NCl, I_2, and NaI, were also evaluated; however, unsatisfactory results were obtained (Table 1, entries 17−20). Finally, the survey on the reaction temperature showed that 80 °C was the optimum.

Received: October 6, 2014
Published: November 11, 2014

Scheme 1. Alkylation of 5-Aryl 1*H*-Tetrazoles and Their Functionalizations

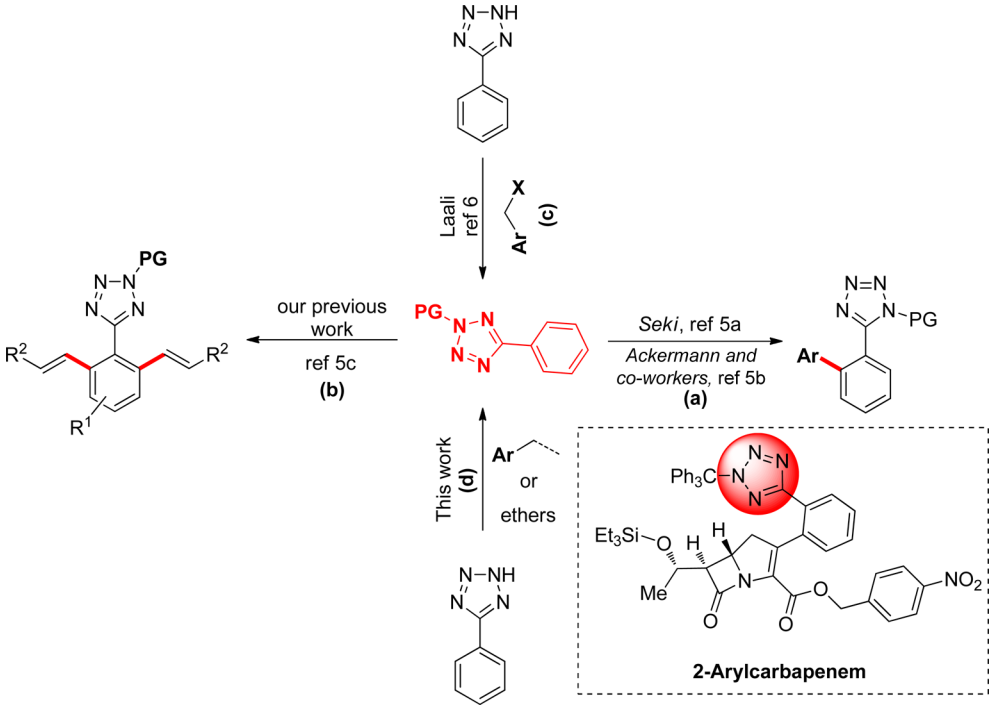
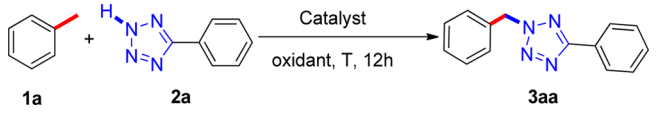


Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

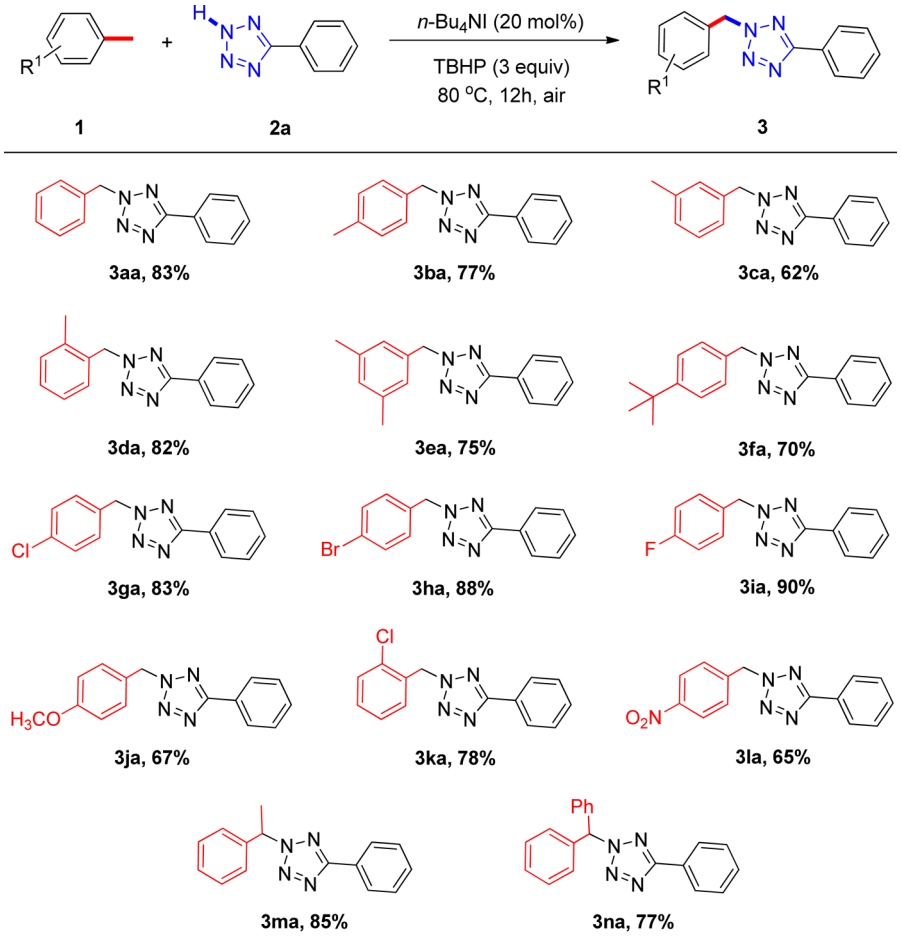
entry	catalyst (mol %)	oxidant[b] (equiv)	T (°C)	solvent	yield (%)[c]
1	*n*-Bu_4NI (20)	TBHP (3)	80	EtOAc	29
2	*n*-Bu_4NI (20)	H_2O_2 (3)	80	EtOAc	[d]
3	*n*-Bu_4NI (20)	DTBP (3)	80	EtOAc	[d]
4	*n*-Bu_4NI (20)	$K_2S_2O_8$ (3)	80	EtOAc	[d]
5	*n*-Bu_4NI (20)	O_2	80	EtOAc	[d]
6	*n*-Bu_4NI (20)	TBHP (3)	80	DMF	[d]
7	*n*-Bu_4NI (20)	TBHP (3)	80	DMSO	trace
8	*n*-Bu_4NI (20)	TBHP (3)	80	DCE	18
9	*n*-Bu_4NI (20)	TBHP (3)	80	CH_3CN	26
10	*n*-Bu_4NI (20)	TBHP (3)	80		67
11	*n*-Bu_4NI (20)	TBHP (3)	80		75[e]
12	**n-Bu_4NI (20)**	**TBHP (3)**	**80**		**83**[f] **(81)**[g]
13		TBHP (3)	80		[d,f]
14	*n*-Bu_4NI (20)		80		[d,f]
15	*n*-Bu_4NI (20)	TBHP (5)	80		74[f]
16	*n*-Bu_4NI (10)	TBHP (3)	80		76[f]
17	*n*-Bu_4NBr (10)	TBHP (3)	80		trace[f]
18	*n*-Bu_4NCl (10)	TBHP (3)	80		[d,f]
19	I_2 (10)	TBHP (3)	80		trace[f]
20	NaI (10)	TBHP (3)	80		trace[f]
21	*n*-Bu_4NI (20)	TBHP (3)	60		38[f]
22	*n*-Bu_4NI (20)	TBHP (3)	100		71[f]
23	*n*-Bu_4NI (20)	TBHP (3)	110		68[f]

[a]Reaction conditions: **1a** (3 mmol), **2a** (0.3 mmol), solvent (1 mL), catalyst, and oxidant were heated in a sealed tube for 12 h. [b]TBHP: *tert*-butyl hydroperoxide 70% in water, H_2O_2 30% in water, DTBP: di-*tert*-butyl peroxide 98%. [c]Isolated yields. [d]Product not observed. [e]Toluene (20 equiv). [f]Toluene (30 equiv, 1 mL). [g]Toluene (1.5 mL).

With the optimized conditions in hand, a series of methylarenes were employed for oxidative coupling with **2a** (Table 2). Generally, methylarenes bearing either electron-donating or electron-withdrawing substituents reacted with **2a** smoothly to afford the desired products in moderate to good yields (**3aa**−**3la**). Both xylenes and mesitylene were efficiently

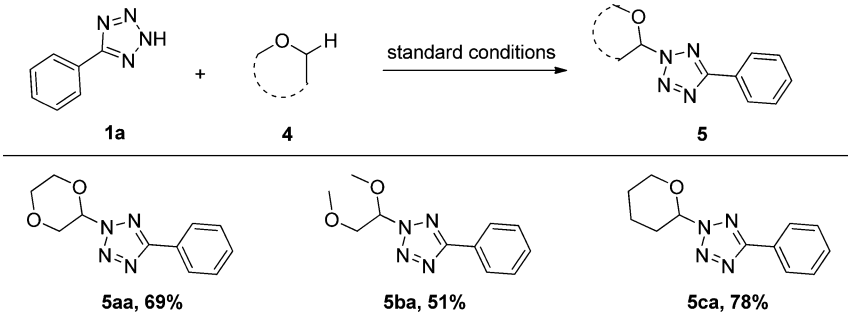
dx.doi.org/10.1021/jo502283h | *J. Org. Chem.* 2014, 79, 11780−11786

Table 2. Reaction Scope for Methylarenes[a]



[a]Reaction conditions: **1** (9 mmol), **2a** (0.3 mmol), TBAI (0.06 mmol, 20 mol %), TBHP (0.9 mmol, 3 equiv), 80 °C, 12 h. Isolated yields.

Scheme 2. Amination Reaction of Selected Alkyl Ethers



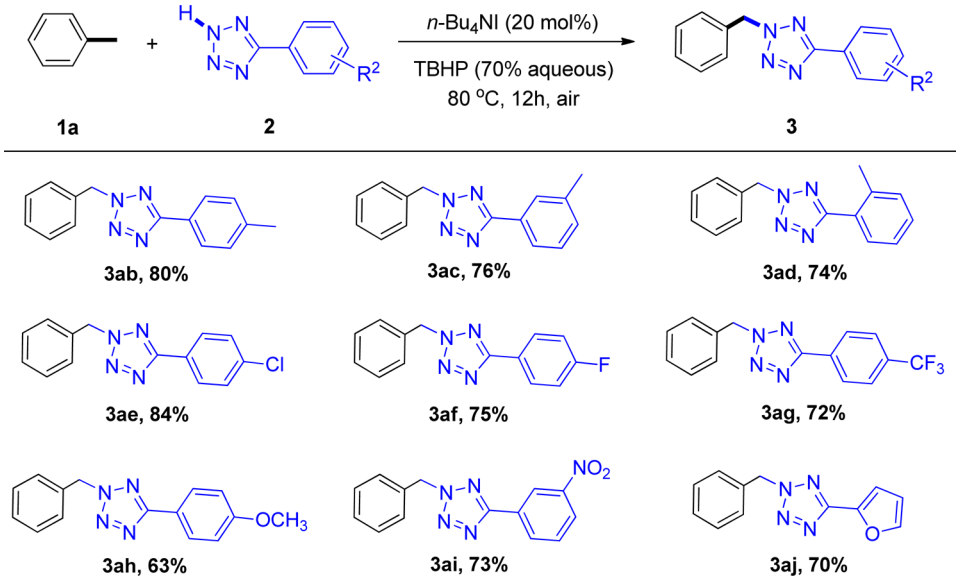
transformed to the corresponding products with high selectivities, giving only *mono*-amination products (**3ba**–**3ea**). Other *para*-substitued toluene substrates with functional groups including *t*-butyl, chloro, bromo, fluoro, methoxyl, and nitro were also tolerated under the conditions (**3fa**–**3la**). Compared with the *halo*-substituted toluene substrates, the starting materials **1j** and **1l** showed relatively lower activities. For substrate **1j**, a small amount of amination product on the methoxyl group was also detected. Moreover, the steric hindrance showed little influence on the reaction, and substrate **1k** underwent this coupling reaction to deliver the product **3ka** in good yield. Other benzylic C–H substrates such as ethylbenzene and diphenylmethane also proceeded smoothly to furnish the corresponding products in 85% and 77% yields, respectively.

As mentioned above, the amination reaction on the methoxyl group of substrate **1j** prompted us to extend this protocol to the alkyl ethers (Scheme 2). Under the optimized conditions, the selected alkyl ethers including dioxane, 1,2-dimethoxyethane, and tetrahydro-2*H*-pyran were found to react smoothly to generate the coupling products **5aa**–**5ca** with moderate to good yields. For the 1,2-dimethoxyethane, it was worth noting that the amination reaction took place mainly on the methylene group.

To further explore the scope of this protocol, a series of aryl tetrazoles were investigated, and the results are summarized in Table 3. To our delight, aryl tetrazoles with various substituents

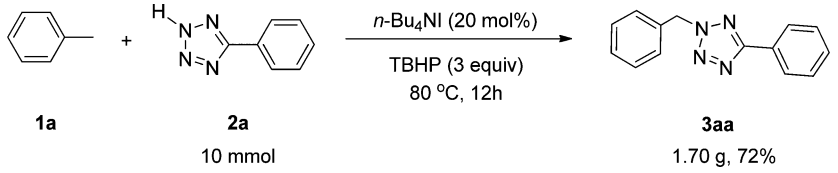
dx.doi.org/10.1021/jo502283h | J. Org. Chem. 2014, 79, 11780–11786

Table 3. Reaction Scope for Tetrazoles[a]



[a]Reaction conditions: toluene (9 mmol), **2** (0.3 mmol), TBAI (0.06 mmol, 20 mol %), TBHP (0.9 mmol, 3 equiv), 80 °C, 12 h, isolated yields.

Scheme 3. Gram-Scale Reaction

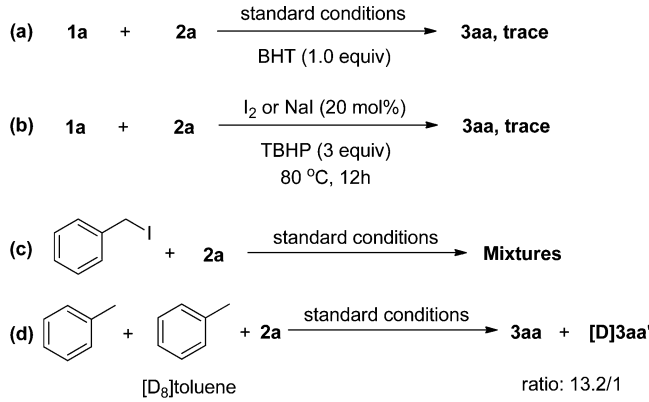


coupled with toluene smoothly to afford the desired products in good yields. Various functional groups, including methyl, methoxyl, chloro, fluoro, trifluoromethyl, and nitro, survived well under the reaction conditions. Negligible steric hindrance influence was observed for the tetrazole substrate (**3ad**, 74%). For the tetrazole substrate bearing methoxyl at the *para* position, however, a lower yield was obtained (**3ah**, 63%). To our delight, 5-(furan-2-yl)-2*H*-tetrazole worked well with toluene to give the desired product **3aj** in 70% yield.

Furthermore, a scale-up reaction was performed to demonstrate the practicability of the developed protocol (10 mmol scale). The amination reaction proceeded smoothly under the optimized conditions to provide the product **3aa** in 72% yield (Scheme 3).

To gain insight into the mechanism, several control experiments were performed (Scheme 4). Initially, when 1 equiv of radical inhibitor, BHT (2,6-di-*tert*-butyl-4-methylphenol), was added to the reaction mixture, only a trace amount of product **3aa** was observed (Scheme 4, (a)). This result indicated that a radical pathway may be involved in this reaction. Next, the role of TBAI was investigated. The color of the reaction mixture turned brown after addition of TBAI, suggesting the generation of iodine. However, replacement of TBAI with I_2 inhibited the reaction (Scheme 4, (b)). A trace amount of product **3aa** was obtained by switching the catalyst to NaI. Additionally, reaction of benzyl iodide and **2a** led to a mixture, which ruled out the possibility of nucleophilic substitution of **2a** to the benzyl iodide. Moreover, the kinetic isotopic effect (KIE) experiment was studied (Scheme 4, (d)). The result shows a significant kinetic isotope effect (k_H/k_D = 13.2), indicating that the C−H bond cleavage of toluene may be the rate-determining step (see the Supporting Information).

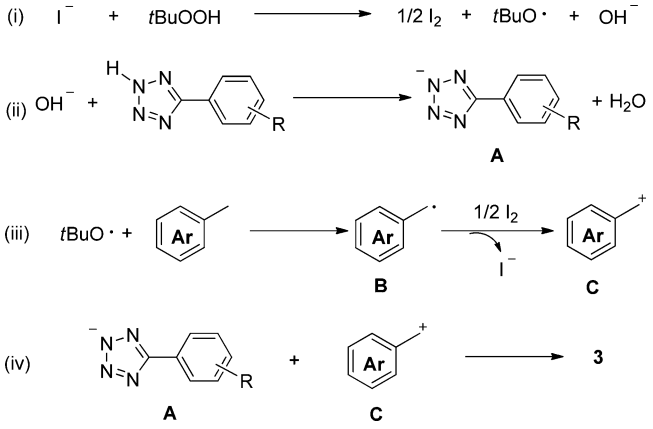
Scheme 4. Control Experiments



On the basis of the above experimental results and literature reports,[9c,10e] a plausible mechanism is proposed (Scheme 5). Initially, the oxidation of TBAI by TBHP gives the *tert*-butoxyl radical, iodine, and a hydroxyl anion (Scheme 5, step (i)). Then, the tetrazole is deprotonated by hydroxyl anion to provide anionic species **A** (Scheme 5, step (ii)). Meanwhile, homolysis of the benzyl C−H bond is induced by *tert*-butoxyl radical to give radical **B**, which is further oxidized by iodine to produce the benzyl cation **C** (Scheme 5, step (iii)). Finally, aryl tetrazole anion **A** reacted with benzyl cation **C** to form the product **3** (Scheme 5, step (iv)). Thus, the I_2/I^- redox system plays a vital role in this reaction.

dx.doi.org/10.1021/jo502283h | J. Org. Chem. 2014, 79, 11780−11786

Scheme 5. Plausible Mechanism



In conclusion, an *n*-Bu_4NI-catalyzed direct oxidative coupling of methylarenes with aryl tetrazoles has been developed. This protocol provides a simple and green approach for the preparation of tetrazole derivatives. Substrates with various functional groups proceeded smoothly to provide the corresponding products in moderate to good yields. Notably, alkyl ethers could also be employed as substrates in the present protocol.

EXPERIMENTAL SECTION

General Information. Chemicals were used as received without special purification unless stated otherwise. ^1H and ^{13}C NMR were recorded at ambient temperature on a 400 MHz NMR spectrometer. NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants J are given in Hz. Melting points (mp) are determined with a MPA 100 apparatus and are not corrected. High-resolution mass spectrometry (HRMS) was performed on a TOF MS instrument with an ESI source.

General Procedure for the Alkylation of Aryl Tetrazoles. In a sealed tube, *n*-Bu_4NI (22.1 mg, 0.06 mmol) was added to the mixture of methylarenes **1** or alkyl ethers (9 mmol), aryl tetrazole **2** (0.3 mmol), and *t*-BuOOH (70% aqueous, 0.9 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. After the reaction, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under vacuum, and the residue was purified by silica gel chromatography using a mixture of PE/EA to afford the desired product **3** and **5**.

*2-Benzyl-5-phenyl-2H-tetrazole (**3aa**).*[6] White solid (58.8 mg, 83%), mp 60−62 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.16 (m, 2H), 7.50−7.45 (m, 3H), 7.35−7.44 (m, 5H), 5.80 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.4, 133.3, 130.2, 129.0, 128.9, 128.7, 128.3, 127.3, 126.8, 56.7 ppm; HRMS (ESI): Calcd for $C_{14}H_{12}N_4Na$ $(M + Na)^+$ 259.0954, found 259.0960.

*2-(4-Methylbenzyl)-5-phenyl-2H-tetrazole (**3ba**).* White solid (57.7 mg, 77%), mp 91−93 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27−7.99 (m, 2H), 7.52−7.41 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 5.75 (s, 2H), 2.34 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 138.8, 130.2, 129.6, 128.7, 128.3, 127.3, 126.8, 56.5, 21.1 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1107.

*2-(3-Methylbenzyl)-5-phenyl-2H-tetrazole (**3ca**).* Light yellow solid (46.5 mg, 62%), mp 61−63 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, J = 7.4, 2.1 Hz, 2H), 7.65−7.49 (m, 3H), 7.46−7.12 (m, 4H), 5.87 (s, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 138.8, 133.2, 130.2, 129.6, 129.15,128.7, 127.4, 126.8, 125.4, 56.8, 21.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1104.

*2-(2-Methylbenzyl)-5-phenyl-2H-tetrazole (**3da**).* Light yellow solid (61.5 mg, 82%), mp 49−50 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30−8.09 (m, 2H), 7.59−7.46 (m, 3H), 7.39−7.25 (m, 4H), 5.87 (s, 2H), 2.54 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 136.9, 131.6, 130.8, 130.2, 129.7, 129.1, 128.8, 127.4, 126.8, 126.5, 54.7, 19.2 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1115.

*2-(3,5-Dimethylbenzyl)-5-phenyl-2H-tetrazole (**3ea**).* White solid (59.4 mg, 75%), mp 80−82 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21−8.10 (m, 2H), 7.55−7.38 (m, 3H), 7.03 (s, 2H), 6.99 (s, 1H), 5.72 (s, 2H), 2.31 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 138.6, 133.1, 130.5, 130.2, 128.8, 127.4, 126.8, 126.0, 56.7, 21.1 ppm; HRMS (ESI): Calcd for $C_{16}H_{16}N_4Na$ $(M + Na)^+$ 287.1267, found 287.1270.

*2-(4-(tert-Butyl)benzyl)-5-phenyl-2H-tetrazole (**3fa**).* White solid (61.3 mg, 70%), mp 122−124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25−8.03 (m, 2H), 7.51−7.43 (m, 3H), 7.39 (q, J = 8.5 Hz, 4H), 5.78 (s, 2H), 1.31 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 152.0, 130.4, 130.2, 128.8, 128.1, 127.4, 126.8, 125.9, 56.5, 34.6, 31.2 ppm; HRMS (ESI): Calcd for $C_{18}H_{20}N_4Na$ $(M + Na)^+$ 315.1580, found 315.1583.

*2-(4-Chlorobenzyl)-5-phenyl-2H-tetrazole (**3ga**).* Light yellow solid (67.4 mg, 83%), mp 69−70 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20−8.04 (m, 2H), 7.52−7.41 (m, 3H), 7.35 (s, 4H), 5.76 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 135.0, 131.7, 130.4, 129.8, 129.2, 128.8, 127.2, 126.8, 99.9, 56.0 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}ClN_4Na$ $(M + Na)^+$ 293.0564, found 293.0569.

*2-(4-Bromobenzyl)-5-phenyl-2H-tetrazole (**3ha**).* White solid (83.2 mg, 88%), mp 80−82 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20−8.07 (m, 2H), 7.53−7.43 (m, 5H), 7.29 (d, J = 8.4 Hz, 2H), 5.74 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 132.2, 132.1, 130.4, 130.0, 128.8, 127.1, 126.8, 123.2, 56.0 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}BrN_4Na$ $(M + Na)^+$ 337.0059, found 337.0051.

*2-(4-Fluorobenzyl)-5-phenyl-2H-tetrazole (**3ia**).* White solid (68.6 mg, 90%), mp 61−63 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.24−8.04 (m, 2H), 7.55−7.36 (m, 5H), 7.06 (t, J = 8.6 Hz, 2H), 5.76 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 163.0 (d, J_{C-F} = 247 Hz), 130.4 (d, J_{C-F} = 8.6 Hz), 129.1, 128.8, 127.2, 126.8, 116.1, 116.0 (d, J_{C-F} = 21.8 Hz), 56.0 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}FN_4Na$ $(M + Na)^+$ 277.0860, found 277.0869.

*2-(4-Methoxybenzyl)-5-phenyl-2H-tetrazole (**3ja**).* White solid (53.5 mg, 67%), mp 57−59 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 1.6 Hz, 2H), 7.51−7.40 (m, 3H), 7.38 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.73 (s, 2H), 3.78 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 160.0, 130.2, 129.9, 128.8, 127.4, 126.8, 125.4, 114.3, 56.3, 55.2 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4NaO$ $(M + Na)^+$ 289.1060, found 289.1067.

*2-(2-Chlorobenzyl)-5-phenyl-2H-tetrazole (**3ka**).* White solid (63.3 mg, 78%), mp 68−70 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20−8.11 (m, 2H), 7.51−7.41 (m, 4H), 7.32−7.24 (m, 2H), 7.18 (dd, J = 7.6, 1.5 Hz, 1H), 5.96 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 133.6, 131.2, 130.3, 130.2, 130.0, 129.8, 128.8, 127.3, 127.2, 126.9, 54.0 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}ClN_4Na$ $(M + Na)^+$ 293.0564, found 293.0573.

*2-(4-Nitrobenzyl)-5-phenyl-2H-tetrazole (**3la**).* White solid (54.8 mg, 65%), mp 122−124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 8.6 Hz, 2H), 8.13 (dd, J = 6.6, 2.9 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.52−7.43 (m, 3H), 5.92 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 148.4, 140.0, 130.6, 129.2, 128.9, 126.9, 124.3, 55.7 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}N_5NaO_2$ $(M + Na)^+$ 304.0805, found 304.0811.

*5-Phenyl-2-(1-phenylethyl)-2H-tetrazole (**3ma**).* Colorless oil (63.8 mg, 85%); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (dd, J = 7.5, 1.6 Hz, 2H), 7.52−7.28 (m, 8H), 6.12 (q, J = 7.1 Hz, 1H), 2.11 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 138.9, 130.1, 128.8, 128.7, 128.6, 127.5, 126.8, 126.6, 63.6, 21.1 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1119.

*2-Benzhydryl-5-phenyl-2H-tetrazole (**3na**).*[12] White solid (72.1 mg, 77%), mp 111−113 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (dd, J = 7.4, 2.2 Hz, 2H), 7.50−7.46 (m, 3H), 7.41−7.34 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 137.1, 130.3, 128.8, 128.7, 128.6, 128.3, 127.4, 126.9, 71.2 ppm; HRMS (ESI): Calcd for $C_{20}H_{16}N_4Na$ $(M + Na)^+$ 335.1267, found 335.1270.

dx.doi.org/10.1021/jo502283h | J. Org. Chem. 2014, 79, 11780−11786

*2-(1,4-Dioxan-2-yl)-5-phenyl-2H-tetrazole (**5aa**).* White solid (48.0 mg, 69%), mp 51−53 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24−8.11 (m, 2H), 7.48−7.47 (m, 3H), 6.09 (dd, J = 6.1, 2.9 Hz, 1H), 4.43 (dd, J = 12.0, 6.1 Hz, 1H), 4.16 (dd, J = 12.0, 2.9 Hz, 1H), 4.09 (dd, J = 9.8, 5.8 Hz, 1H), 3.98−3.92 (m, 1H), 3.90−3.85 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 165.2, 130.5, 128.8, 127.0, 126.9, 84.0, 67.1, 65.8, 64.9 ppm; HRMS (ESI): Calcd for $C_{11}H_{12}N_4NaO_2$ $(M + Na)^+$ 255.0852, found 255.0860.

*2-(1,2-Dimethoxyethyl)-5-phenyl-2H-tetrazole (**5ba**).* Colorless oil (35.8 mg, 51%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dd, J = 7.4, 2.3 Hz, 2H), 7.55−7.43 (m, 3H), 5.97 (t, J = 6.1 Hz, 1H), 4.05 (d, J = 6.1 Hz, 2H), 3.41 (s, 3H), 3.39 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 130.5, 128.8, 127.2, 127.0, 91.5, 72.1, 59.5, 57.4 ppm; HRMS (ESI): Calcd for $C_{11}H_{14}N_4NaO_2$ $(M + Na)^+$ 257.1009, found 257.1017.

*5-Phenyl-2-(tetrahydro-2H-pyran-2-yl)-2H-tetrazole (**5ca**).* Colorless oil (53.8 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26−8.12 (m, 2H), 7.47 (dd, J = 5.0, 2.4 Hz, 3H), 6.05 (dd, J = 7.7, 2.8 Hz, 1H), 4.01 (dd, J = 9.6, 5.3 Hz, 1H), 3.88−3.74 (m, 1H), 2.49 (dd, J = 16.7, 8.9 Hz, 1H), 2.18−2.14 (m, 2H), 1.77−1.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 130.3, 128.8, 127.2, 126.9, 87.7, 66.8, 29.0, 24.5, 20.7 ppm; HRMS (ESI): Calcd for $C_{12}H_{14}N_4NaO$ $(M + Na)^+$ 253.1060, found 253.1054.

*2-Benzyl-5-(p-tolyl)-2H-tetrazole (**3ab**).*[6] White solid (60.0 mg, 80%), mp 115−117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 8.1 Hz, 2H), 7.48−7.31 (m, 5H), 7.30−7.25 (m, 2H), 5.79 (s, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 140.4, 133.4, 129.5, 128.9, 128.8, 128.3, 126.8, 124.5, 56.7, 21.4 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1118.

*2-Benzyl-5-(m-tolyl)-2H-tetrazole (**3ac**).* White solid (57.0 mg, 76%), mp 116−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11−7.81 (m, 2H), 7.45−7.32 (m, 6H), 7.27 (d, J = 6.2 Hz, 1H), 5.80 (s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 138.6, 133.4, 131.1, 129.0, 128.9, 128.7, 128.3, 127.4, 127.2, 124.0, 56.7, 21.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1102.

*2-Benzyl-5-(o-tolyl)-2H-tetrazole (**3ad**).* White solid (55.5 mg, 74%), mp 113−115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01−7.91 (m, 2H), 7.39 (m, 6H), 7.27 (d, J = 6.2 Hz, 1H), 5.80 (s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5,138.5, 133.4, 131.0, 129.0, 128.8, 128.7, 128.3, 127.4, 127.2, 124.0, 56.7, 21.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4Na$ $(M + Na)^+$ 273.1111, found 273.1107.

*2-Benzyl-5-(4-chlorophenyl)-2H-tetrazole (**3ae**).* Yellow solid (68.2 mg, 84%), mp 119−121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.6 Hz, 2H), 7.53−7.27 (m, 7H), 5.79 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 136.3, 133.2, 129.2, 128.9, 128.4, 128.1, 125.8, 56.8 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}ClN_4Na$ $(M + Na)^+$ 293.0564, found 293.0570.

*2-Benzyl-5-(4-fluorophenyl)-2H-tetrazole (**3af**).* Yellow solid (57.2 mg, 75%), mp 77−79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18−8.07 (m, 2H), 7.46−7.32 (m, 5H), 7.19−7.08 (m, 2H), 5.79 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 164.2 (d, J_{C-F} = 188.0 Hz), 133.2, 129.0 (d, J_{C-F} = 4.2 Hz), 128.9, 128.8, 128.4, 119.4, 115.9 (d, J_{C-F} = 22.0 Hz), 56.8 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}FN_4Na$ $(M + Na)^+$ 277.0860, found 277.0871.

*2-Benzyl-5-(4-(trifluoromethyl)phenyl)-2H-tetrazole (**3ag**).*[6] White solid (65.7 mg, 72%), mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.43−7.38 (m, 5H), 5.82 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2, 133.1, 132.0 (q, J = 33.2 Hz), 131.8, 130.7, 129.0, 128.4, 127.1, 125.8 (q, J = 3.7 Hz), 123.8 (q, J = 270.8 Hz), 57.0 ppm; HRMS (ESI): Calcd for $C_{15}H_{11}F_3N_4Na$ $(M + Na)^+$ 327.0828, found 327.0821.

*2-Benzyl-5-(4-methoxyphenyl)-2H-tetrazole (**3ah**).*[6] White solid (50.3 mg, 63%), mp 121−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.9 Hz, 2H), 7.47−7.29 (m, 5H), 6.98 (d, J = 8.9 Hz, 2H), 5.78 (s, 2H), 3.85 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 161.2, 133.4, 129.0, 128.8, 128.3, 128.2, 119.9, 114.2, 56.6, 55.3 ppm; HRMS (ESI): Calcd for $C_{15}H_{14}N_4NaO$ $(M + Na)^+$ 289.1060, found 289.1048.

*2-Benzyl-5-(3-nitrophenyl)-2H-tetrazole (**3ai**).* Yellow solid (61.5 mg, 73%), mp 82−84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.46−7.38 (m, 5H), 5.82 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 148.8, 132.9, 132.5, 130.0, 129.1, 129.0, 128.5, 124.8, 121.8, 57.1 ppm; HRMS (ESI): Calcd for $C_{14}H_{11}N_5NaO_2$ $(M + Na)^+$ 304.0805, found 304.0813.

*2-Benzyl-5-(furan-2-yl)-2H-tetrazole (**3aj**).*[6] Pale red oil (47.5 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J = 1.8 Hz, 1H), 7.47−7.29 (m, 5H), 7.01 (d, J = 3.5 Hz, 1H), 6.70 (d, J = 3.5 Hz, 1H), 5.80 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8 (two coinciding carbon resonances), 144.3, 143.0, 133.1, 129.1, 128.4, 118.4, 111.5, 57.0 ppm; HRMS (ESI): Calcd for $C_{12}H_{10}N_4NaO$ $(M + Na)^+$ 249.0747, found 249.0752.

General Procedure for Gram-Scale Reaction of Toluene with 5-Phenyl-2*H*-tetrazole. *n*-Bu_4NI (736.7 mg, 0.2 mmol) was added to the mixture of toluene (30 mL), 5-phenyl-2*H*-tetrazole **2a** (10 mmol), and *t*-BuOOH (70% aqueous, 30 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 80 °C for 12 h. After the reaction, the reaction mixture was transferred to a round-bottom flask. The solvent was then removed under vacuum, and the residue was purified by silica gel chromatography using a mixture of PE/EA to afford the desired product **3aa** (1.70 g, 72%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all the compounds and kinetic isotope experiments are available in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lwcczu@126.com (L.W.).

*E-mail: hemingyangjpu@yahoo.com (M.H.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21302014), the Natural Science Foundation for Colleges and Universities of Jiangsu Province (13KJB150002), and the Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110).

■ REFERENCES

(1) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH Publishers: New York, 1989.

(2) (a) Fernandez-Bachiller, M. I.; Perez, C.; Monjas, L.; Rademann, J.; Rodríguez-Franco, M. I. *J. Med. Chem.* **2012**, *55*, 1303. (b) Das, S. G.; Srinivasan, B.; Hermanson, D. L.; Bleeker, N. P.; Doshi, J. M.; Tang, R.; Beck, W. T.; Xing, C. *J. Med. Chem.* **2011**, *54*, 5937.

(3) (a) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. *Coord. Chem. Rev.* **2011**, *255*, 485. (b) Singh, R. P.; Verma, R. D.; Meshri, D. T.; Shreeve, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3584. (c) Tao, G. H.; Guo, Y.; Joo, Y. H.; Twamley, B.; Shreeve, J. M. *J. Mater. Chem.* **2008**, *18*, 5524.

(4) Birnbaum, J.; Kahan, F. M.; Kropp, H. *Am. J. Med.* **1985**, *78*, 3.

(5) (a) Seki, M. *ACS Catal.* **2011**, *1*, 607. (b) Diers, E.; Kumar, N. Y. P.; Mejuch, T.; Marek, I.; Ackermann, L. *Tetrahedron* **2013**, *69*, 4445. (c) Wang, L.; Wu, W. T.; Chen, Q.; He, M. Y. *Org. Biomol. Chem.* **2014**, *12*, 7923.

(6) Aridoss, G.; Laali, K. K. *Eur. J. Org. Chem.* **2011**, 6343.

(7) For reviews on this topic, see: (a) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436. (c) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

(8) (a) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827. (b) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (c) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (d) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177. (e) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (f) Mai, W.; Wang, H.; Li, Z.; Yuan, J.; Xiao, Y.; Yang, L.; Mao, P.; Qu, L. *Chem. Commun.* **2012**, *48*, 10117. (g) Tan, B.; Toda, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12538. (h) Li, L.; Huang, J.; Li, H.; Wen, L.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 5187. (i) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979.

(9) (a) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (c) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085. (d) Huang, J.; Li, L.; Li, H.; Husan, E.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 10204. (e) Shi, E.; Chen, S.; Chen, S.; Hu, H.; Chen, S.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384. (f) Feng, J.; Liang, S.; Chen, S.; Zhang, J.; Fu, S.; Yu, X. *Adv. Synth. Catal.* **2012**, *354*, 1287.

(10) (a) Dian, L.; Wang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Chem. Commun.* **2014**, *50*, 11738. (b) Guo, S.; Yu, J.; Dai, Q.; Yang, H.; Cheng, J. *Chem. Commun.* **2014**, *50*, 6240. (c) Xue, Q.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 3700. (d) Ochiai, M.; Yamane, S.; Hoque, M. M.; Saito, M.; Miyamoto, K. *Chem. Commun.* **2012**, *48*, 5280. (e) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (f) He, L.; Yu, J.; Zhang, J.; Yu, X.-Q. *Org. Lett.* **2007**, *9*, 2277. (g) Bhuyan, R.; Nicholas, K. M. *Org. Lett.* **2007**, *9*, 3957. (h) Fructos, M. R.; Trofimenko, S.; Diaz-Requejo, M. M.; Perez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784. (i) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233.

(11) Ali, W.; Guin, S.; Rout, S. K.; Gogoi, A.; Patel, B. K. *Adv. Synth. Catal.* **2014**, *356*, 3099.

(12) Han, F.; Yang, L.; Li, Z.; Xia, C. *Adv. Synth. Catal.* **2012**, *354*, 1052.