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Iron-Catalyzed Oxidative Coupling of Alkylamides with Arenes through Oxidation of Alkylamides Followed by Friedel−Crafts Alkylation

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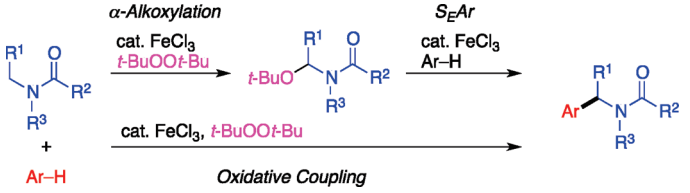

$FeCl_3$ in combination with *t*-BuOO*t*-Bu as an oxidant was found to be an efficient catalyst for oxidation of alkylamides to α-(*tert*-butoxy)alkylamides. $FeCl_2$ and CuCl showed, respectively, almost the same and slightly lower activities compared with $FeCl_3$ in the *tert*-butoxylation of *N*-phenylpyrrolidone (**1a**), whereas no *tert*-butoxylated product was obtained by use of $Fe(OTf)_3$, $RuCl_3$, or $Zr(OTf)_4$. $FeCl_3$ was found to be effective also as a catalyst for the Friedel−Crafts alkylation with thus obtained α-(*tert*-butoxy)alkylamides. The Friedel−Crafts alkylation proceeded smoothly also in the presence of a catalytic amount of $Fe(OTf)_3$, $RuCl_3$, or $Zr(OTf)_4$. In contrast, $FeCl_2$ and CuCl, which showed certain activity toward the *tert*-butoxylation, failed to promote the Friedel−Crafts alkylation. Among the transition metal complexes thus far examined, only $FeCl_3$ showed high catalytic activities for both the oxidation and the Friedel−Crafts alkylation. The bifunctionality of $FeCl_3$ was utilized for the oxidative coupling of alkylamides with arenes through a tandem reaction consisting of oxidation of alkylamides to α-(*tert*-butoxy)alkylamides and the following Friedel−Crafts alkylation. The $FeCl_3$-catalyzed oxidative coupling is applicable to a wide variety of alkylamides and arenes, though a combination of $FeCl_3$ with $Fe(OTf)_3$ was found to be effective for the reaction of arenes with low nucleophilicity. A Fe(II)−Fe(III) catalytic cycle is concerned with the *tert*-butoxylation, whereas a Fe(III) complex as a Lewis acid catalyzes the Friedel−Crafts alkylation.

Introduction

The Friedel−Crafts alkylation is one of the most versatile methods for introduction of $C(sp^3)$ substituents into aromatic rings.[1] The most frequently used electrophiles in this electrophilic aromatic substitution (S_EAr) are alkyl halides, whereas oxy compounds such as alcohols and ethers also act as efficient alkylating reagents, which do not give any halogen-containing waste. α-Oxyalkylamides, which are converted into acyliminium ions upon elimination of the oxygen leaving group, are used for amidoalkylation of arenes to give α-arylalkylamides.[2] Amidoalkylations of arenes with α-oxyalkylamides are often conducted in the presence of a stoichiometric amount of a Brønsted or Lewis acid, but use of a Lewis acid as a catalyst also is possible.[3] Oxidation of alkylamides is one of the most convenient methods to obtain α-oxyalkylamides. In addition to anodic oxidation using an alcohol as a solvent giving α-alkoxyalkylamides,[4] combinations of a transition metal catalyst with an oxygen-based

(1) For a review, see: Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Pattenden, G., Eds.; Pergamon Press; Oxford, 1991; Vol. 3, Chapter 1.8; pp 293−339.

(2) For reviews on generation of acyliminium salts and reactions with nucleophiles including arenes, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2; Chapter 4.5; pp 1047−1082. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (d) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

(3) Amidoalkylation of arenes has been extensively studied with simple alkylation reagents such as *N*-(hydroxymethyl)-α-chloroacetamide and *N*-(hydroxymethyl)phthalimide, which are used on the assumption that the acyl groups are removed after amidoalkylation to give H_2NCH_2-substituted arenes. For reviews, see: (a) Zaugg, H. E. *Synthesis* **1970**, 49–73. (b) Zaugg, H. E. *Synthesis* **1984**, 85–110. (c) Zaugg, H. E. *Synthesis* **1984**, 181–212. See also refs 2 and 4.

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oxidant are useful for preparation of α-oxyalkylamides. Among the combinations, Cu/*t*-BuOOCOPh[5] and Ru/*t*-BuOOH[6] are particularly effective to give α-benzoyloxyamides and α-(*tert*-butyldioxy)amides, respectively.[7]

As mentioned above, α-arylalkylamides can be obtained from alkylamides and arenes through oxidation of alkylamides followed by S_EAr with the resulting α-oxyalkylamides, but tandem reaction consisting of these two reactions is more convenient because introduction of oxy substituents in advance is not required. In this context, we have previously reported the $Zr(OTf)_4$-catalyzed oxidative coupling of alkylamides with arenes using O_2 as an oxidant, but the scope is severely limited to γ-lactams and electron-rich heteroarenes.[8,9] This oxidative coupling is considered to be a tandem reaction consisting of oxidation and S_EAr both catalyzed by the zirconium complex, though the existence of any intermediary α-oxygenated alkylamide is not confirmed. It is not so easy to effectively operate this type of tandem catalysis, where one catalyst sequentially promotes two mechanistically distinct reactions in a single reactor,[10] because the catalyst is required to show two different types of catalytic abilities. The narrow scope in the zirconium-catalyzed reaction is likely to be ascribed mainly to its low catalytic activity for oxidation.

Expansion of the substrate scope of the oxidative coupling apparently requires a more effective transition metal catalyst, which oxidizes a wide variety of alkylamides in combination with a properly chosen oxidant and has strong Lewis acidity to smoothly promote S_EAr with the resulting α-oxygenated alkylamides. We anticipated that high valent iron complexes fulfill the requirement. They are known to catalyze oxidation[11,12] of $C(sp^3)-H$ bonds to $C(sp^3)-O$ bonds and have strong Lewis acidity[13] to promote S_EAr with various electrophiles. Here we report that $FeCl_3$ effectively catalyzes the following three reactions: (1) oxidation of alkylamides into α-alkoxyalkylamides, (2) S_EAr with the α-alkoxyalkylamides, and (3) oxidative coupling of alkylamides with arenes as a sequence of these two reactions to give a wide variety of α-arylalkylamides.[14]

Results and Discussion

Oxidation of Alkylamides to α-(*tert*-Butoxy)alkylamides. We examined efficiency of $FeCl_3$ as a catalyst for oxidation of alkylamides using *t*-BuO*t*-Bu as an oxidant in the expectation that the oxidation gives relatively stable α-(*tert*-butoxy)alkylamides. Thus, treatment of *N*-phenylpyrrolidone (**1a**) with $FeCl_3$ (1 mol %) and *t*-BuO*t*-Bu (3 equiv) in 1,2-dichloroethane (DCE) at 90 °C for 24 h gave 5-(*tert*-butoxy)-1-phenyl-2-pyrrolidone (**2a**) in 53% yield with 89% conversion (entry 1 of Table 1). The yield was increased by use of 1,2-dichloroisobutane (DCB) as a solvent in combination with *t*-BuOH (TBA), which possibly stabilizes **2a** (entry 2). *N*-Methylpyrrolidone (**1b**) accepted *tert*-butoxylation preferentially on the ring over at the methyl (entry 3), where a higher conversion resulted in a lower efficiency with coproduction of a considerable amount of di(*tert*-butoxy)amide **2b″** (entry 4). The oxidation proceeded also with acyclic amides (entries 5 and 6), but again dibutoxylation is troublesome with *N*,*N*-dimethylacetamide (DMA, **1d**), which has two reaction sites. Selective monobutoxylation of **1d** and **1b** was observed by use of the amides in large excess as solvents (entries 7 and 8). The catalytic activity of $FeCl_2$ was comparable to that of $FeCl_3$, whereas **2a** was not obtained at all with $Fe(OTf)_3$ (entries 9 and 10). Among transition metals that are known to be effective for oxidation of alkylamides to α-oxylated products,[5,6] CuCl showed certain activity, but oxidation of **1a** was not completed even after 48 h (entries 11 and 12). No *tert*-butoxylation product was obtained with $RuCl_3$ or $Zr(OTf)_4$, which is known to catalyze oxidative coupling of five-membered lactams with indoles using oxygen as an oxidant (entries 13 and 14).[8] Only a small amount of **2a** was obtained in the absence of a metal catalyst (entry 15).

(4) For reviews on anodic oxidation of organic compounds including alkylamides and synthetic applications of the oxidation products, see: (a) Shono, T. *Tetrahedron* **1984**, *40*, 811–850. (b) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554.

(5) For a review, see: Rawlinson, D. A.; Sosnovsky, G. *Synthesis* **1972**, 1–28.

(6) (a) Murahashi, S.-I.; Naota, T.; Kuwabata, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822. For reviews, see: (b) Murahashi, S.-I. *Angew. Chem., Int. Ed.* **1995**, *34*, 2443–2465. (c) Murahashi, S.-I.; Komiya, N. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; Chapter 3.4.4; pp 79−81. (c) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501.

(7) For examples of oxidation of alkylamides to α-oxyalkylamides, see: (a) Mitani, M.; Watanabe, K.; Tachizawa, O.; Koyama, K. *Chem. Lett.* **1992**, *21*, 813–814. (b) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387–3390.

(8) Tsuchimoto, T.; Ozawa, Y.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 4231–4233.

(9) As a part of extensive work on homolytic aromatic substitution (HAS), Minisci has reported the oxidative coupling of alkylamides with *N*-heteroarenes such as pyridine in the use of a peroxy oxidant including *t*-BuO*t*-Bu, but the scope of arenes is limited to pyridine derivatives, which as protonated forms accept addition of nucleophilic acylaminomethyl radical intermediates. (a) Arnone, A.; Cecere, M.; Galli, R.; Minisci, F.; Perchinunno, M.; Porta, O.; Gardini, G. *Gazz. Chim. Ital.* **1973**, *103*, 13–29. For a review on HAS: (b) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489–519. For an iron-catalyzed reaction: (c) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Chem. Soc., Chem. Commun.* **1983**, 916–917.

(10) Fogg and dos Santos call this, in their review, "auto-tandem catalysis" with the definition "processes of this type involve two or more mechanistically distinct catalyses promoted by a single catalyst precursor: both cycles occur spontaneously by cooperative interaction of the various species (catalyst, substrate, additional reagents if required) present at the outset of reaction." (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379. For other recent reviews on tandem catalysis, see: (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. (c) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 12168–12179.

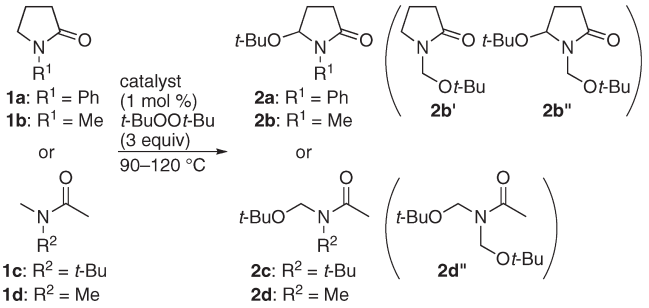
(11) For reviews, see: (a) Díaz, D. D.; Miranda, P. O.; Padrón, J. I.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 457–476. (b) Mayer, A. C.; Bolm, C. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH; Weinheim, 2008; Chapter 3.1; pp 73−83. (c) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730–2744.

(12) Demethylation of *N*-methylamides through iron-catalyzed oxidation has been reported as a side reaction of homolytic aromatic substitution. (a) Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *J. Org. Chem.* **1984**, *49*, 3364–3367. (b) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146–7150.

(13) For reviews, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Kischel, J.; Mertins, K.; Jovel, I.; Zapf, A.; Beller, M. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH; Weinheim, 2008; Chapter 6.2.5; pp 183−188.

(14) Very recently, a report on iron-catalyzed oxdiative coupling of *N*-acyl-1,2,3,4-tetrahydroisoquinolines with indoles or polymethoxybenzenes appeared. (a) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836–8838. For iron-catalyzed homo- and cross-coupling of alkylamines with arenes: (b) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116–118. (c) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wünsch, B.; Itami, K. *Chem. Asian J.* **2009**, *4*, 1416–1419. (d) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739–2741. For oxidative couplings catalyzed by an iron(II) or iron(0) complex: (e) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505–6507. (f) Zhang, Y.; Li, C.-J. *Eur. J. Org. Chem.* **2007**, 4654–4657. (g) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497–7500. (h) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701–1704. (i) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817–3820. (j) Richter, H.; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, 4460–4467.

TABLE 1. Oxidation of Amides with *t*-BuOO*t*-Bu[a]



entry	1	catalyst	solvent[b]	temp (°C)	time (h)	conv (%)[c]	yield (%)[c,d]	product(s) (ratio)[c]
1	**1a**	$FeCl_3$	DCE	90	24	89	53	**2a**
2	**1a**	$FeCl_3$	DCB/TBA	100	21	88	65[e]	**2a**
3	**1b**	$FeCl_3$	DCE/TBA	90	3	55	53	**2b**/**2b′**/**2b″** (83/13/4)
4	**1b**	$FeCl_3$	DCE/TBA	90	24	88	65	**2b**/**2b′**/**2b″** (75/9/16)
5	**1c**	$FeCl_3$	DCB	100	24	94	62	**2c**
6	**1d**	$FeCl_3$	DCB	100	3	64	51	**2d**/**2d″** (90/10)
7	**1d**	$FeCl_3$	**1d**[f]	120	1		84[g]	**2d**/**2d″** (> 99/1)
8	**1b**	$FeCl_3$	**1b**/TBA[h]	90	1		79[g]	**2b**/**2b′**/**2b″** (86/14/ < 1)
9	**1a**	$FeCl_2$	DCB/TBA	100	23	91	66	**2a**
10	**1a**	$Fe(OTf)_3$	DCB/TBA	100	21	92	< 1	**2a**
11	**1a**	CuCl	DCB/TBA	100	21	53	44	**2a**
12	**1a**	CuCl	DCB/TBA	100	48	68	59	**2a**
13	**1a**	$RuCl_3$	DCB/TBA	100	21	39	< 1	**2a**
14	**1a**	$Zr(OTf)_4$	DCB/TBA	100	21	65	< 1	**2a**
15	**1a**	—	DCB/TBA	100	24	32	4	**2a**

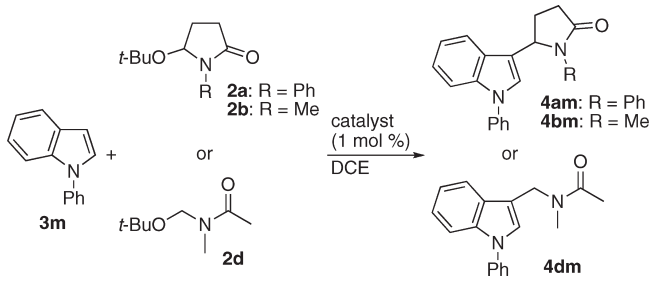
[a]The reaction was carried out under a nitrogen atmosphere using an amide (**1**, 1.5 mmol), *t*-BuOO*t*-Bu (4.5 mmol), and a metal complex (15 μmol) in a solvent (1.0 mL) or a 1:1 mixture of solvents (1.0 mL). [b]DCE = 1,2-dichloroethane, DCB = 1,2-dichloroisobutane, TBA = *tert*-butyl alcohol. [c]Determined by ^{1}H NMR. [d]Yield based on **1**. [e]Yield after purification was 66%. [f]**1d**/$FeCl_3$/*t*-BuOO*t*-Bu = 14/0.01/1. [g]Yield based on *t*-BuOO*t*-Bu. [h]**1b**/$FeCl_3$/*t*-BuOO*t*-Bu/*t*-BuOH = 14/0.01/1/1.

Friedel–Crafts Alkylation with α-(*tert*-Butoxy)alkylamides. $FeCl_3$ was found to be an effective catalyst for S_EAr with thus obtained α-(*tert*-butoxy)alkylamides. The reaction of *N*-phenylindole (**3m**, 1 equiv) with 5-(*tert*-butoxy)-1-phenyl-2-pyrrolidone (**2a**, 1.2 equiv) in the presence of $FeCl_3$ (1 mol %) in DCE at 40 °C for 2 h gave 1-phenyl-5-(1-phenyl-3-indolyl)-2-pyrrolidone (**4am**) in 94% yield (entry 1 of Table 2).[15] In contrast, the other complexes ($FeCl_2$ and CuCl) that showed activities toward the oxidation of alkylamides (cf. entries 9, 11, and 12 of Table 1) did not catalyze the Friedel–Crafts alkylation at all (entries 2 and 3). $Fe(OTf)_3$, which has Lewis acidity higher than that of $FeCl_3$ but lacks the *tert*-butoxylation ability (cf. entry 10 of Table 1), was effective as a catalyst for the S_EAr as same as $RuCl_3$ and $Zr(OTf)_4$ (entries 4–6). α-(*tert*-Butoxy)alkylamides **2b** and **2d** also underwent efficient coupling with **3m** in the presence of $FeCl_3$ as a catalyst (entries 7 and 8).

Oxidative Coupling of Alkylamides with Arenes through Tandem Reaction Consisting of Oxidation and the Friedel–Crafts Alkylation. Among the transition metal complexes examined, only $FeCl_3$ showed high catalytic activities for both oxidation of alkylamides and S_EAr with the resulting alkoxyalkylamides. Now the oxidative coupling of alkylamides with arenes as a sequence of these two reactions definitely is possible with $FeCl_3$ as a catalyst. Thus, treatment of *N*-phenylindole (**3m**, 1 equiv) and *N*-phenylpyrrolidone (**1a**, 6 equiv) with $FeCl_3$ (3 mol %) and *t*-BuOO*t*-Bu (3 equiv) in DCE at 90 °C for 7 h gave 72% yield of coupling product **4am** (entry 1 of Table 3).[16] Other cyclic and acyclic amides also underwent the coupling with **3m** in DCE or DCB (entries 2–5). The coupling is applicable to less nucleophilic arenes (entries 6–8), though the reaction of arenes that have multiple reaction points such as 2-methoxythiophene (**3o**) and 1,3-dimethoxybenzene (**3p**) gave a mixture of regioisomers in addition to 1:2 coupling products. This is an inherent drawback of the Friedel–Crafts alkylation. The reaction of a naphthalene having an electron-withdrawing ester group with DMA (**1d**) gave no coupling products even with an increased amount (10 mol %) of $FeCl_3$ (entry 9). To facilitate the S_EAr step by enhancing Lewis acidity, $FeCl_3$ (7 mol %) was used in combination with $Fe(OTf)_3$ (3 mol %), which has Lewis acidity higher than that of $FeCl_3$ and thus is more efficient in S_EAr (cf. entries 1 and 4 of Table 2) but poorly catalyzes the oxidation (cf. entries 2 and 10 of Table 1), to give coupling product **4dq** in 84% yield (entry 10). This protocol was applied to other arenes of low nucleophilicity (entries 11–13).

Highly nucleophilic arenes such as *N*-methylindole (**3u**) did not undergo efficient oxidative coupling under the standard conditions of Table 3. For example, the coupling of **3u** (1 equiv) with DMA (**1d**, 6 equiv) in DCB using $FeCl_3$ (3 mol %) and *t*-BuOO*t*-Bu (3 equiv) at 110 °C for 9 h gave only 28% yield of **4du** with full conversion of **3u** (Scheme 1).

TABLE 2. S_EAr with α-(*tert*-Butoxy)alkylamides[a]



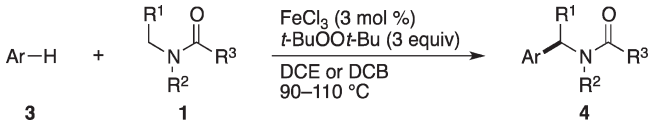
entry	2	catalyst	temp (°C)	time (h)	conv (%)[b]	yield (%)[c]
1	**2a**	$FeCl_3$	40	2	> 99	94
2	**2a**	$FeCl_2$	40	2	< 2	< 1
3	**2a**	CuCl	40	2	< 2	< 1
4	**2a**	$Fe(OTf)_3$	40	0.8	> 99	96
5	**2a**	$RuCl_3$	40	2	> 99	99
6	**2a**	$Zr(OTf)_4$	40	2	> 99	98
7	**2b**	$FeCl_3$	70	2	> 99	96
8	**2d**	$FeCl_3$	70	2	> 99	96

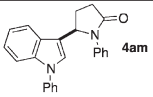
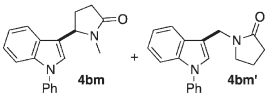
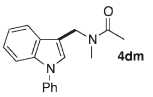
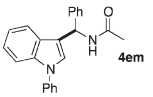
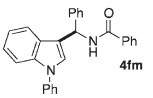
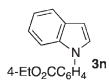
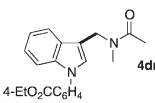
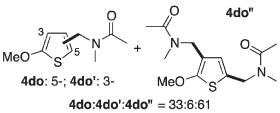
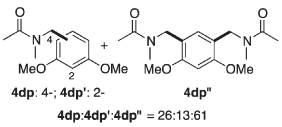
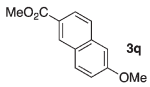
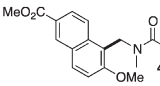
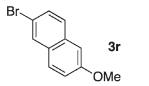
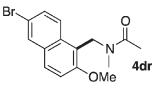
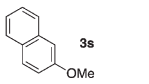
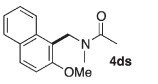
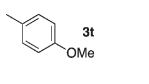
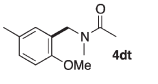
[a]The reaction was carried out in 1,2-dichloroethane (DCE, 1.0 mL) under a nitrogen atmosphere using **3m** (0.25 mmol) and **2** (0.30 mmol; for entry 8, 0.38 mmol) in the presence of a metal complex (2.5 μmol). [b]Determined by ^{1}H NMR. [c]Yield based on **3m**.

(15) The reaction of **3m** with **2a** in the presence of HCl (1 mol %) under the same conditions (40 °C, 2 h, DCE) gave **4am** in 2% yield (5% conv).

(16) The reaction of **3m** with **1a** by use of $FeCl_2$ instead of $FeCl_3$ as a catalyst under the same conditions gave 73% yield of **4am**. However, the $FeCl_2$-catalyzed coupling of **1d** with **3n**, which is less nucleophilic than **3m**, scored a lower yield (46%) under the same conditions as entry 6 of Table 3.

TABLE 3. Oxidative Coupling of Alkylamides with Arenes[a]

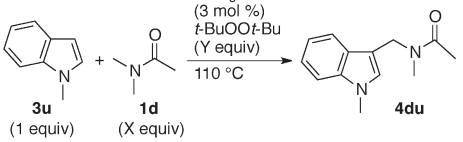


entry	arene (**3**)	amide (**1**)	time (h)	yield (%)[b]	product(s) (ratio)[c]
1[d]	 **3m**	 **1a**	7	72	 **4am**
2[d]	 **3m**	 **1b**	7	79	 **4bm** + **4bm'** **4bm**:**4bm'** = 96:4
3	 **3m**	 **1d**	12	70	 **4dm**
4	 **3m**	 **1e**	8	76	 **4em**
5	 **3m**	 **1f**	20	78	 **4fm**
6	 **3n**	 **1d**	12	65	 **4dn**
7[e]	 **3o**	 **1d**	26	64	 **4do**: 5-; **4do'**: 3- **4do"** **4do**:**4do'**:**4do"** = 33:6:61
8	 **3p**	 **1d**	8	84	 **4dp**: 4-; **4dp'**: 2- **4dp"** **4dp**:**4dp'**:**4dp"** = 26:13:61
9[f]	 **3q**	 **1d**	15	<1	 **4dq**
10[g]			15	84	
11[g]	 **3r**	 **1d**	15	66	 **4dr**
12[g]	 **3s**	 **1d**	10	80	 **4ds**
13[g]	 **3t**	 **1d**	16	53	 **4dt**

[a]The reaction was carried out at 110 °C under a nitrogen atmosphere using an arene (**3**, 0.50 mmol), an amide (**1**, 3.0 mmol), and *t*-BuOO*t*-Bu (1.5 mmol) in the presence of $FeCl_3$ (15 μmol) in 1,2-dichloroisobutane (DCB, 2 mL). [b]Yield based on **3**. [c]Determined by GC, GC−MS, and ^{1}H NMR. [d]Conducted in 1,2-dichloroethane (DCE) at 90 °C. [e]At 100 °C. [f]$FeCl_3$ (0.050 mmol). [g]$FeCl_3$ (0.035 mmol)/$Fe(OTf)_3$ (0.015 mmol).

The low efficiency is ascribed, at least in part, to loss of coupling product **4du** by oxidation at the methylene carbon adjacent to the amide nitrogen because the carbon atom becomes more electron-rich upon substitution by the highly electron-rich indole nucleus. Reduction of the amount (2 equiv) of *t*-BuOO*t*-Bu was partially effective, whereas the yield was considerably improved by use of an increased amount (18 equiv) of **1d**. Use of **1d** in much excess as a solvent further increased the yield to 86%, though a higher temperature and a higher catalyst loading are required to compensate deceleration of the S_EAr step by an increased amount of the Lewis basic amide. This protocol was applied to the oxidative coupling of highly nucleophilic heteroarenes and arenes with liquid amides (Table 4). Amide **1d**, used as a solvent, underwent coupling with indoles, 2-pentylfuran, and 1,3,5-trimethoxybenzene (entries 1−4). The oxidative coupling is applicable to an *N*-monoalkylamide (entries 5 and 6). The methyl group on nitrogen was preferred over the ethyl as a coupling partner (entry 7). Arylation took place predominantly on the ring in the oxidative coupling of cyclic amides (entries 8−11). An arene of moderate nucleophilicity also underwent the coupling in a high yield under these conditions (entry 12, cf. entry 3 of Table 3).

SCHEME 1. Oxidative Coupling Using a Highly Nucleophilic Arene

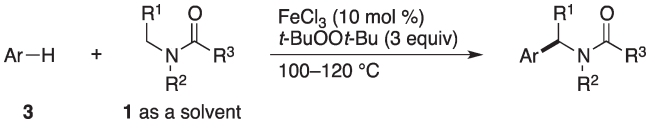


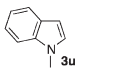
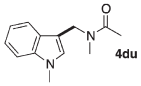
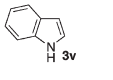
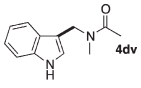
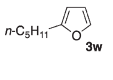
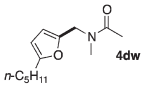
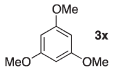
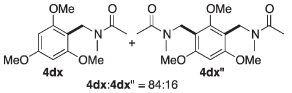
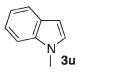
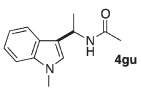
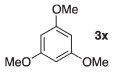
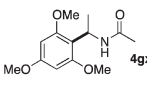
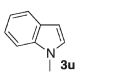
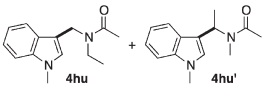
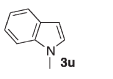
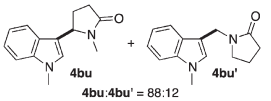
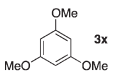
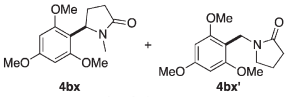
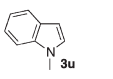
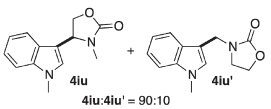
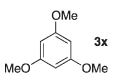
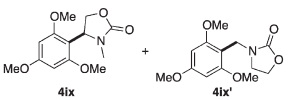
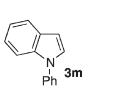
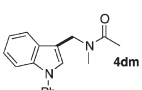
X	Y	time	solvent	yield
6	3	9 h	DCB	28%
6	2	12 h	DCB	36%
18	3	6 h	DCB	51%
51	3	6 h	—	86% (10 mol%, 120 °C, Table 4, entry 1)

The tandem oxidative coupling is valuable not only in its operational simplicity but also in efficient utilization of reactive intermediates, especially in the reaction of amides that gives unstable *tert*-butoxylated amides upon oxidation. For example, *N*-[1-(*tert*-butoxy)ethyl]acetamide was obtained only in ≤20% yield by oxidation of *N*-ethylacetamide (**1g**) under the conditions (entry 6 or 7 in Table 1) suitable for *tert*-butoxylation of DMA (**1d**). Despite the instability, the tandem reaction of **1g** with **3u** for 2 h under the conditions of Table 4 gave **4gu** in 69% yield (Scheme 2). In contrast, a reaction with sequential additions, where arene **3u** was added after full consumption of *t*-BuOO*t*-Bu, under conditions similar to the tandem reaction gave only 26% yield of **4gu**, clearly showing the advantage of the tandem reaction.

Application of the Oxidative Coupling to Synthesis of Isoquinoline Alkaloids. The present oxidative coupling gives α-arylalkylamides, which are often observed as substructures in natural products. We synthesized isoquinoline alkaloids utilizing an intramolecular oxidative coupling as a key carbon−carbon bond-forming step (Scheme 3). Although the oxidative cyclization of 1-[2-(3,4-dimethoxyphenyl)ethyl]-pyrrolidone (**5**) under the standard conditions of Table 3 using *t*-BuOO*t*-Bu (3 equiv) scored a low yield probably because of overoxidation of the amide moiety, the yield/conversion ratio was greatly improved by reduction of the amount of *t*-BuOO*t*-Bu at the cost of a lower conversion. Cyclization product **6** was transformed to (±)-crispine A[17] or (±)-trolline[18] by reduction with $LiAlH_4$ or demethylation of ethers with BBr_3, respectively.

TABLE 4. Oxidative Coupling of Alkylamides with Arenes Using the Amides as Solvents[a]

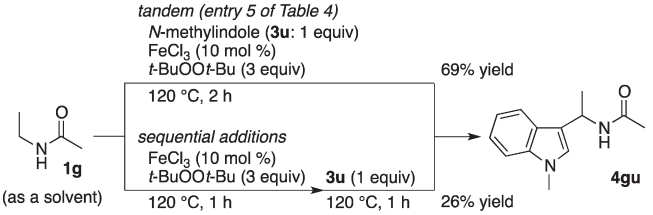


entry	arene (**3**)	amide (**1**)	time (h)	yield (%)[b]	product(s) (ratio)[c]
1			6	86	
2			5.5	71	
3[d]			48	88	
4			12	74	 4dx:4dx'' = 84:16
5			2	69	
6			5.5	82	
7			5	64	 4hu:4hu' = 91:9
8[e]			9	80	 4bu:4bu' = 88:12
9			2	88	 4bx:4bx' = 66:34
10			2	87	 4iu:4iu' = 90:10
11			2.5	85	 4ix:4ix' = 87:13
12			48	91	

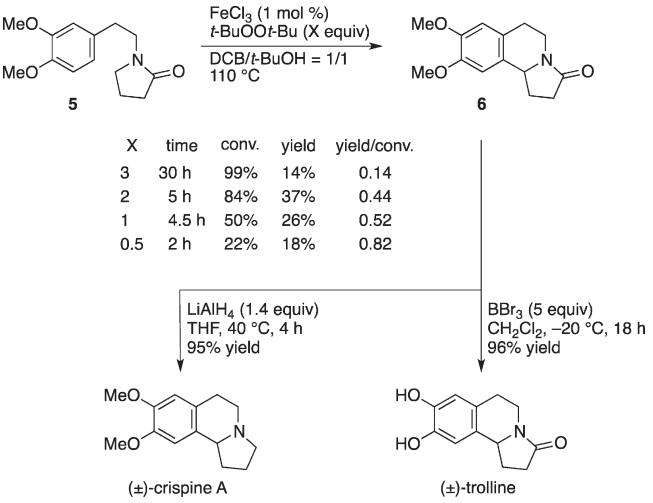
[a]The reaction was carried out at 120 °C under a nitrogen atmosphere using an arene (**3**, 0.25 mmol), an amide (**1**, 1.0 mL), and *t*-BuOO*t*-Bu (0.75 mmol) in the presence of $FeCl_3$ (25 μmol). [b]Yield based on **3**. [c]Determined by GC, GC−MS, and ^{1}H NMR. [d]$FeCl_3$ (50 μmol) was used. [e]At 100 °C.

Reaction Mechanism. A plausible mechanism of the tandem reaction is shown in Scheme 4. The catalytic cycle of oxidation of alkylamides, exemplified by DMA (**1d**), is described

SCHEME 2. Tandem versus Sequential Additions



SCHEME 3. Application to Synthesis of Isoquinoline Alkaloids



as Cycle A, whereas Cycle B shows the mechanism of the Friedel−Crafts alkylation. Cycle A starts with abstraction of H$^\bullet$ from **1d** by *t*-BuO$^\bullet$, which is generated in a small amount by thermal homolysis of *t*-BuOO*t*-Bu, giving AcN(Me)$CH_2^\bullet$ (**7d**). The reaction of **1d** with *t*-BuOO*t*-Bu is reported to give AcN(Me)CH_2CH_2N(Me)Ac through hydrogen radical abstraction from **1d** by *t*-BuO$^\bullet$ followed by dimerization of resulting **7d**.[19] Iron(III) complexes are known to oxidize acylaminomethyl radicals to acyliminium salts.[12] Thus, $FeCl_3$ oxidizes **7d** to **8d**, which readily reacts with *t*-BuOH to give *tert*-butoxyamide **2d** and HCl. $FeCl_2$, produced during transformation of **7d** to **8d**, reacts with *t*-BuOO*t*-Bu, giving *t*-BuO$^\bullet$ and (*t*-BuO)$FeCl_2$. The combination of an iron(II) complex with a peroxy compound is often used in homolytic aromatic substitution to generate an oxy radical, which abstracts a hydrogen radical from an organic compound to give a nucleophilic carbon radical attacking a protonated *N*-heteroarene.[20] Acid−base reaction between HCl and (*t*-BuO)$FeCl_2$ gives $FeCl_3$ and *t*-BuOH to complete Cycle A.

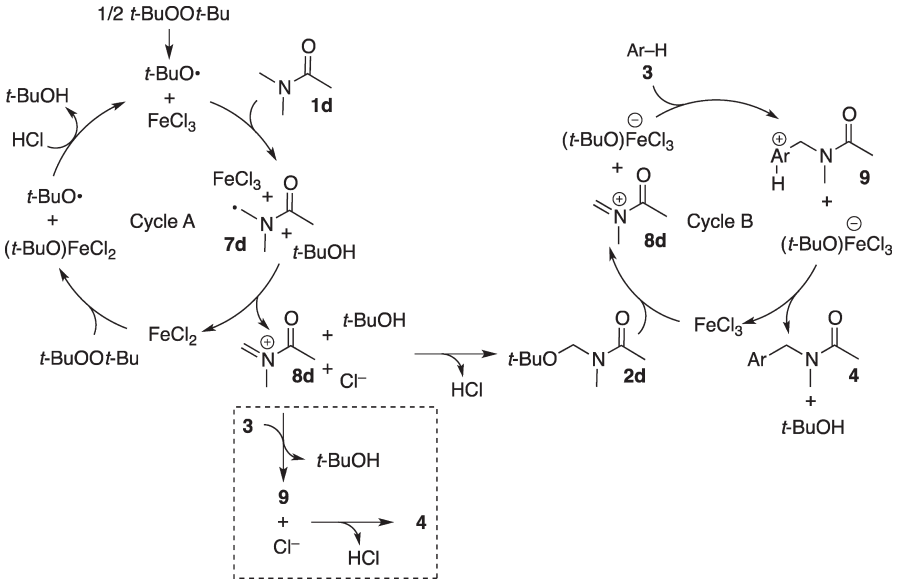
(17) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795–6798.

(18) Wang, R. F.; Yang, X. W.; Ma, C. M.; Cai, S. Q.; Li, J. N.; Shoyama, Y. *Heterocycles* **2004**, *63*, 1443–1448.

(19) The reaction of DMA (**1d**, 12 equiv) with *t*-BuOO*t*-Bu (1 equiv) at 140 °C for 22 h gave AcN(Me)CH_2CH_2N(Me)Ac (85% yield) through dimerization of radical **7d**. Friedman, L.; Shechter, H. *Tetrahedron Lett.* **1961**, *2*, 238–243. The reaction of **1d** with **3u** using *t*-BuOO*t*-Bu (0.75 mmol) under the same conditions as entry 1 of Table 4 but in the absence of an iron catalyst gave AcN(Me)CH_2CH_2N(Me)Ac (0.22 mmol) in addition to **4du** (2% yield) and the corresponding 2-indolyl isomer (5% yield).

(20) (a) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157–4170. (b) Giordano, C.; Minisci, F.; Vismara, E.; Levi, S. *J. Org. Chem.* **1986**, *51*, 536–537. (c) Minisci, F.; Vismara, E.; Fontana, F.; Redaelli, D. *Gazz. Chim. Ital.* **1987**, *117*, 363–367. See also ref 9b.

SCHEME 4. A Plausible Reaction Mechanism



The $FeCl_3$-catalyzed Friedel−Crafts alkylation of arenes with α-(*tert*-butoxy)alkylamides (Table 2) should follow the generally accepted catalytic cycle of Lewis acid-catalyzed amidoalkylation as shown in Cycle B.[2] $FeCl_3$ promotes elimination of the *tert*-butoxy group to give acyliminium ion **8d**,[21] which adds to arene **3**. Elimination of a proton from adduct **9** gives **4** with regeneration of $FeCl_3$.

In the tandem reaction consisting of the oxidation and the Friedel−Crafts alkylation, α-(*tert*-butoxy)alkylamide **2d** produced through Cycle A is likely to get into Cycle B. α-(*tert*-Butoxy)alkylamide **2d** is relatively stable and always observed in the reaction of DMA (**1d**), and arene **3** is usually converted to α-arylalkylamide **4** even after full conversion of *t*-BuOO*t*-Bu, showing that **2d** is an intermediate. However, in the reaction of arenes having nucleophilicity higher than that of *t*-BuOH, acyliminium salt **8d** generated by oxidation possibly reacts directly with the arene without being trapped by *t*-BuOH as shown in the dotted square.

Conclusion

The oxidative coupling of alkylamides with arenes to give α-arylalkylamides through a tandem reaction consisting of oxidation of alkylamides and the Friedel−Crafts alkylation with the resulting oxidized alkylamides is possible when a catalyst can promote both reactions. We expected high valent iron complexes to fulfill the requirement. $FeCl_3$ was found to be active as a catalyst for oxidation of alkylamides with *t*-BuOO*t*-Bu to give α-(*tert*-butoxy)alkylamides. $FeCl_2$ and CuCl also showed activities for the oxidation, whereas $Fe(OTf)_3$, $RuCl_3$, and $Zr(OTf)_4$ failed to catalyze the *tert*-butoxylation. On the other hand, for the Friedel−Crafts alkylation of arenes with α-(*tert*-butoxy)alkylamides, metal complexes showed activities according to their Lewis acidities. $FeCl_2$ and CuCl, both of which have formal charges of less than 3, were ineffective as catalysts, whereas $FeCl_3$, $Fe(OTf)_3$, $RuCl_3$, and $Zr(OTf)_4$ effectively catalyzed the Friedel−Crafts alkylation. Among the examined transition metal complexes, only $FeCl_3$ showed high catalytic activities for both the oxidation and the Friedel−Crafts alkylation. As a natural consequence, $FeCl_3$ effectively catalyzed the oxidative coupling consisting of these two reactions. The oxidative coupling was found to be applicable to a wide variety of alkylamides and arenes, including an intramolecular one that was utilized for synthesis of simple alkaloids. For the reaction of arenes not having sufficient nucleophilicity, a combination of $FeCl_3$ with $Fe(OTf)_3$, which has higher activity than $FeCl_3$ in S_EAr but poorly catalyzes the oxidation, is effective. In the reaction of alkylamides that give unstable α-(*tert*-butoxy)alkylamides, an advantage of the tandem reaction in efficient utilization of reactive intermediates was disclosed in comparison with a common sequential reaction. Thus, the tandem coupling of *N*-ethylacetamide with *N*-methylindole scored a much higher yield than a reaction with sequential additions, where the arene was added after oxidation of the amide was completed.

Considering the mechanism in homolytic aromatic substitution, a Fe(II)−Fe(III) catalytic cycle is likely to be operative in the oxidation. Fe(III) oxidizes an amidomethyl radical, which is generated by the reaction of an alkylamide and *t*-BuO•, to the acyliminium salt, whereas the resulting Fe(II) is oxidized by *t*-BuOO*t*-Bu to give Fe(III) and *t*-BuO•. The acyliminium salt is readily converted to α-(*tert*-butoxy)-alkylamides. The Friedel−Crafts alkylation is considered to be catalyzed by a Lewis acidic iron complex, probably in the Fe(III) state.

Experimental Section

General Remarks. All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique under a nitrogen atmosphere. Nuclear magnetic resonance spectra (^1H, 500 MHz; ^{13}C, 125 MHz) were taken using tetramethylsilane as an internal standard. Preparative recycling gel permeation chromatography (GPC) was performed

(21) (a) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010–14011. (b) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859–5871.

using chloroform as an eluent. Unless otherwise noted, reagents were commercially available and used without further purification. 1-Phenylindole and 1-(4-ethoxycarbonylphenyl)indole were prepared according to the literature procedure.[22] 2-Methoxy-6-(methoxycarbonyl)naphthalene was prepared by esterification of the corresponding carboxylic acid with methanol in the presence of a catalytic amount of H_2SO_4. *N*-Ethyl-*N*-methylacetamide was prepared by the reaction of acetyl chloride with ethyl(methyl)amine in an aqueous solution.

Oxidation of Alkylamides with *t*-BuOO*t*-Bu (Table 1). To a solution of an iron complex (15 μmol) in a solvent specified in Table 1 (1.0 mL) in a 20 mL Schlenk tube were added successively an amide (**1**, 1.5 mmol) and *t*-BuOO*t*-Bu (850 μL, 4.5 mmol). After stirring at the temperature for the time both specified in Table 1, the reaction mixture was diluted with EtOAc−Et_3N (95:5, 100 mL) and passed through a pad of SiO_2, and the solvent was evaporated. The NMR yield was determined using $MeNO_2$ as an internal standard. For entry 2, purification with SiO_2 column chromatography (hexane/EtOAc/Et_3N = 75:20:5) gave **2a**.

5-(*tert*-Butoxy)-1-phenyl-2-pyrrolidone (2a). A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 9 H), 2.00−2.06 (m, 1 H), 2.37−2.49 (m, 2 H), 2.73−2.82 (m, 1 H), 5.40 (dd, J = 5.9, 1.6 Hz, 1 H), 7.28 (t, J = 7.3 Hz, 1 H), 7.28 (d, J = 7.7 Hz, 2 H), 7.38 (t, J = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 29.3, 29.4, 73.9, 85.9, 127.2, 127.3, 128.8, 137.1, 174.6. HRMS (ESI) calcd for $C_{14}H_{19}NO_2$: $[M + Na]^+$, 256.1313. Found: m/z 256.1307.

5-(*tert*-Butoxy)-1-methyl-2-pyrrolidone (2b). A colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.83−1.90 (m, 1 H), 2.20−2.29 (m, 2 H), 2.49−2.57 (m, 1 H), 2.80 (s, 3 H), 5.01 (dd, J = 5.9, 2.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 28.5, 28.7, 28.8, 73.8, 84.8, 174.6. HRMS (ESI) calcd for $C_9H_{17}NO_2$: $[M + Na]^+$, 194.1157. Found: m/z 194.1154.

1-(*tert*-Butoxymethyl)-2-pyrrolidone (2b′).[23] A colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 2.01 (quint., J = 7.7 Hz, 2 H), 2.37 (t, J = 8.0 Hz, 2 H), 3.49 (t, J = 7.1 Hz, 2 H), 4.75 (s, 2 H).

5-(*tert*-Butoxy)-1-(*tert*-butoxymethyl)-2-pyrrolidone (2b″). A colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.26 (s, 9 H), 1.84−1.90 (m, 1 H), 2.18−2.29 (m, 2 H), 2.50−2.58 (m, 1 H), 4.30 (d, J = 9.7 Hz, 1 H), 5.14 (d, J = 9.7 Hz, 1 H), 5.28 (dd, J = 6.0, 2.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 28.5, 28.6, 29.3, 63.2, 73.6, 73.8, 80.9, 174.2. HRMS (ESI) calcd for $C_{13}H_{25}NO_3$: $[M + Na]^+$, 266.1732. Found: m/z 266.1727.

***N*-(*tert*-Butoxymethyl)-*N*-(*tert*-butyl)acetamide (2c).** A colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.44 (s, 9 H), 2.16 (s, 3 H), 4.64 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 27.7, 28.8, 57.0, 70.3, 72.2, 172.8. HRMS (ESI) calcd for $C_{11}H_{23}NO_2$: $[M + Na]^+$, 224.1627. Found: m/z 224.1619.

***N*-(*tert*-Butoxymethyl)-*N*-methylacetamide (2d).** A colorless liquid. Observed as two rotamers of 57/43 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24/1.22 (s, 9 H), 2.14/2.06 (s, 3 H), 2.95/3.00 (s, 3 H), 4.65/4.85 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.0, 27.5, 27.7, 33.0, 33.8, 69.9, 72.6, 73.6, 74.3, 170.6, 171.3. HRMS (ESI) calcd for $C_8H_{17}NO_2$: $[M + Na]^+$, 182.1151. Found: m/z 182.1145.

***N*,*N*-Di(*tert*-butoxymethyl)acetamide (2d″).** A colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.26 (s, 9 H), 2.16 (s, 3 H), 4.72 (s, 2 H), 4.89 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 27.7, 27.9, 67.7, 70.2, 72.8, 73.7, 171.6. HRMS (ESI) calcd for $C_{12}H_{25}NO_3$: $[M + Na]^+$, 254.1732. Found: m/z 254.1717.

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Electrophilic Aromatic Substitution with α-(*tert*-Butoxy)alkylamides (Table 2). To a solution of an iron complex (2.5 μmol) in 1,2-dichloroethane (DCE, 1.0 mL) in a 20 mL Schlenk tube were added successively 1-phenylindole (**3m**, 0.25 mmol) and an α-(*tert*-butoxy)alkylamide (**2**, 0.30 mmol; for entry 8, 0.38 mmol). After stirring at the temperature for the time both specified in Table 2, the reaction mixture was diluted with $CHCl_3$−MeOH (9:1, 100 mL) and passed through a pad of SiO_2. Evaporation of the solvent followed by purification with PTLC (SiO_2) gave the corresponding product (**4**).

1-Phenyl-5-(1-phenyl-3-indolyl)-2-pyrrolidone (4am). A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31−2.36 (m, 1 H), 2.63−2.71 (m, 2 H), 2.81−2.90 (m, 1 H), 5.64−5.66 (m, 1 H), 7.06 (t, J = 7.3 Hz, 1 H), 7.11 (s, 1 H), 7.21 (t, J = 7.8 Hz, 1 H), 7.24−7.27 (m, 3 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.37 (d, J = 7.7 Hz, 2 H), 7.47 (t, J = 7.7 Hz, 2 H), 7.53−7.57 (m, 3 H), 7.68 (d, J = 7.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 31.5, 57.6, 111.0, 116.8, 119.0, 120.5, 121.9, 122.9, 124.2, 124.8, 125.6, 126.4, 126.6, 128.6, 129.6, 136.7, 138.5, 139.2, 174.6. HRMS (ESI) calcd for $C_{24}H_{20}N_2O$: $[M + Na]^+$, 375.1473. Found: m/z 375.1467.

1-Methyl-5-(1-phenyl-3-indolyl)-2-pyrrolidone (4bm).[8] A pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22−2.30 (m, 1 H), 2.47−2.57 (m, 2 H), 2.63−2.70 (m, 1 H), 2.78 (s, 3 H), 4.92 (t, J = 7.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.26 (t, J = 8.2 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.57 (d, J = 7.2 Hz, 1 H), 7.59, (d, J = 6.9 Hz, 1 H).

***N*-Methyl-*N*-[(1-phenyl-3-indolyl)methyl]acetamide (4dm).** A colorless liquid. Observed as two rotamers of 68/32 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14/2.30 (s, 3 H), 2.97/3.05 (s, 3 H), 4.82/4.75 (s, 2 H), 7.18−7.37 (m, 4 H), 7.48−7.80 (m, 5 H). For aromatic region, only two peaks were defined. δ 7.34 (s, 1 H, major isomer), 7.79 (d, J=7.5, 1 H, major isomer). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.0, 33.4, 35.0, 41.4, 46.6, 110.4, 110.8, 112.8, 113.3, 118.7, 119.9, 120.4, 120.5, 122.7, 123.0, 124.1, 124.2, 125.6, 126.4, 126.6, 127.37, 127.44, 128.3, 129.5, 129.6, 136.2, 136.4, 139.3, 139.5, 170.3, 170.7. HRMS (ESI) calcd for $C_{18}H_{18}N_2O$: $[M + Na]^+$, 301.1317. Found: m/z 301.1321.

Iron-Catalyzed Oxidative Coupling of Alkylamides with Arenes in a Chlorinated Hydrocarbon (Table 3). To a solution of (an) iron complex(es) in 2.0 mL of 1,2-dichloroethane (DCE) or 1,2-dichloroisobutane (DCB, 1,2-dichloro-2-methylpropane) in a 20 mL Schlenk tube were added successively an arene (**3**, 0.50 mmol), an amide (**1**, 3.0 mmol), and *t*-BuOO*t*-Bu (280 μL, 1.5 mmol). After stirring at the temperature for the time both specified in Table 3, the reaction mixture was diluted with $CHCl_3$/MeOH (9:1, 100 mL) and passed through a pad of SiO_2. Evaporation of the solvent followed by purification with PTLC (SiO_2) gave the corresponding coupling products (**4**). The product was further purified with GPC if necessary.

1-[(1-Phenyl-3-indolyl)methyl]-2-pyrrolidone (4bm′).[8] A pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (quint, J = 7.6 Hz, 1 H), 2.43 (t, J = 8.2 Hz, 2 H), 3.33 (t, J = 7.1 Hz, 1 H), 4.69 (s, 2 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.25 (t, J = 7.1 Hz, 1 H), 7.32 (s, 1 H), 7.36 (t, J = 6.9 Hz, 1 H), 7.48−7.53 (m, 4 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H).

***N*-[Phenyl(1-phenyl-3-indolyl)methyl]acetamide (4em).** A yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 3 H), 6.16 (bs, 1 H), 6.61 (d, J = 8.2 Hz, 1 H), 6.92 (s, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 7.23−7.37 (m, 3 H), 7.37 (t, J = 7.3 Hz, 2 H), 7.41−7.45 (m, 4 H), 7.48 (d, J = 7.3 Hz, 1 H), 7.48 (t, J = 8.3 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 50.1, 110.7, 118.4, 119.7, 120.5, 122.9, 124.2, 126.5, 126.9, 127.0, 127.3, 128.4, 129.5, 136.6, 139.3, 141.1, 169.1. HRMS (ESI) calcd for $C_{23}H_{20}N_2O$: $[M + Na]^+$, 363.1473. Found: m/z 363.1474.

***N*-[Phenyl(1-phenyl-3-indolyl)methyl]benzamide (4fm).** A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (bs, 2 H), 6.94 (s, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.30−7.53 (m, 13 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 7.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.8, 110.8, 118.3, 119.7, 120.7, 123.0, 124.4, 126.7, 127.0, 127.1, 127.3, 127.36, 127.44, 128.59, 128.60, 129.6, 131.6, 134.4, 136.7, 139.3, 141.1, 166.5. HRMS (ESI) calcd for $C_{28}H_{22}N_2O$: $[M + Na]^+$, 425.1630. Found: m/z 425.1612.

***N*-{[1-(4-Ethoxycarbonylphenyl)-3-indolyl]methyl}-*N*-methylacetamide (4dn).** A yellow oil. Observed as two rotamers of 65/35 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43/1.43 (t, J = 7.1/7.1 Hz, 3 H), 2.14/2.28 (s, 3 H), 2.98/3.04 (s, 3 H), 4.42/4.43 (q, J = 7.1/7.1 Hz, 2 H), 4.80/4.75 (s, 2 H), 7.37/7.23 (s, 1 H), 7.21/7.23 (t, J = 7.6/7.6 Hz, 1 H), 7.27/7.31 (t, J = 7.7/7.7 Hz, 1 H), 7.58/7.56 (d, J = 8.6/8.1 Hz, 2 H), 7.62/7.58 (d, J = 8.3/8.3 Hz, 1 H), 7.78/7.64 (d, J = 7.8/8.4 Hz, 1 H), 8.19/8.21 (d, J = 8.6/8.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.5, 21.9, 33.4, 35.1, 41.4, 46.6, 61.07, 61.12, 110.5, 110.9, 114.1, 114.5, 119.0, 120.1, 121.0, 121.1, 123.0, 123.1, 123.2, 123.5, 124.9, 126.8, 127.8, 127.9, 128.2, 128.7, 131.1, 131.2, 135.7, 136.0, 143.0, 143.2, 165.7, 165.8, 170.3, 170.7. HRMS (ESI) calcd for $C_{21}H_{22}N_2O_3$: $[M + Na]^+$, 373.1523. Found: m/z 373.1520.

***N*-[(5-Methoxy-2-thienyl)methyl]-*N*-methylacetamide (4do).** A colorless oil. Observed as two rotamers of 65/35 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10/2.19 (s, 3 H), 2.96/2.93 (s, 3 H), 3.84/3.86 (s, 3 H), 4.53/4.47 (s, 2 H), 6.00/6.03 (d, J = 3.8/3.8 Hz, 1 H), 6.57/6.53 (d, J = 3.8/3.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.8, 33.0, 35.2, 46.3, 50.2, 60.2, 60.3, 102.8, 103.1, 123.2, 124.2, 125.4, 125.9, 166.0, 166.3, 170.3, 170.4. HRMS (ESI) calcd for $C_9H_{13}NO_2S$: $[M + Na]^+$, 222.0559. Found: m/z 222.0553.

***N*-[(2-Methoxy-3-thienyl)methyl]-*N*-methylacetamide (4do′).** This product could not be isolated in a pure form. The following data were obtained from spectra of a mixture with **4do** (**4do**:**4do′** = 53:47). **4do′** was observed as two rotamers of 55/45 ratio in ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08/2.19 (s, 3 H), 2.91/2.89 (s, 3 H), 3.91/3.92 (s, 3 H), 4.44/4.33 (s, 2 H), 6.55/6.59 (d, J = 5.9/5.9 Hz, 1 H), 6.75/6.65 (d, J = 5.8/5.9 Hz, 1 H). GC−MS m/z: 199, 184, 156, 142, 127, 99. These ions were observed also in the GC−MS of **4do**, which appears later than **4do′** on GC.

The above two compounds (**4do** and **4do′**) were characterized as follows. The aromatic methyne protons of 2-methoxythiophene appear in ^{1}H NMR at 6.19 ppm (dd, J = 3.8, 1.5 Hz, C-3), 6.52 ppm (dd, J = 5.8, 1.5 Hz, C-5), and 6.70 ppm (dd, J = 5.8, 3.8 Hz, C-4),[24] which are reported not to change largely upon introduction of aminomethyl[25,14c] or alkyl[26,27] groups into the thiophene ring. NOE analysis (Figure 1) of **4do** and **4do′** shows that both of these have two adjacent methyne protons on the thiophene ring and that the methyne proton at 6.00 ppm and the methoxy group in **4do** are located next to each other. These observations imply that **4do** and **4do′** have an acylaminomethyl group at C-5 and C-3, respectively. In addition, ^{1}H NMR of the reduction product ($LiAlH_4$, Et_2O, 40 °C, 4.5 h, 74% yield) of **4do** is similar to that of 2-(*N*-benzyl-*N*-methylaminomethyl)-5-methoxythiophene [δ 2.22 (s, 3 H), 3.53 (s, 2 H), 3.59 (s, 2 H), 3.87 (s, 3 H), 6.00 (d, J = 3.2 Hz, 1 H), 6.51 (d, J = 3.2 Hz, 1 H), 7.20−7.40 (m, 5 H)],[26] being consistent with the above determined structure of **4do**.

2-(*N*-Ethyl-*N*-methylaminomethyl)-5-methoxythiophene. A colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H), 2.24 (s, 3 H), 2.46 (q, J = 7.2 Hz, 2 H), 3.57 (s, 2 H), 3.86 (s, 3 H), 6.00 (d, J = 3.7 Hz, 1 H), 6.49 (d, J = 3.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 41.3, 50.4, 56.6, 60.1, 102.7, 123.1, 128.4, 165.8. GC−MS m/z: 185, 127.

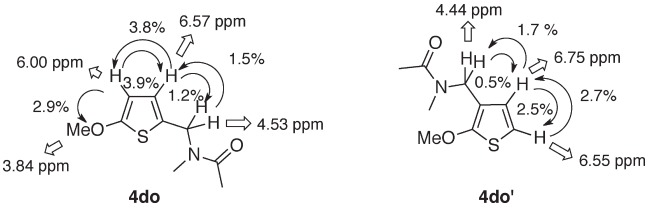

FIGURE 1. NOE analysis (irradiation to the major rotamers).

3,5-Bis(*N*-acetyl-*N*-methylaminomethyl)-2-methoxythiophene (4do″). A pale yellow oil. Each component was observed as a set of 4−7 peaks in ^{1}H NMR due to existence of 4 rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09/2.10/2.11/2.19 (s, 6 H), 2.89/2.91/2.92/2.93/2.95/2.97 (s, 6 H), 3.87/3.888/3.892 (s, 3 H), 4.27/4.28/4.37/4.44/4.48/4.49/4.51 (s, 4 H), 6.48/6.50/6.62/6.63 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 21.8, 21.9, 29.7, 33.0, 33.1, 33.2, 35.3, 35.4, 35.56, 35.63, 41.6, 41.7, 46.0, 46.5, 50.19, 50.22, 61.6, 61.8, 62.1, 67.1, 114.9, 116.0, 117.1, 124.0, 124.8, 125.4, 125.6, 125.8, 126.0, 126.5, 161.5, 162.2, 170.2, 170.49, 170.54, 170.56, 170.58, 170.59. HRMS (ESI) calcd for $C_{13}H_{20}N_2O_3S$: $[M + Na]^+$, 307.1087. Found: m/z 307.1099.

***N*-[(2,4-Dimethoxylphenyl)methyl]-*N*-methylacetamide (4dp).** A pale brown oil. Observed as two rotamers of 63/37 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15/2.11 (s, 3 H), 2.88/2.93 (s, 3 H), 3.80/3.79 (s, 3 H), 3.805/3.797 (s, 3 H), 4.41/4.53 (s, 2 H), 6.45/6.44 (d/dd, J = 8.5/8.8, 2.3 Hz, 1 H), 6.46/6.44 (s/d, J = 2.3 Hz, 1 H), 6.95/7.14 (d, J = 8.5/8.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.9, 33.3, 35.8, 44.7, 49.5, 55.2, 55.31, 55.34, 55.4, 98.3, 98.6, 103.9, 104.2, 116.9, 118.0, 128.1, 130.4, 158.2, 158.5, 160.1, 160.5, 170.7, 171.2. HRMS (ESI) calcd for $C_{12}H_{17}NO_3$: $[M + Na]^+$, 246.1101. Found: m/z 246.1103.

***N*-[(2,6-Dimethoxylphenyl)methyl]-*N*-methylacetamide (4dp′).** A pale brown solid. This product could not be isolated in a pure form, being contaminated with **4dp** (**4dp′**:**4dp** = 93:7). **4dp′** was observed as two rotamers of 80/20 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30/2.08 (s, 3 H), 2.73/2.73 (s, 3 H), 3.82/3.81 (s, 6 H), 4.54/4.72 (s, 2 H), 6.56/6.55 (d, J = 8.4/8.3 Hz, 2 H), 7.24/7.23 (t, J = 8.4/8.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 29.7, 31.4, 38.4, 42.4, 55.6, 55.8, 103.60, 103.63, 112.3, 112.8, 129.0, 129.5, 159.0, 159.4. HRMS (ESI) calcd for $C_{12}H_{17}NO_3$: $[M + Na]^+$, 246.1101. Found: m/z 246.1089.

1,5-Bis(*N*-acetyl-*N*-methylaminomethyl)-2,4-dimethoxybenzene (4dp″). A white solid. Each component was observed as a set of 2−4 peaks in ^{1}H NMR due to existence of 3 rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11/2.17/2.18 (s, 6 H), 2.82/2.91/2.92 (s, 6 H), 3.82/3.83/3.84/3.85 (s, 6 H), 4.38/4.40/4.52 (s, 4 H), 6.42/6.44/6.46 (s, 1 H), 6.77/6.88/6.94 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.8, 21.9, 29.6, 32.8, 32.9, 35.8, 35.9, 44.92, 44.94, 49.50, 49.52, 55.37, 55.44, 55.57, 55.58, 94.78, 94.81, 95.0, 116.0, 116.1, 117.0, 128.6, 129.7, 130.2, 157.6, 157.8, 158.1, 158.2, 170.7 (broad), 171.0 (broad). HRMS (ESI) calcd for $C_{16}H_{24}N_2O_4$: $[M + Na]^+$, 331.1628. Found: m/z 331.1614.

***N*-[(2-Methoxy-6-methoxycarbonyl-1-naphthyl)methyl]-*N*-methylacetamide (4dq).** A white solid. Observed as two rotamers of 84/16 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10/2.41 (s, 3 H), 2.72/2.62 (s, 3 H), 3.95/3.97 (s, 3 H), 4.00/4.00 (s, 3 H), 5.16/4.96 (s, 2 H), 7.34/7.36 (d, J = 9.1/9.0 Hz, 1 H), 7.94/7.96 (d, J = 9.1/9.0 Hz, 1 H), 8.05/7.99 (d, J = 8.9/9.1 Hz, 1 H), 8.15/8.09 (d, J = 9.1/8.8 Hz, 1 H), 8.53/8.58

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(s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 21.9, 30.7, 33.7, 39.0, 43.7, 52.0, 52.1, 56.1, 56.3, 113.2, 113.3, 116.2, 117.8, 122.1, 124.3, 125.1, 125.3, 126.5, 126.6, 127.8, 128.0, 131.4, 131.5, 131.98, 132.01, 135.67, 135.72, 157.4, 157.9, 166.9, 167.2, 170.3, 170.8. HRMS (ESI) calcd for $C_{17}H_{19}NO_4$: $[M + Na]^+$, 324.1212. Found: m/z 324.1194.

***N*-[(6-Bromo-2-methoxy-1-naphthyl)methyl]-*N*-methylacetamide (4dr).** A brownish solid. Observed as two rotamers of 87/13 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09/2.39 (s, 3 H), 2.72/2.60 (s, 3 H), 3.96/3.95 (s, 3 H), 5.12/4.91 (s, 2 H), 7.29/7.31 (d, J = 9.1/8.7 Hz, 1 H), 7.53/7.56 (d, J = 9.2/9.2 Hz, 1 H), 7.72/7.76 (d, J = 9.1/8.7 Hz, 1 H), 7.91/7.96 (s, 1 H), 8.02/7.79 (d, J = 9.2/9.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 21.9, 30.7, 33.8, 39.0, 43.7, 56.2, 56.5, 113.7, 113.8, 116.4, 117.2, 117.6, 118.1, 123.8, 126.2, 127.9, 129.0, 129.5, 130.0, 130.2, 130.4, 130.5, 130.7, 131.9, 132.0, 156.17, 156.23, 170.3, 170.7. HRMS (ESI) calcd for $C_{15}H_{16}BrNO_2$: $[M + Na]^+$, 344.0262. Found: m/z 344.0250.

***N*-[(2-Methoxy-1-naphthyl)methyl]-*N*-methylacetamide (4ds).** A white solid. Observed as two rotamers of 82/18 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11/2.42 (s, 3 H), 2.73/2.63 (s, 3 H), 3.966/3.959 (s, 3 H), 5.17/4.96 (s, 2 H), 7.29/7.30 (d, J = 8.4/8.4 Hz, 1 H), 7.35/7.37 (t, J = 7.6/7.6 Hz, 1 H), 7.50/7.52 (t, J = 7.4/7.4 Hz, 1 H), 7.78/7.82 (d, J = 8.2/8.2 Hz, 1 H), 7.83/7.87 (d, J = 9.0/9.0 Hz, 1 H), 8.11/7.92 (d, J = 8.7/8.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.0, 30.6, 33.6, 39.0, 43.7, 56.1, 56.4, 112.7, 112.8, 115.9, 117.6, 121.9, 123.5, 123.7, 124.0, 127.1, 127.2, 128.1, 128.75, 128.82, 129.0, 129.9, 130.3, 133.3, 133.4, 155.9, 156.0, 170.4 (broad). HRMS (ESI) calcd for $C_{15}H_{17}NO_2$: $[M + Na]^+$, 266.1151. Found: m/z 266.1138.

***N*-[(2-Methoxy-5-methylphenyl)methyl]-*N*-methylacetamide (4dt).** A pale yellow oil. Observed as two rotamers of 62/38 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13/2.15 (s, 3 H), 2.28/2.26 (s, 3 H), 2.93/2.95 (s, 3 H), 3.81/3.79 (s, 3 H), 4.46/4.59 (s, 2 H), 6.78/6.76 (d, J = 8.4/8.2 Hz, 1 H), 6.85/6.99 (s, 1 H), 7.06/7.02 (d, J = 8.4/8.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.47, 20.52, 21.3, 21.8, 33.6, 35.9, 45.0, 49.7, 55.2, 55.4, 110.1, 110.3, 124.2, 125.1, 127.6, 128.6, 128.8, 129.8, 129.86, 129.89, 155.0, 155.5, 170.7, 171.3. HRMS (ESI) calcd for $C_{12}H_{17}NO_2$: $[M + Na]^+$, 230.1157. Found: m/z 230.1143.

Iron-Catalyzed Oxidative Coupling of Alkylamides with Arenes Using the Amides as Solvents (Table 4). To a solution of $FeCl_3$ (4.1 mg, 25 μmol) in an amide (**1**, 1.0 mL) in a 20 mL Schlenk tube were added successively an arene (**3**, 0.25 mmol) and *t*-BuOO*t*-Bu (140 μL, 0.75 mmol). After stirring at 120 °C for the time specified in Table 4, the reaction mixture was diluted with $CHCl_3$−MeOH (9:1, 100 mL) and passed through a pad of SiO_2. Evaporation of the solvent and the amide followed by purification with PTLC (SiO_2) gave the corresponding coupling products (**4**). The products were further purified with GPC if necessary.

***N*-Methyl-*N*-[(1-methyl-3-indolyl)methyl]acetamide (4du).**[28] A yellow oil. Observed as two rotamers of 65/35 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11/2.26 (s, 3 H), 2.91/2.98 (s, 3 H), 3.76/3.78 (s, 3 H), 4.73/4.67 (s, 2 H), 7.04/6.91 (s, 1 H), 7.12/7.14 (t, J = 7.3/7.5 Hz, 1 H), 7.24/7.25 (t, J = 7.9/8.3 Hz, 1 H), 7.30/7.33 (d, J = 8.3/8.2 Hz, 1 H), 7.70/7.52 (d, J = 7.9/8.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.9, 32.6, 32.7, 33.2, 34.9, 41.4, 46.6, 109.1, 109.5, 110.0, 110.6, 118.5, 119.2, 119.4, 119.5, 121.7, 122.0, 126.5, 126.6, 127.3, 128.5, 137.0, 137.2, 170.1, 173.9. HRMS (ESI) calcd for $C_{13}H_{16}N_2O$: $[M + Na]^+$, 239.1155. Found: m/z 239.1154.

***N*-(3-Indolylmethyl)-*N*-methylacetamide (4dv).**[29] A pale yellow oil. Observed as two rotamers of 65/35 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12/2.26 (s, 3 H), 2.91/2.99 (s, 3 H), 4.76/4.69 (s, 2 H), 7.18/7.06 (d, J = 2.4/2.3 Hz, 1 H), 7.13/7.15 (t, J = 7.5/7.5 Hz, 1 H), 7.21/7.24 (t, J = 7.6/7.6 Hz, 1 H), 7.37/7.41 (d, J = 8.1/8.2 Hz, 1 H), 7.72/7.53 (d, J = 7.9/7.9 Hz, 1 H), 8.18/8.29 (bs, 1 H).

***N*-Methyl-*N*-[(5-pentyl-2-furyl)methyl]acetamide (4dw).** A pale yellow oil. Observed as two rotamers of 52/48 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−0.94 (m, 3 H), 1.27−1.38 (m, 4 H), 1.61/1.61 (quint, J = 7.3/7.3 Hz, 2 H), 2.22/2.10 (s, 3 H), 2.57/2.57 (t, J = 7.6/7.6 Hz, 2 H), 2.98/2.93 (s, 3 H), 4.36/4.51 (s, 2 H), 5.90/5.89 (d, J = 3.1/2.9 Hz, 1 H), 6.08/6.11 (d, J = 3.1/2.9 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.92, 13.94, 21.5, 21.8, 22.30, 22.33, 27.5, 27.6, 27.9, 28.0, 31.29, 31.30, 33.2, 35.4, 43.3, 47.6, 105.18, 105.24, 108.4, 108.8, 148.0, 149.0, 156.4, 156.9, 170.3, 170.7. HRMS (ESI) calcd for $C_{13}H_{21}NO_2$: $[M + Na]^+$, 246.1465. Found: m/z 246.1475.

***N*-Methyl-*N*-[(2,4,6-trimethoxyphenyl)methyl]acetamide (4dx).** A white solid. Observed as two rotamers of 80/20 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26/2.05 (s, 3 H), 2.70/2.70 (s, 3 H), 3.78/3.77 (s, 6 H), 3.803/3.799 (s, 3 H), 4.43/4.61 (s, 2 H), 6.11/6.11 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.1, 31.1, 33.7, 38.0, 42.1, 55.2, 55.3, 55.5, 55.7, 90.2, 90.3, 104.9, 105.4, 159.7, 160.0, 160.9, 161.1, 170.0, 170.7. HRMS (ESI) calcd for $C_{13}H_{19}NO_4$: $[M + Na]^+$, 276.1206. Found: m/z 276.1203.

2,4-Bis(*N*-acetyl-*N*-methylaminomethyl)-1,3,5-trimethoxybenzene (4dx″). A white solid. Each component was observed as a set of 2−4 peaks in ^{1}H NMR due to existence of 3 rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ2.06/2.07/2.27/2.28 (s, 6 H), 2.68/2.69/2.70 (s, 6 H), 3.64/3.66 (s, 3 H), 3.817/3.824/3.830 (s, 6 H), 4.45/4.46/4.65/4.66 (s, 4 H), 6.28/6.29 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.0, 22.1, 31.15, 31.17, 33.68, 33.71, 38.5, 38.6, 43.0, 55.5, 55.6, 55.71, 55.74, 62.2, 62.6, 63.1, 91.29, 91.31, 91.5, 109.9, 110.1, 110.3, 110.5, 159.4, 159.6, 159.7, 159.86, 159.90, 160.3, 160.7, 170.2, 170.3, 170.7, 170.8. HRMS (ESI) calcd for $C_{17}H_{26}N_2O_5$: $[M + Na]^+$, 361.1734. Found: m/z 361.1727.

***N*-[1-(1-Methyl-3-indolyl)ethyl]acetamide (4gu).** A brownish solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (d, J = 6.8 Hz, 3 H), 1.96 (s, 3 H), 3.76 (s, 3 H), 5.46 (quint, J = 6.8 Hz, 1 H), 5.68 (bs, 1 H), 6.99 (s, 1 H), 7.13 (t, J = 7.4 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 7.9 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 23.5, 32.7, 41.9, 109.4, 116.7, 119.3, 119.5, 122.1, 126.0, 126.3, 137.3, 169.0. HRMS (ESI) calcd for $C_{13}H_{16}N_2O$: $[M + Na]^+$, 239.1155. Found: m/z 239.1165.

***N*-[1-(2,4,6-Trimethoxyphenyl)ethyl]acetamide (4gx).** A colorless oil. Observed as two rotamers of 94/6 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34/1.45 (d, J = 6.8/6.8 Hz, 3 H), 1.93/2.04 (s, 3 H), 3.79/3.79 (s, 3 H), 3.84/3.83 (s, 6 H), 5.76/5.18 (dq, J = 9.5, 6.8/10.3, 6.8 Hz, 1 H), 6.13/6.12 (s, 2 H), 6.83/6.83 (d, J = 8.8/8.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.2, 23.6, 28.5, 29.6, 40.2, 44.2, 55.2, 55.6, 55.7, 90.7, 91.0, 111.2, 111.6, 157.9, 158.3, 160.1, 160.3, 168.5 (broad). HRMS (ESI) calcd for $C_{13}H_{19}NO_4$: $[M + Na]^+$, 276.1206. Found: m/z 276.1203.

***N*-Ethyl-*N*-[(1-methyl-3-indolyl)methyl]acetamide (4hu).** A brownish oil. Observed as two rotamers of 64/36 ratio in ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15/1.12 (t, J = 7.1/7.1 Hz, 3 H), 2.13/2.21 (s, 3 H), 3.27/3.47 (q, J = 7.1/7.1 Hz, 2 H), 3.76/3.77 (s, 3 H), 4.73/4.66 (s, 2 H), 7.05/6.89 (s, 1 H), 7.12/7.14 (t, J = 7.4/7.4 Hz, 1 H), 7.23/7.27 (t, J = 7.6/7.6 Hz, 1 H), 7.29/7.33 (d, J = 8.3/8.2 Hz, 1 H), 7.68/7.52 (d, J = 7.8/8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8, 13.5, 21.5, 21.8, 32.6, 32.8, 38.4, 40.2, 41.5, 44.1, 109.1, 109.5, 110.6, 111.0, 118.5, 119.26, 119.33, 119.4, 121.7, 122.1, 126.6, 127.0, 127.4, 128.6, 136.9, 137.3, 169.8, 170.3. HRMS (ESI) calcd for $C_{14}H_{18}N_2O$: $[M + Na]^+$, 253.1311. Found: m/z 253.1302.

***N*-Methyl-*N*-[1-(1-methyl-3-indolyl)ethyl]acetamide (4hu′).** This product could not be isolated in a pure form. The following data were obtained from spectra of a mixture with **4hu**

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(**4hu**:**4hu′** = 91:9). In ^{1}H NMR, several peaks of the aromatic region (3 protons of the benzene ring of the indole) of **4hu′**, which was observed as two rotamers of 70/30 in ^{1}H NMR, could not be read because they are not sufficiently separated from those of **4hu**. In ^{13}C NMR, many peaks could not be detected. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49/1.61 (d, J = 6.8/6.8 Hz, 3 H), 1.94/2.35 (s, 3 H), 2.61/2.63 (s, 3 H), 3.76/3.75 (s, 3 H), 6.29/5.30 (q, J = 6.8/6.8 Hz, 1 H), 6.95/6.91 (s, 1 H), 7.54/7.41 (d, J = 7.9/7.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 16.4, 22.4, 23.3, 29.6, 44.2, 109.0, 109.4, 119.8, 122.0, 122.1, 126.5. GC−MS gave no information as **4hu** and **4hu′** have the same retention time on GC.

1-Methyl-5-(1-methyl-3-indolyl)-2-pyrrolidone (4bu).[8] A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14−2.23 (m, 1 H), 2.40−2.56 (m, 2 H), 2.60−2.68 (m, 1 H), 2.71 (s, 3 H), 3.78 (s, 3 H), 4.84 (t, J = 7.2 Hz, 1 H), 6.97 (s, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.27 (t, J=7.6 Hz, 1 H), 7.34 (d, J=8.3 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H).

1-[(1-Methyl-3-indolyl)methyl]-2-pyrrolidone (4bu′).[8] A pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (quint, J = 7.4 Hz, 2 H), 2.41 (t, J = 8.0 Hz, 2 H), 3.27 (t, J = 7.1 Hz, 2 H), 3.77 (s, 3 H), 4.62 (s, 2 H), 7.03 (s, 1 H), 7.13 (t, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.67 (d, J = 7.9 Hz, 1 H).

1-Methyl-5-(2,4,6-trimethoxyphenyl)-2-pyrrolidinone (4bx).[30] A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97−2.07 (m, 1 H), 2.25−2.36 (m, 1 H), 2.38−2.47 (m, 1 H), 2.53 (s, 3 H), 2.53−2.63 (m, 1 H), 3.77 (bs, 3 H), 3.81 (s, 6 H), 5.23 (dd, J = 9.6, 4.6 Hz, 1 H), 6.12 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 27.4, 31.2, 54.0, 55.3, 55.8, 90.6 (broad), 108.5, 159.8 (broad), 160.9, 175.4. HRMS (ESI) calcd for $C_{14}H_{19}NO_4$: $[M + Na]^+$, 288.1206. Found: m/z 288.1201.

1-[(2,4,6-Trimethoxyphenyl)methyl]-2-pyrrolidinone (4bx′). A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (quint, J = 7.5 Hz, 2 H), 2.36 (t, J = 8.1 Hz, 2 H), 3.12 (t, J = 7.0 Hz, 2 H), 3.79 (s, 6 H), 3.82 (s, 3 H), 4.48 (s, 2 H), 6.12 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 31.4, 34.6, 46.1, 55.3, 55.7, 90.3, 104.7, 159.9, 161.0, 174.2. HRMS (ESI) calcd for $C_{14}H_{19}NO_4$: $[M + Na]^+$, 288.1206. Found: m/z 288.1202.

3-Methyl-4-(1-methyl-3-indolyl)-1,3-oxazolidin-2-one (4iu). A pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (s, 3 H), 3.80 (s, 3 H), 4.36 (dd, J = 8.8, 7.7 Hz, 1 H), 4.60 (t, J = 8.8 Hz, 1 H), 4.97 (dd, J = 8.8, 7.7 Hz, 1 H), 7.09 (s, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.6 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 7.60 (d, J = 7.9 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 32.9, 55.4, 68.4, 109.8, 110.3, 118.9, 120.0, 122.5, 125.3, 128.3, 137.7, 158.4. HRMS (ESI) calcd for $C_{13}H_{14}N_2O_2$: $[M + Na]^+$, 253.0947. Found: m/z 253.0938.

3-[(1-Methyl-3-indolyl)methyl]-1,3-oxazolidin-2-one (4iu′). An orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 (t, J = 8.0 Hz, 2 H), 3.78 (s, 3 H), 4.22 (t, J = 8.0 Hz, 2 H), 4.61 (s, 2 H), 7.06 (s, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 39.3, 43.9, 61.6, 109.0, 109.4, 119.1, 119.7, 122.1, 127.3, 128.5, 137.1, 158.3. HRMS (ESI) calcd for $C_{13}H_{14}N_2O_2$: $[M + Na]^+$, 253.0947. Found: m/z 253.0955.

3-Methyl-4-(2,4,6-trimethoxyphenyl)-1,3-oxazolidin-2-one (4ix). A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.80 (s, 6 H), 3.82 (s, 3 H), 4.22 (dd, J = 8.2, 5.5 Hz, 1 H), 4.47 (dd, J = 9.9, 8.2 Hz, 1 H), 5.38 (dd, J = 9.9, 5.5 Hz, 1 H), 6.13 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 51.0, 55.3, 55.8, 66.9, 90.6 (broad), 105.1, 159.0, 160.1 (broad), 161.7. HRMS (ESI) calcd for $C_{13}H_{17}NO_5$: $[M + Na]^+$, 290.0999. Found: m/z 290.0993.

3-[(2,4,6-Trimethoxyphenyl)methyl]-1,3-oxazolidin-2-one (4ix′). A white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (t, J = 8.1 Hz, 2 H), 3.80 (s, 6 H), 3.82 (s, 3 H), 4.18 (t, J = 8.1 Hz, 2 H), 4.47 (s, 2 H), 6.12 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 43.8, 55.3, 55.7, 61.6, 90.3, 104.0, 158.1, 159.9, 161.3. HRMS (ESI) calcd for $C_{13}H_{17}NO_5$: $[M + Na]^+$, 290.0999. Found: m/z 290.0990.

Synthesis of (±)-Crispine and (±)-Trolline (Scheme 3). To a solution of $FeCl_3$ (1.2 mg, 7.4 μmol) in 1,2-dichloroisobutane (DCB, 1,2-dichloro-2-methylpropane, 0.50 mL) and t-BuOH (0.50 mL) in a 20 mL Schlenk tube were added N-[2-(3,4-dimethoxyphenyl)ethyl]-2-pyrrolidone[31] (**5**, 187 mg, 0.750 mmol) and t-BuOOt-Bu (the amount specified in Scheme 3). After stirring at 110 °C for the time specified in Scheme 3, the reaction mixture was diluted with $CHCl_3$−MeOH (9:1, 100 mL) and passed through a pad of SiO_2. Evaporation of the solvent followed by purification with PTLC (SiO_2, $CHCl_3$/MeOH = 95/5) and GPC gave 8,9-dimethoxy-1,5,6,10b-tetrahydro-2H-pyrrolo[2,1-a]isoquinolin-3-one (**6**) as a pale brown solid.[32,33] MP: 108−109 °C (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.88 (m, 1 H), 2.40−2.48 (m, 1 H), 2.51−2.72 (m, 3 H), 2.82−2.93 (m, 1 H), 3.00 (td, J = 12.2, 4.4 Hz, 1 H), 3.847 (s, 3 H), 3.854 (s, 3 H), 4.29 (ddd, J = 12.9, 6.1, 2.0 Hz, 1 H), 4.71 (t, J = 7.9 Hz, 1 H), 6.56 (s, 1 H), 6.61 (s, 1 H).

To a suspension of $LiAlH_4$ (10.4 mg, 0.274 mmol) in THF (0.50 mL) in a 20 mL Schlenk tube was added dropwise a solution of **6** (61.8 mg, 0.250 mmol) in THF (1.0 mL) at 0 °C. After stirring at 40 °C for 4 h, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification with PTLC (SiO_2, EtOAc/Et_3N = 95/5) gave (±)-crispine A (55.4 mg, 95% yield) as a pale yellow solid.[17] MP: 90−91 °C (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67−1.78 (m, 1 H), 1.80−2.00 (m, 2 H), 2.27−2.37 (m, 1 H), 2.54−2.62 (m, 1 H), 2.62−2.69 (m, 1 H), 2.69−2.77 (m, 1 H), 2.96−3.09 (m, 2 H), 3.13−3.19 (m, 1 H), 3.45 (t, J = 8.2 Hz, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.56 (s, 1 H), 6.60 (s, 1 H).

To a solution of **6** (49.5 mg, 0.200 mmol) in CH_2Cl_2 (0.20 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) at −20 °C. After stirring for 18 h at −20 °C, the reaction mixture was quenched with MeOH (5.0 mL), and the solvent was evaporated under the reduced pressure. The MeOH addition/evaporation process was repeated 5 times. The residue was washed with a small amount (0.50 mL) of MeOH to give (±)-trolline (42.0 mg, 96% yield) as a white solid.[18,34] MP: 252 °C dec (MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.49−1.65 (m, 1 H), 2.18−2.26 (m, 1 H), 2.35−2.45 (m, 1 H), 2.50−2.64 (m, 3 H), 2.84−2.96 (m, 1 H), 3.93−3.99 (m, 1 H), 4.57 (t, J = 7.8 Hz, 1 H), 6.49 (s, 1 H), 6.51 (s, 1 H).

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Supporting Information Available: Characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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