JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

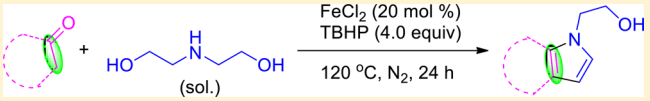
Iron-Mediated Annulation between Methylene Ketones and Diethanolamines: A Sustainable and Scalable Procedure toward *N*-(2-Hydroxyethyl) Pyrroles

Weiming Hu, Jin-Tao Yu, Dengman Ye, Zhou Zhou, Song Sun, and Jiang Cheng*

School of Petrochemical Engineering, Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Jiangsu Province Key Laboratory of Fine Petrochemical Engineering, Changzhou University, Changzhou 213164, PR China

Supporting Information

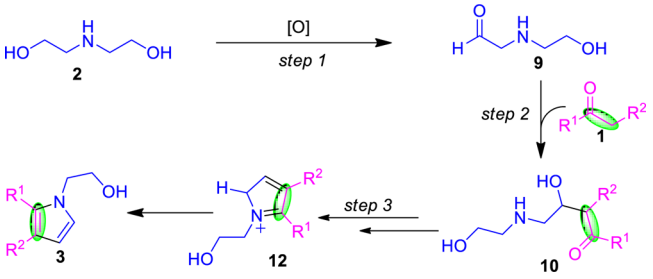
ABSTRACT: An iron-mediated direct annulation between methylene ketones and diethanolamines was developed for the efficient synthesis of *N*-(2-hydroxyethyl) pyrroles. This protocol shows high efficiency, operational simplicity, good functional group compatibility as well as broad substrates scope.



Pyrrole and its derivatives[1,2] are not only ubiquitous in natural products and pharmaceuticals,[3] but also important synthetic intermediates toward a series of functional materials, dyes, agrochemicals as well as flavors.[4] Among which, the *N*-(2-hydroxyethyl) analogues present significant properties in many fields. For example, they could serve as important monomers of conductive polypyrroles,[5] and key skeleton of medicines for treating hypertension,[6] as well as starting materials toward structurally diverse and biologically interesting *N*-bridgehead azepine skeletons by transforming the *N*-(2-hydroxyethyl) group to corresponding *N*-(2-alkoxyethyl)),[7] *N*-(2-haloethyl),[8] *N*-(2-aminoethyl),[9] *N*-(2-carboxymethyl).[10] Moreover, those compounds were widely employed in intramolecular cyclization.[11]

However, to date, there are few studies developed for the synthesis of *N*-(2-hydroxyethyl) pyrroles.[5a,e,12] Previously, we developed the copper-catalyzed annulation of 1,3-dicarbonyl compounds with diethylene glycol toward 2,3-disubstituted furans.[13] The formation of C−C bond between the methylene of 1,3-dicarbonyl compounds and the α'-carbon of diethylene glycol was believed to be the key step in the cyclization. Similarly, bearing two hydroxyl groups, diethanolamine is envisioned to take part in the cyclization process whereby the predicted C−C formation between the between the β-carbon of diethanolamine and methylene ketone (Scheme 1, step 2).

Scheme 1. Design of the Reaction Pathway



Subsequently, the reaction between carbonyl and amino in diethanolamine furnishes the ring closure (Scheme 1, step 3). The left hydroxyl keeps untouched, allowing the direct construction of *N*-(2-hydroxyethyl) pyrroles along with the releasing of H_2O as a clean byproduct via a sustainable approach (Scheme 1).

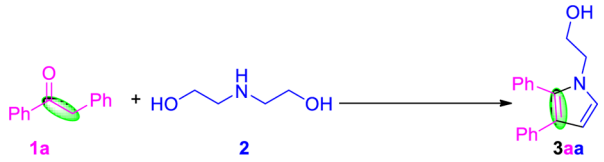
With this idea in mind, we initially selected the combination of 1,2-diphenylethanone **1a** (0.2 mmol, 1.0 equiv), diethanolamine **2a** (1 mL) and $FeCl_2$ (20 mol %) in the presence of di-*tert*-butyl peroxide (DTBP) (0.8 mmol, 4.0 equiv) as the model reaction. To our delight, the desired annulation product **3aa** was isolated in 46% yield at 120 °C for 24 h under N_2 (Table 1, entry 1). Other oxidants, such as benzoyl peroxide (BPO), dicumyl peroxide (DCP), *tert*-butyl peroxybenzoate (TBPB), benzoquinone (BQ) and $Na_2S_2O_8$ were tested (Table 1, entries 2−6). However, only benzoyl peroxide showed a positive effect, generating **3aa** in a comparable 49% yield (Table 1, entry 3). Gratifyingly, the yield increased to 89% by using *tert*-butyl hydroperoxide (TBHP, 70% aqueous) (Table 1, entry 7). Blank experiments indicated that no **3aa** was detected in the absence of any oxidant (Table 1, entry 8), while **3aa** was obtained in 32% yield even no catalyst was added, (Table 1, entry 9). No positive effect on the reaction efficiency was found by replacing $FeCl_2$ with $AgNO_3$, $Cu(BF_4)_2$, $CuCl_2$, CuI, Cu_2O, $FeCl_3$, $FeBr_3$, FeS, $Fe(acac)_2$, FeF_2, and $FeBr_2$, respectively (Table 1, entries 10−20). Varying either the atmosphere (air or O_2) or reaction temperature (80, 90, or 110 °C) all decreased the yield (Table 1, entry 21). Finally, the optimized conditions were established as follows: 1,2-diphenylethanone **1a** (0.2 mmol), $FeCl_2$ (0.2 equiv), TBHP (4.0 equiv) in diethanolamine **2a** (1 mL) at 120 °C for 24 h under N_2.

With the optimal reaction conditions in hand, the generality and limitation of this procedure were studied. First, a variety of diarylethanones were investigated (Figure 1). As expected, almost all substrates ran smoothly under the standard

Received: May 19, 2016
Published: September 7, 2016

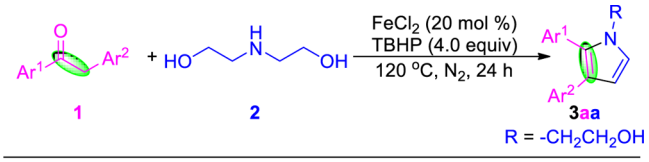
DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389−9395

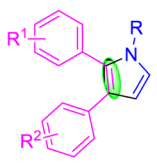
Table 1. Screening the Optimal Conditions[a]



entry	catalyst	oxidant[b]	yield[d] (%)
1	$FeCl_2$	DTBP	46
2	$FeCl_2$	DCP	35
3	$FeCl_2$	BPO	49
4	$FeCl_2$	TBPB	20
5	$FeCl_2$	$Na_2S_2O_8$	15
6	$FeCl_2$	BQ	<1
7	$FeCl_2$	TBHP	89
8	$FeCl_2$	–	<1
9	–	TBHP	32
10	$AgNO_3$	TBHP	41
11	$Cu(BF_4)_2$[c]	TBHP	66
12	$CuCl_2$	TBHP	43
13	CuI	TBHP	52
14	Cu_2O	TBHP	56
15	$FeCl_3$	TBHP	76
16	$FeBr_3$	TBHP	53
17	FeS	TBHP	57
18	$Fe(acac)_2$	TBHP	68
19	FeF_2	TBHP	60
20	$FeBr_2$	TBHP	71
21	$FeCl_2$	TBHP	52,[e] 63,[f] 72,[g] 78,[h] 85[i]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1 mL), oxidant (4.0 equiv) at 120 °C under N_2 for 24 h in a sealed tube. [b]TBPB = *tert*-butyl peroxybenzoate, BPO = benzoyl peroxide, DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide, BQ = 1,4-benzoquinone, TBHP = *tert*-butyl hydroperoxide (70% aqueous). [c]$Cu(BF_4)_2$ (45% in water). [d]Isolated yields. [e]Under O_2. [f]Under air. [g]80 °C. [h]90 °C. [i]110 °C.



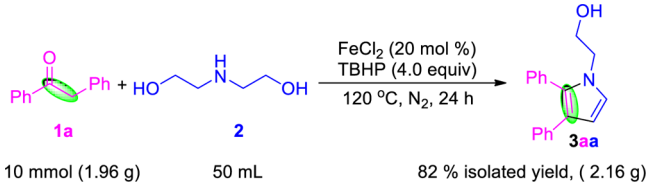


R^1 = H, R^2 = H, **3aa**, 89%, (82%)*;
R^1 = 3-Me, R^2 = H, **3ba**, 75%;
R^1 = 3,5-diMe, R^2 = H, **3ca**, 78%;
R^1 = 4-Me, R^2 = H, **3da**, 81%;
R^1 = 4-^{t}Bu, R^2 = H, **3ea**, 83%;
R^1 = 3-OMe, R^2 = H, **3fa**, 87%;
R^1 = 4-OMe, R^2 = H, **3ga**, 72%;
R^1 = H , R^2 = 4'-OMe, **3ha**, 78%;
R^1 = 4-CF_3, R^2 = H, **3ia**, 86%;
R^1 = H, R^2 = 4-CF_3, **3ja**, 81%;
R^1 = H, R^2 = 4-F, **3ka**, 83%;
R^1 = 4-Cl, R^2 = H, **3la**, 69%;
R^1 = H, R^2 = 4-Cl, **3ma**, 82%;
R^1 = 4-Br, R^2 = H, **3na**, 81%;
R^1 = H , R^2 = 4-Br, **3oa**, 85%;

Figure 1. Substrate Scope of Diarylethanones. Reaction conditions: **1a** (0.2 mmol), **2a** (1 mL), $FeCl_2$ (0.2 equiv), TBHP (4.0 equiv) at 120 °C under N_2 for 24 h in a sealed tube. Isolated yield. *10 mmol scale.

conditions, providing the desired annulated products in good to excellent yields (**3aa**–**3oa**, 69–89%). Electron-donating groups on the aryl rings such as methyl, methoxyl and *tert*-butyl (**3ba**–**3ha**, 72–87%) as well as electron-withdrawing groups like fluoro, chloro, bromo and trifluoromethyl (**3ia**–**3oa**, 69–86%) were all tolerated well. The practicality of this procedure was further improved by a 10 mmol scale reaction (82% of **3aa**, Scheme 2). The structure of **3na** was further confirmed by X-ray crystal structure analysis (for details, please see SI).[16]

Scheme 2. Gram-Scale Reaction of 1a



Apart from the diarylethanone substrates, indanones also worked well under the standard conditions, affording the corresponding fused cyclic products in moderate yields (Figure 2, **4aa**–**4ga**, 52–59%). Notably, halo groups survived well,

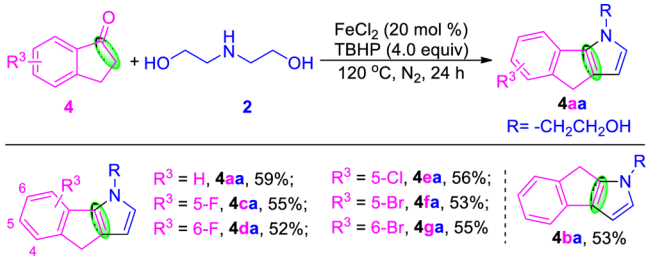


Figure 2. Substrate scope of indanones. Reaction conditions: **4a** (0.2 mmol), **2a** (1 mL), $FeCl_2$ (0.2 equiv), TBHP (4.0 equiv) at 120 °C under N_2 for 24 h in a sealed tube. Isolated yield.

which provided handles for further functionalizations (**4ca**–**4ga**, 43–56%). Moreover, other α-methylene ketones, such as aryl alkyl ketone, benzenepropanal, cycloalkyl ketone and 1,3-dicarbonyl compound were also good reaction partners, giving the corresponding pyrroles in moderate yields (Figure 3, **5aa**–**5ga**, 53–69%).

Meanwhile, functionalizations of *N*-hydroxyethyl group in **3aa** were carried out, affording corresponding derivatives **6**,[7] **7**[8] and **8**[14] in 81, 85 and 93% yields, respectively (Scheme 3 and see Supporting Information for details).

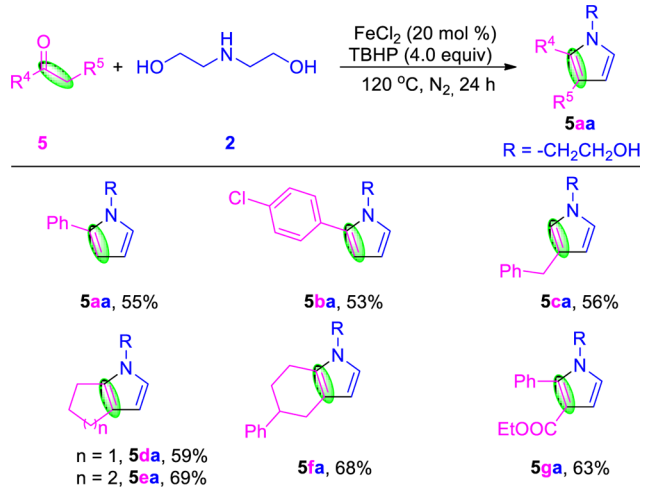
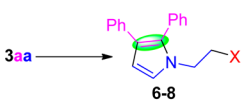


Figure 3. Substrate scope of other α-methylene ketones. Reaction conditions: **5a** (0.2 mmol), **2a** (1 mL), $FeCl_2$ (0.2 equiv), TBHP (4.0 equiv) at 120 °C under N_2 for 24 h in a sealed tube. Isolated yield.

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389–9395

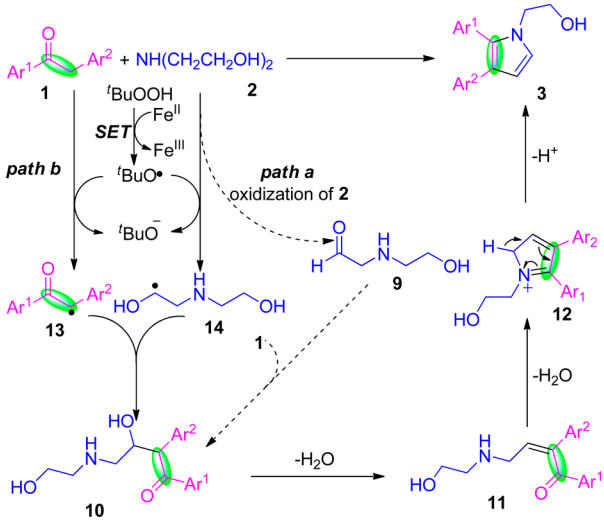
Scheme 3. Functionalizations of *N*-Hydroxyethyl Group in 3aa



Product	X =	Reaction Condition	Yield (%)
6	OMe	MeI, NaH, THF	81
7	Cl	Cl_3CCONH_2, PPh_3	85
8	OTs	*p*-TsCl, DMAP, Et_3N	93

To gain some insights into the mechanism, control experiments were conducted. The annulation reaction was totally shut down when the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl, 4.0 equiv) was added, indicating the involvement of radical intermediates. In the pathway predicated in Scheme 1, the presumed intermediate **9** is produced via the oxidization of **2**. Unfortunately, we failed to prepare **9** to confirm it (Scheme 4, path *a*), which was at least

Scheme 4. Plausible Reaction Pathway



partly due to its instability. Although intermediate **9** was not detected in the whole procedure (for detailed information, please see SI). At the current stage, path *a* could not be totally ruled out and radical may be involved in the oxidation of **2** to **9** (Scheme 4). Alternatively, in path *b* (Scheme 4), the cleavage of *tert*-butoxyl assisted by Fe(II) produced *tert*-butoxyl radical via SET, which abstracted α-hydrogen of **1** and **2** to form radical specie **13** and **14**, respectively. Subsequently, intermediate **10** was formed by the coupling between **13** and **14**.[15] Then the dehydration of **10** produced intermediate **11**. Finally, the cyclization of intermediate **12** by the formation of iminium C=N bond followed by the loss of one proton delivered *N*-(2-hydroxyethyl) pyrrole.

In summary, a direct and efficient procedure leading to *N*-hydroxyethyl pyrroles has been developed via iron-mediated annulation between methylene ketones and diethanolamines. On the account of its efficiency, operational simplicity, good functional group tolerance and high yield on gram scale, this procedure might potentially offer a practical route toward *N*-(2-hydroxyethyl) pyrroles.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. ^{1}H NMR, ^{13}C NMR and ^{19}F spectra were recorded at ambient temperature on a 400 (100 MHz for ^{13}C, 282 MHz for ^{19}F) or 300 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. IR spectra were recorded on a spectrometer using KBr discs. Column chromatography was performed using silica gel (300–400 mesh). High-resolution mass spectra (HRMS) were obtained using a micro TOF focus spectrometer. All melting points were uncorrected.

Experimental Procedure. *Annulation between α-Methylene Ketone and Diethanolamine.* Under N_2, a 20 mL of Schlenk tube equipped with a stir bar was charged with α-methylene ketone (0.2 mmol), *tert*-butyl hydroperoxide (0.8 mmol, 4.0 equiv, 70% aqueous), $FeCl_2$ (5.1 mg, 20 mol %), diethanolamine (1.0 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 120 °C for 24 h in oil bath. After the completion of the reaction, 6 mL of saturated brines was added, and extracted with ethyl acetate (8 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, v_1/v_2 = 3:1, R_f = 0.3) to give the desired products.

*Experiment on 10 mmol Scale of **3a**.* Under N_2, a 250 mL of Schlenk tube equipped with a stir bar was charged with 2-phenylacetophenone (10 mmol, 1.96 g), *tert*-butyl hydroperoxide (40 mmol, 5.4 mL), $FeCl_2$ (2 mmol, 255 mg), diethanolamine (50 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 120 °C for 24 h in oil bath. After the completion of the reaction, 80 mL of saturated brines was added and extracted with ethyl acetate (80 mL × 3) with. The combined organic extracts were dried over anhydrous Na_2SO_4. Subsequently, the solvent was filtered and concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, v_1/v_2 = 3:1, R_f = 0.3) to give the desired product **3aa** as a colorless oil (82%, 2.16 g).

*Functionalizations of N-hydroxyethyl Group in **3aa**. Preparation of 1-(2-Methoxyethyl)-2,3-diphenyl-1H-pyrrole (**6**).*[7] To a solution of **3aa** (53 mg, 0.2 mol) in THF (0.5 mL), NaH (60%-oil, 16 mg, 0.4 mmol) was added and stirred at rt for 2 h. MeI (50 mg, 0.35 mmol) in THF (0.2 mL) was added to the mixture and stirred at rt for 4 h. After the completion of the reaction, the solvent was removed. Then brine was added to the mixture and extracted with EtOAc. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc to give 1-(2-methoxyethyl)-2,3-diphenyl-1*H*-pyrrole as a colorless oil (81% yield, 44.9 mg).

*Preparation of 1-(2-Chloroethyl)-2,3-diphenyl-1H-pyrrole (**7**).*[8] To a stirred solution of **3aa** (66 mg, 0.25 mmol) and PPh_3 (0.5 mmol) in dry CH_2Cl_2 (0.5 mL), Cl_3CCONH_2 (0.5 mmol) was added (0.5 mmol) at rt under N_2. After 15 min, the reaction was quenched with cold water and extracted with EtOAc. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc to give 1-(2-chloroethyl)-2,3-diphenyl-1*H*-pyrrole hypochlorite as a white solid (85% yield, 50.5 mg).

*Preparation of 2-(2,3-Diphenyl-1H-pyrrol-1-yl)ethyl 4-methylbenzenesulfonate (**8**).*[14] A flame-dried Schlenk flask was charged with **3aa** (131.5 mg, 0.5 mmol) in CH_2Cl_2 (0.7 M) and cooled to 0 °C. Subsequently, *p*-TsCl (1.2 equiv), Et_3N (1.2 equiv), and DMAP (10 mol %) were added. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 12 h. Then the reaction was quenched by saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers are dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate) provides 2-(2,3-diphenyl-1*H*-pyrrol-1-yl)ethyl 4-methylbenzenesulfonate as a white solid (194 mg, 93%).

*2-(2,3-Diphenyl-1H-pyrrol-1-yl)ethanol (**3aa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.30) gives **3aa** (46.8 mg, 89% yield) as a colorless oil: ^{1}H NMR

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389–9395

($CDCl_3$, 400 MHz) δ 7.40−7.36 (m, 3H), 7.32−7.29 (m, 2H), 7.17−7.16 (m, 4H), 7.11−7.06 (m, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 3.97 (t, J = 5.5 Hz, 2 H), 3.68 (t, J = 5.5 Hz, 2 H), 1.67 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3, 132.7, 131.2, 130.4, 128.6, 128.0, 127.8, 127.6, 125.1, 123.1, 121.4, 108.3, 62.5, 49.1; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO$ $(M + H)^+$ 264.1383, found 264.1377; IR (KBr) 3358, 3057, 2922, 2851, 1659, 1631, 1600, 1547, 1504, 1470, 1440, 1421, 1343, 1262, 1069, 1207 cm^{-1}.

*2-(3-Phenyl-2-(m-tolyl)-1H-pyrrol-1-yl)ethanol (**3ba**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3ba** (41.6 mg, 75% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.26 (m, 1H), 7.20−7.09 (m, 8H), 6.87 (d, J = 2.7 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.67 (s, 2H), 2.36 (s, 3H), 1.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 136.3, 132.6, 131.7, 130.5, 128.6, 128.5, 128.3, 128.0, 127.4, 124.9, 122.9, 121.3, 108.0, 62.5, 49.1, 21.4; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO$ $(M + H)^+$ 278.1539, found 278.1535; IR (KBr) 3404, 3051, 2942, 1674, 1601, 1504, 1470, 1344, 1278, 1220, 1054 cm^{-1}.

*2-(2-(3,5-Dimethylphenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3ca**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3ca** (45.4 mg, 78% yield) as a yellowish solid: mp 87−88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.16 (m, 4H), 7.11−7.07 (m, 1H), 7.02 (s, 1 H), 6.94 (s, 2H), 6.85 (d, J = 2.5 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.67 (s, 2H), 2.32 (s, 6H), 1.75 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0, 136.4, 132.5, 130.6, 129.5, 128.9, 128.0, 127.3, 124.9, 122.6, 121.2, 107.9, 62.6, 49.1, 21.3; HRMS (ESI) m/z calcd for $C_{20}H_{22}NO$ $(M + H)^+$ 292.1696, found 292.1695; IR (KBr) 3404, 3029, 2922, 2731, 1675, 1600, 1504, 1441, 1343, 1235, 1070 cm^{-1}.

*2-(3-Phenyl-2-(p-tolyl)-1H-pyrrol-1-yl)ethanol (**3da**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3da** (44.9 mg, 81% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21−7.19 (m, 8H), 7.13−7.09 (m, 1H), 6.87 (d, J = 2.7 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.67 (d, J = 4.7 Hz, 2H), 2.42 (s, 3H), 1.84 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 136.4, 131.0, 130.4, 129.6, 129.4, 128.0, 127.5, 124.9, 122.9, 121.3, 108.1, 62.5, 49.0, 21.3; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO$ $(M + H)^+$ 278.1539, found 278.1540; IR (KBr) 3397, 3052, 2924, 1675, 1601, 1513, 1500, 1447, 1344, 1278, 1206, 1058 cm^{-1}.

*2-(2-(4-(tert-Butyl)phenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3ea**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.30) gives **3ea** (53.0 mg, 83% yield) as a brown solid: mp 97−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 8.2 Hz, 2H), 7.25−7.18 (m, 6H), 7.12−7.09 (m, 1 H), 6.87 (d, J = 2.7 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.69 (s, 2H), 1.82 (s, 1 H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 136.4, 130.8, 130.5, 129.5, 128.0, 127.5, 125.5, 124.9, 122.9, 121.2, 108.1, 62.6, 49.0, 34.6, 31.3; HRMS (ESI) m/z calcd for $C_{22}H_{26}NO$ $(M + H)^+$ 320.2009, found 320.2010; IR (KBr) 3396, 3054, 2961, 2868, 1678, 1601, 1513, 1499, 1398, 1362, 1268, 1207, 1110, 1069 cm^{-1}.

*2-(2-(3-Methoxyphenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3fa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.25) gives **3fa** (51.0 mg, 87% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (t, J = 7.9 Hz, 1H), 7.24−7.19 (m, 4H), 7.13−7.10 (m, 1 H), 6.95−6.88 (m, 4H), 6.49 (d, J = 2.6 Hz, 1H), 3.98 (t, J = 5.5 Hz, 3H), 3.78 (s, 3H), 3.67 (t, J = 5.2 Hz, 2H), 2.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 136.1, 133.9, 130.0, 129.5, 127.9, 127.4, 125.0, 123.5, 122.9, 121.4, 116.5, 113.4, 108.0, 62.4, 55.1, 49.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1489, found 294.1490; IR (KBr) 3416, 3056, 3000, 2935, 2834, 2360, 1678, 1601, 1577, 1501, 1463, 1344, 1285, 1229, 1166, 1038 cm^{-1}.

*2-(2-(4-Methoxyphenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3ga**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.25) gives **3ga** (42.2 mg, 72% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 4.3 Hz, 4H), 7.09−7.05 (m, 1H), 6.92 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 2.7 Hz, 1H), 6.46 (d, J = 2.7 Hz, 1H), 3.95 (t, J = 5.4 Hz, 2 H), 3.84 (s, 3H), 3.69 (t, J = 5.3 Hz, 2 H), 1.64 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 136.4, 132.4, 130.2, 128.0, 127.5, 124.9, 124.8, 122.9, 121.1, 114.1, 108.1, 62.6, 55.2, 49.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1489, found 294.1489; IR (KBr) 3396, 3065, 2963, 2853, 2042, 1677, 1609, 1513, 1463, 1286, 1247, 1174, 1029 cm^{-1}.

*2-(3-(4-Methoxyphenyl)-2-phenyl-1H-pyrrol-1-yl)ethanol (**3ha**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.25) gives **3ha** (45.7 mg, 78% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.30 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 2.4 Hz, 1H),6.75−6.71 (m, 2H) 6.43 (d, J = 2.4 Hz, 1H), 3.95 (t, J = 5.4 Hz, 2 H), 3.76 (s, 3H), 3.65 (t, J = 5.3 Hz, 2 H), 1.91 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.2, 132.7, 131.2, 129.7, 128.9, 128.58, 128.56, 127.6, 122.7, 121.3, 113.5, 108.0, 62.5, 55.1, 49.1; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1489, found 294.1489; IR (KBr) 3423, 3057, 2954, 2923, 2852, 2040, 1603, 1509, 1459, 1348, 1260, 1175, 1027 cm^{-1}.

*2-(3-Phenyl-2-(4-(trifluoromethyl)phenyl)-1H-pyrrol-1-yl)ethanol (**3ia**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3ia** (56.9 mg, 86% yield) as a yellowish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.23−7.12 (m, 5H), 6.92 (d, J = 2.8 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 3.98 (t, J = 5.4 Hz, 2 H), 3.70 (t, J = 5.2 Hz, 2 H), 1.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.36, 136.35, 135.8, 131.5, 129.5 (q, J_{C-F} = 32 Hz), 129.0 (q, J_{C-F} = 1.5 Hz), 128.2, 127.9, 125.5 (q, J_{C-F} = 3.8 Hz), 124.2, 124.1 (q, J_{C-F} = 270 Hz), 122.2, 108.9, 62.4, 49.1 ; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.4; HRMS (ESI) m/z calcd for $C_{19}H_{17}F_3NO$ $(M + H)^+$ 332.1257, found 332.1256; IR (KBr) 3385, 3058, 2928, 2292, 1682, 1616, 1602, 1498, 1405, 1324, 1166, 1119, 1019 cm^{-1}.

*2-(2-Phenyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrol-1-yl)ethanol (**3ja**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3ja** (53.6 mg, 81% yield) as a yellowish solid: mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.40 (m, 5H), 7.31−7.29 (m, 2H), 7.24 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 2.9 Hz, 1H), 6.50 (d, J = 2.9 Hz, 1H), 3.96 (t, J = 5.5 Hz, 2 H), 3.68 (t, J = 4.9 Hz, 2 H), 1.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0, 132.2, 131.1, 129.0 (q, J_{C-F} = 2 Hz), 128.9, 128.2, 127.3, 126.7 (q, J_{C-F} = 32 Hz), 125.0 (q, J_{C-F} = 3.8 Hz), 124.5 (q, J_{C-F} = 270 Hz), 121.8, 121.7, 108.1, 62.4, 49.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.1; HRMS (ESI) m/z calcd for $C_{19}H_{17}F_3NO$ $(M + H)^+$ 332.1257, found 332.1257; IR (KBr) 3374, 3060, 2936, 2881, 2644, 1682, 1615, 1518, 1478, 1406, 1324, 1282, 1163, 1015 cm^{-1}.

*2-(3-(4-Fluorophenyl)-2-phenyl-1H-pyrrol-1-yl)ethanol (**3ka**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.30) gives **3ka** (46.6 mg, 83% yield) as a yellowish solid: mp 91−92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.28 (m, 5H), 7.09 (t, J = 6.9 Hz, 2H), 6.88−6.84 (m, 3H), 6.42 (d, J = 2.4 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.67 (s, 2H), 1.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.8 (d, J_{C-F} = 242.0 Hz), 132.4, 132.3 (d, J_{C-F} = 4.0 Hz), 131.2, 130.2, 128.9 (d, J_{C-F} = 7.0 Hz), 128.7, 127.8, 122.2, 121.5, 114.8 (d, J_{C-F} = 21.0 Hz), 108.1, 62.5, 49.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −118.2; HRMS (ESI) m/z calcd for $C_{18}H_{17}FNO$ $(M + H)^+$ 282.1289, found 282.1288; IR (KBr) 3346, 3062, 2922, 1556, 1509, 1474, 1440, 1342, 1275, 1213, 1158, 1067 cm^{-1}.

*2-(2-(4-Chlorophenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3la**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3la** (41.0 mg, 69% yield) as a brownish solid: mp 105−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 8.2 Hz, 2H), 7.28−7.13 (m, 7H), 6.91 (d, J = 2.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H), 3.98 (t, J = 5.3 Hz, 2H), 3.71 (s, 2H), 1.83 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.0, 133.7, 132.5, 131.1, 129.0, 128.9, 128.1, 127.7, 125.3, 123.6, 121.7, 108.5, 62.4, 49.0; HRMS (ESI) m/z calcd for $C_{18}H_{17}ClNO$ $(M + H)^+$ 298.0993, found 298.0992; IR (KBr) 3404, 3056, 2926, 1676, 1601, 1501, 1471, 1394, 1343, 1277, 1206, 1091, 1013 cm^{-1}.

*2-(3-(4-Chlorophenyl)-2-phenyl-1H-pyrrol-1-yl)ethanol (**3ma**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3ma** (48.7 mg, 82% yield) as a brownish

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389−9395

solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.36 (m, 3H), 7.29−7.27 (m, 2H), 7.13−7.05 (m, 4 H), 6.87 (d, J = 2.7 Hz, 1H), 6.43 (t, J = 2.7 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.67 (t, J = 5.1 Hz, 2H), 1.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.8, 132.4, 131.1, 130.7, 130.5, 128.8, 128.7, 128.1, 128.0, 122.0, 121.6, 108.1, 62.5, 49.1; HRMS (ESI) m/z calcd for $C_{18}H_{17}ClNO$ (M + H)$^+$ 298.0993, found 298.0995; IR (KBr) 3386, 3057, 2927, 1678, 1595, 1546, 1499, 1442, 1342, 1265, 1206, 1090, 1012 cm^{-1}.

*2-(2-(4-Bromophenyl)-3-phenyl-1H-pyrrol-1-yl)ethanol (**3na**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3na** (55.2 mg, 81% yield) as a white solid: mp 120−121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, J = 8.2 Hz, 2H), 7.21−7.13 (m, 7H), 6.88 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 3.95 (t, J = 5.3 Hz, 2H), 3.68 (s, 2H), 1.84 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.0, 132.8, 131.8, 131.5, 129.0, 128.1, 127.7, 125.3, 123.6, 122.0, 121.8, 108.5, 62.4, 49.0; HRMS (ESI) m/z calcd for $C_{18}H_{17}BrNO$ (M + H)$^+$ 342.0488, found 342.0486; IR (KBr) 3404, 3057, 2933, 2878, 1671, 1601, 1545, 1503, 1492, 1422, 1390, 1343, 1276, 1070, 1007 cm^{-1}.

*2-(3-(4-Bromophenyl)-2-phenyl-1H-pyrrol-1-yl)ethanol (**3oa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **3oa** (58.0 mg, 85% yield) as a white solid: mp 126−127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 5.4 Hz, 3H), 7.30−7.28 (m, 4H), 7.02 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.6 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 3.97 (t, J = 5.4 Hz, 2 H), 3.69 (d, J = 4.6 Hz, 2 H), 1.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.3, 132.3, 131.10, 131.06, 130.5, 129.1, 128.7, 128.0, 121.9, 121.6, 118.8, 107.9, 62.4, 49.1; HRMS (ESI) m/z calcd for $C_{18}H_{17}BrNO$ (M + H)$^+$ 342.0488, found 342.0488; IR (KBr) 3393, 3057, 2925, 1676, 1591, 1496, 1441, 1341, 1264, 1205, 1070, 1008 cm^{-1}.

*2-(Indeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4aa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4aa** (23.5 mg, 59% yield) as a black solid: mp 57−58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.4 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 2.1 Hz, 1H), 6.22 (d, J = 1.9 Hz, 1H), 4.30 (t, J = 5.2 Hz, 2H), 3.96 (s, 2H), 3.51 (s, 2H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.1, 137.7, 135.4, 129.6, 126.3, 125.6, 125.4, 123.0, 116.0, 104.1, 62.6, 50.6, 30.7; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO$ (M + H)$^+$ 200.1070, found 200.1066; IR (KBr) 3386, 3053, 2925, 1674, 1605, 1522, 1465, 1420, 1358, 1290, 1224, 1053, 1026 cm^{-1}.

*2-(Indeno[2,1-b]pyrrol-1(8H)-yl)ethanol (**4ba**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4ba** (21.1 mg, 53% yield) as a brown solid: mp 89−90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (t, J = 8.9 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.04 (t, J = 5.2 Hz, 2H), 3.89 (s, 2H), 3.56 (s, 2H), 1.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 140.11, 140.07, 128.6, 126.7, 124.8, 124.2, 122.5, 118.2, 100.7, 62.3, 50.7, 30.0; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO$ (M + H)$^+$ 200.1070, found 200.1065; IR (KBr) 3405, 3098, 3047, 2925, 2360, 1670, 1607, 1507, 1448, 1420, 1401, 1361, 1281, 1224, 1062 cm^{-1}.

*2-(6-Fluoroindeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4ca**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4ca** (23.9 mg, 55% yield) as a brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.24 (m, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.97 (t, J = 8.8 Hz, 1H), 6.73 (s, 1H), 6.21 (s, 1H), 4.27 (t, J = 5.1 Hz, 2H), 3.96 (t, J = 5.0 Hz, 2H), 3.49 (s, 2H), 1.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9 (d, J_{C-F} = 240.0 Hz), 149.4 (d, J_{C-F} = 8.0 Hz), 137.0, 131.6 (d, J_{C-F} = 3.0 Hz), 129.1 (d, J_{C-F} = 3.0 Hz), 125.2, 116.1 (d, J_{C-F} = 9.0 Hz), 113.4 (d, J_{C-F} = 23.0 Hz), 112.7 (d, J_{C-F} = 22.0 Hz), 104.2, 62.7, 50.5, 30.8 (d, J_{C-F} = 2.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −120.3; HRMS (ESI) m/z calcd for $C_{13}H_{13}FNO$ (M + H)$^+$ 218.0976, found 218.0973; IR (KBr) 3393, 3056, 3042, 2925, 2360, 1677, 1590, 1523, 1460, 1359, 1271, 1236, 1207, 1062 cm^{-1}.

*2-(7-Fluoroindeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4da**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4da** (22.6 mg, 52% yield) as a brown solid: mp 85−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (t, J = 6.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 6.79−6.75 (m, 2H), 6.19 (s, 1H), 4.23 (t, J = 5.1 Hz, 2H), 3.92 (t, J = 4.8 Hz, 2H), 3.43 (s, 2H), 1.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2 (d, J_{C-F} = 240.0 Hz), 142.2 (d, J_{C-F} = 2.0 Hz), 136.9 (d, J_{C-F} = 3.0 Hz), 136.7 (d, J_{C-F} = 10.0 Hz), 131.5, 126.2, 125.8 (d, J_{C-F} = 9.0 Hz), 109.0 (d, J_{C-F} = 23.0 Hz), 104.2, 103.6 (d, J_{C-F} = 25.0 Hz), 62.6, 50.5, 30.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −116.8; HRMS (ESI) m/z calcd for $C_{13}H_{13}FNO$ (M + H)$^+$ 218.0976, found 218.0972; IR (KBr) 3340, 3071, 2927, 1678, 1614, 1593, 1519, 1470, 1451, 1423, 1358, 1323, 1269, 1222, 1174, 1068 cm^{-1}.

*2-(6-Chloroindeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4ea**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4ea** (26.1 mg, 56% yield) as a brown solid: mp 66−67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (s, 1H), 7.25−7.20 (m, 2H), 6.74 (d, J = 2.3 Hz, 1H), 6.19 (d, J = 2.1 Hz, 1H), 4.25 (t, J = 5.2 Hz, 2H), 3.93 (t, J = 5.2 Hz, 2H), 3.46 (s, 2H), 1.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.9, 136.9, 133.9, 129.8, 128.5, 126.3, 125.9, 125.8, 116.5, 104.3, 62.6, 50.5, 30.6; HRMS (ESI) m/z calcd for $C_{13}H_{13}ClNO$ (M + H)$^+$ 234.0680, found 234.0676; IR (KBr) 3404, 3078, 3052, 2925, 1678, 1602, 1571, 1571, 1522, 1451, 1425, 1269, 1163, 1069 cm^{-1}.

*2-(6-Bromoindeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4fa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4fa** (29.4 mg, 53% yield) as a greenish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.19 (d, J = 2.1 Hz, 1H), 4.25 (t, J = 5.2 Hz, 2H), 3.94 (s, 2H), 3.46 (s, 2H), 1.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.2, 137.2, 134.3, 129.8, 129.2, 128.6, 126.1, 116.9, 116.4, 104.3, 62.7, 50.6, 30.6; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrNO$ (M + H)$^+$ 278.0175, found 278.0170; IR (KBr) 3393, 3099, 3059, 2925, 1678, 1600, 1567, 1522, 1448, 1424, 1270, 1160, 1059 cm^{-1}.

*2-(7-Bromoindeno[1,2-b]pyrrol-1(4H)-yl)ethanol (**4ga**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **4ga** (30.5 mg, 55% yield) as a greenish solid: mp 98−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1H), 7.29−7.19 (m, 2H), 6.78 (d, J = 1.8 Hz, 1H), 6.21 (d, J = 1.6 Hz, 1H), 4.26 (t, J = 5.2 Hz, 2H), 3.95 (s, 2H), 3.43 (s, 2H), 1.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.8, 137.2, 136.4, 130.9, 126.5, 126.4, 125.5, 120.3, 119.0, 104.2, 62.6, 50.5, 30.4; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrNO$ (M + H)$^+$ 278.0175, found 278.0171; IR (KBr) 3335, 3254, 3096, 2926, 2868, 1685, 1598, 1566, 1526, 1452, 1439, 1359, 1338, 1265, 1163, 1062 cm^{-1}.

*2-(2-Phenyl-1H-pyrrol-1-yl)ethanol (**5aa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5aa** (20.6 mg, 55% yield) as a reddish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 4.3 Hz, 4H), 7.36−7.30 (m, 1H), 6.85 (s, 1H), 6.25−6.23 (m, 2H), 4.10 (t, J = 5.4 Hz, 2H), 3.73 (t, J = 5.4 Hz, 2H),1.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 134.6, 133.2, 129.1, 128.4, 127.0, 122.3, 109.3, 108.2, 62.6, 49.1; HRMS (ESI) m/z calcd for $C_{12}H_{14}NO$ (M + H)$^+$ 188.1070, found 188.1067; IR (KBr) 3385, 3100, 3058, 2926, 2854, 1678, 1602, 1541, 1493, 1471, 1377, 1307, 1239, 1057 cm^{-1}.

*2-(2-(4-Chlorophenyl)-1H-pyrrol-1-yl)ethanol (**5ba**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5ba** (23.4 mg, 53% yield) as a reddish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.33 (m, 4H), 6.85 (s, 1H), 6.24 (d, J = 2.6 Hz, 1H), 6.21 (d, J = 1.4 Hz, 1H), 4.06 (t, J = 5.3 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 1.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 133.4, 133.0, 131.6, 130.3, 128.6, 122.7, 109.6, 108.4, 62.5, 49.0; HRMS (ESI) m/z calcd for $C_{12}H_{13}ClNO$ (M + H)$^+$ 222.0680, found 222.0675; IR (KBr) 3404, 3101, 2926, 1905, 1685, 1596, 1541, 1491, 1467, 1421, 1308, 1239, 1092, 1057 cm^{-1}.

*2-(3-Benzyl-1H-pyrrol-1-yl)ethanol (**5ca**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5ca** (22.5 mg, 56% yield) as a reddish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.21 (m, 5H), 6.64 (s, 1H), 6.46 (s, 1H), 6.05 (s, 1H), 3.94 (t, J = 4.9 Hz, 2H), 3.85−3.81 (m, 4H), S 1.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 142.2, 128.6, 128.2, 125.7, 123.8, 121.0, 118.8, 109.0, 62.8, 51.9, 33.5; HRMS (ESI) m/z calcd for $C_{13}H_{16}NO$ (M + H)$^+$ 202.1226, found 202.1225; IR (KBr) 3400, 3083, 3060, 3025, 2924, 2853, 1705, 1666, 1602, 1495, 1453, 1359, 1159, 1071 cm^{-1}.

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389−9395

*2-(5,6-Dihydrocyclopenta[b]pyrrol-1(4H)-yl)ethanol (**5da**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5da** (17.8 mg, 59% yield) as a greenish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.58 (s, 1H), 5.94 (d, J = 2.0 Hz, 1H), 3.91 (t, J = 5.1 Hz, 2H), 3.82 (t, J = 5.1 Hz, 2H), 2.68−2.61 (m, 4H), 2.45−2.39 (m, 2H), 1.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 126.5, 123.3, 103.4, 62.6, 50.4, 29.1, 25.6, 24.5; HRMS (ESI) m/z calcd for $C_9H_{14}NO$ $(M + H)^+$ 152.1070, found 152.1068; IR (KBr) 3397, 3099, 2929, 2854, 1667, 1494, 1455, 1404, 1362, 1272, 1061 cm^{-1}.

*2-(4,5,6,7-Tetrahydro-1H-indol-1-yl)ethanol (**5ea**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5ea** (22.8 mg, 69% yield) as a reddish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.57 (d, J = 2.1 Hz, 1H), 5.96 (d, J = 2.3 Hz, 1H), 3.90 (t, J = 5.4 Hz, 2H), 3.78 (t, J = 5.3 Hz, 2H), 2.56−2.52 (m, 4H), 2.13 (s, 1H), 1.86−1.82 (m, 2H), 1.77−1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.6, 119.0, 117.4, 106.4, 62.3, 48.1, 23.4, 23.1, 23.0, 21.7; HRMS (ESI) m/z calcd for $C_{10}H_{16}NO$ $(M + H)^+$ 166.1226, found 166.1224; IR (KBr) 3396, 3087, 2928, 2852, 1699, 1670, 1487, 1442, 1370, 1298, 1260, 1061 cm^{-1}.

*2-(5-Phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)ethanol (**5fa**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5fa** (32.8 mg, 68% yield) as a reddish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.28 (m, 5H), 6.67 (d, J = 1.8 Hz, 1H), 6.04 (d, J = 2.1 Hz, 1H), 3.98 (t, J = 5.3 Hz, 2H), 3.87 (t, J = 5.1 Hz, 2H), 3.01−2.96 (m, 1H), 2.91−2.86 (m, 1H), 2.76−2.70 (m, 3H), 2.23−2.20 (m, 1H), 2.11−2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 128.3, 127.4, 126.9, 126.0, 119.6, 117.6, 106.5, 62.5, 48.5, 41.4, 31.5, 30.5, 22.2; HRMS (ESI) m/z calcd for $C_{16}H_{20}NO$ $(M + H)^+$ 242.1539, found 242.1536; IR (KBr) 3408, 3084, 3058, 3025, 3000, 2922, 1670, 1601, 1492, 1452, 1373, 1326, 1262, 1156, 1062 cm^{-1}.

*Ethyl 1-(2-hydroxyethyl)-2-phenyl-1H-pyrrole-3-carboxylate (**5ga**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:3, R_f = 0.35) gives **5ga** (32.6 mg, 63% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.32 (m, 5H), 6.77 (d, J = 2.6 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.87 (t, J = 5.4 Hz, 2H), 3.66 (d, J = 4.2 Hz, 2H), 1.87 (s, 1H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 164.7, 138.4, 131.7, 130.7, 128.3, 128.0, 121.2, 114.0, 110.3, 62.2, 59.3, 49.0, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{18}NO_3$ $(M + H)^+$ 260.1281, found 260.1282; IR (KBr) 3439, 3115, 3059, 3026, 2980, 2930, 1790, 1682, 1606, 1549, 1485, 1443, 1373, 1211, 1061 cm^{-1}.

*1-(2-Methoxyethyl)-2,3-diphenyl-1H-pyrrole (**6**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:10) give **6** (44.9 mg, 81% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.36 (m, 3H), 7.33−7.31 (m, 2H), 7.18−7.14 (m, 4H), 7.11−7.06 (m, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 3.98 (t, J = 5.8 Hz, 2H), 3.51 (t, J = 5.8 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 136.5, 132.9, 131.3, 130.3, 128.5, 127.9, 127.63, 127.62, 124.9, 122.7, 121.5, 108.1, 72.2, 58.9, 46.5.

*1-(2-Chloroethyl)-2,3-diphenyl-1H-pyrrole (**7**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:10) give **7** (50.5 mg, 85% yield) as a white solid: mp 94−95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.40 (m, 3H), 7.34−7.31 (m, 2H), 7.19 (d, J = 4.3 Hz, 4H), 7.13−7.08 (m, 1H), 6.87 (d, J = 2.9 Hz, 1H), 6.50 (d, J = 2.9 Hz, 1H), 4.15 (t, J = 6.8 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 136.1, 132.4, 131.1, 130.0, 128.8, 128.01, 127.99, 127.6, 125.1, 123.3, 121.5, 108.4, 48.5, 43.0.

*2-(2,3-Diphenyl-1H-pyrrol-1-yl)ethyl 4-methylbenzenesulfonate (**8**).* Flash column chromatography on a silica gel (ethyl acetate:petroleum ether, 1:8) give **8** (194 mg, 93% yield) as a white solid: mp 98−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.3 Hz, 2H), 7.36−7.33 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 7.21−7.15 (m, 4H), 7.13−7.05 (m, 3H), 6.81 (d, J = 2.9 Hz, 1H), 6.46 (d, J = 2.9 Hz, 1H), 4.07 (t, J = 5.2 Hz, 2H), 4.00 (t, J = 5.3 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 144.8, 136.0, 132.14, 132.09, 130.9, 129.74, 129.67, 128.6, 127.9, 127.8, 127.7, 127.3, 125.0, 123.2, 121.8, 108.2, 68.6, 45.4, 21.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01195.

Crystal data (CIF)

Experimental details on the mechanism study, along with copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of compounds **3aa**−**3oa**, **4aa**−**4ga**, **5aa**−**5ga**, **6**, **7**, **8** and X-ray crystal structure analysis of **3na** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jiangcheng@cczu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (nos. 21272028, 21672028 and 21572025), "Innovation & Entrepreneurship Talents" Introduction Plan of Jiangsu Province, the Natural Science Foundation for Colleges and Universities of Jiangsu Province (15KJA150001 and 16KJB150002), Jiangsu Key Laboratory of Advanced Catalytic Materials &Technology (BM2012110) and Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, Changzhou University for financial supports.

■ REFERENCES

(1) For selected examples on synthesis: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539. (c) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (d) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (e) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012. (f) Jiang, Y.; Chan, W. C.; Park, C.-M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (g) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290. (h) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (i) Lei, T.; Liu, W.-Q.; Li, J.; Huang, M.-Y.; Yang, B.; Meng, Q.-Y.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2016**, *18*, 2479.

(2) (a) Iida, K.; Miura, T.; Ando, J.; Saito, S. 2013, *15*, 1436;. (b) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *10*, 121. (c) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539.

(3) (a) Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446. (b) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2010**, *110*, 3850. (d) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (e) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, *2007*, 3095. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.

(4) (a) Mason, M. E.; Johnson, B.; Hamming, M. J. *J. Agric. Food Chem.* **1966**, *14*, 454. (b) Lunak, S.; Vala, M.; Vynuchal, J.; Ouzzane, I.; Horakova, P.; Moziskova, P.; Elias, Z.; Weiter, M. *Dyes Pigm.* **2011**, *91*, 269. (c) Jr, S. L.; Havel, L.; Vynuchal, J.; Horakova, P.; Kucerik, J.; Weiter, M.; Hrdina, R. *Dyes Pigm.* **2010**, *85*, 27. (d) Blangy, V.; Heiss, C.; Khlebnikov, V.; Letondor, C.; Evans, H. S.; Neier, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1688. (e) Wienk, M. M.; Turbiez, M.; Gilot, J.; Janssen, R. A. J. *Adv. Mater.* **2008**, *20*, 2556. (f) Wu, D.; Descalzo, A. B.; Weik, F.; Emmerling, F.; Shen, Z.; You, X.- Z.; Rurack, K. *Angew. Chem., Int. Ed.* **2007**, *47*, 193.

(5) (a) Mecerreyes, D.; Pomposo, J. A.; Bengoetxea, M.; Grande, H. *Macromolecules* **2000**, *33*, 5846. (b) Stanke, D.; Hallensleben, M. L.; Toppare, L. *Synth. Met.* **1995**, *73*, 267. (c) Chen-Yang, Y. W.; Li, J. L.; Wu, T. L.; Wang, W. S.; Hon, T. F. *Electrochim. Acta* **2004**, *49*, 2031.

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389−9395

(d) Mecerreyes, D.; Stevens, R.; Nguyen, C.; Pomposo, J. A.; Bengoetxea, M.; Grande, H. *Synth. Met.* **2002**, *126*, 173. (e) Bidan, G. *Tetrahedron Lett.* **1985**, *26*, 735.

(6) (a) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley, 2010. (b) Watanabe, M.; Kochi, T.; Kawahara, M.; Nagasawa, H.; Sato, N.; Takita, T.; Hasegawa, G. *Crystal of pyrrole derivative and method for producing the same*. United State Patent, NO. US20160096803A1. (c) Masashi, W.; Takahiro, O.; Michiaki, K.; Hiroshi, N.; Noritada, S.; Takashi, T.; Gen, H. *Dipyrromethene crystal and method for manufacturing same*, European Patent, NO. EP2985277A1. (d) Kazumasa, A.; Hiroyuki, T.; Noriyuki, H.; Juri, Y.; Yusuke, A. *Atropisomer of pyrrole derivative*, European Patent, NO. EP2133330A1.

(7) Kagawa, T.; Fujita, K.; Kawada, K. *J. Fluorine Chem.* **2013**, *152*, 77.

(8) Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 6821.

(9) (a) Iranpoor, N.; Firouzabadi, H.; Nowrouziy, N.; Khalili, D. *Tetrahedron* **2009**, *65*, 3893. (b) Bala, M.; Verma, P. K.; Sharma, U.; Kumar, N.; Singh, B. *Green Chem.* **2013**, *15*, 1687. (c) Asencio, A. M.; Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **2010**, *51*, 325.

(10) (a) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999. (b) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *New J. Chem.* **2013**, *37*, 1700.

(11) (a) Ghosh, A. K.; Chen, Z.-H. *Org. Biomol. Chem.* **2014**, *12*, 3567. (b) Zhang, M.; Duan, Y.; Li, W.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2016**, *52*, 4761. (c) Yang, J.-M.; Li, P.-H.; Wei, Y.; Tang, X.-Y.; Shi, M. *Chem. Commun.* **2016**, *52*, 346. (d) Yang, J.-M.; Zhu, C.-Z.; Tang, X.-Y.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5142.

(12) (a) Alberti, M. N.; Vougioukalakis, G. C.; Orfanopoulos, M. *J. Org. Chem.* **2009**, *74*, 7274. (b) Kumar, S.; Krishnakanth, S.; Mathew, J.; Pomerantz, Z.; Lellouche, J.-P.; Ghosh, S. *J. Phys. Chem. C* **2014**, *118*, 2570. (c) Carpio, H.; Galeazzi, E.; Greenhouse, R.; Guzman, A.; Velarde, E.; Antonio, Y.; Franco, F.; Leon, A.; Perez, V.; Sakas, R.; Valdes, D. *Can. J. Chem.* **1982**, *60*, 2295. (d) Jefford, C. W.; Sienkiewicz, K.; Thronton, S. R. *Tetrahedron Lett.* **1994**, *35*, 6271. (e) Demel, J.; Cejka, J.; Bakardjieva, S.; Stepnicka, P. *J. Mol. Catal. A: Chem.* **2007**, *263*, 259. (f) Trombach, N.; Hild, O.; Schlettwein, D.; Wohrle, D. *J. Mater. Chem.* **2002**, *12*, 879.

(13) Yu, J.-T.; Shi, B.; Peng, H.; Sun, S.; Chu, H.; Jiang, Y.; Cheng, J. *Org. Lett.* **2015**, *17*, 3643.

(14) Schiffner, J. A.; Woste, T. H.; Oestreich, M. *Eur. J. Org. Chem.* **2010**, *2010*, 174.

(15) For the C−C bond formation between the α-methylene ketone and carbon atom adjacent to the oxygen atom, please see: (a) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937. (b) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (c) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (d) Yoo, W.-J.; Correia, C. A.; Zhang, Y.; Li, C.-J. *Synlett* **2009**, *1*, 138. (e) Huang, X.-F.; Zhu, Z.-Q.; Huang, Z.-Z. *Tetrahedron* **2013**, *69*, 8579.

(16) The molecular structure of **3na** was determined by X-ray crystallographic analysis. CCDC 1480594 (**3na**) contains the supplementary crystallographic data for this paper.

DOI: 10.1021/acs.joc.6b01195
J. Org. Chem. 2016, 81, 9389−9395