Selective Synthesis of β-Alkylpyrroles

Teruhisa Tsuchimoto*[^a]
Abstract: β-Alkylpyrroles are key structural motifs found in many natural products and biologically active compounds as well as functional organic materials. For this reason, synthetic chemists continue to be interested in construction of the framework of β-alkylpyrroles. Due to sufficient aromaticity and π-excessive nature of pyrroles, a straightforward approach to β-alkylpyrroles should be electrophilic aromatic substitution (S_{E}Ar) toward the pyrrole ring. However, since a primary nucleophilic site of pyrroles is an α-position, some “trick” is required to direct incoming alkyl electrophiles toward a β-position. This Concept article focuses on presenting previous efforts that have been devoted to the synthesis of β-alkylpyrroles, mainly through the S_{E}Ar route.

Keywords: alkylation · electrophilic aromatic substitution · heterocycles · pyrroles · regioselectivity

Introduction

Pyrroles, in which two electrons on a nitrogen atom and four π-electrons from each of four carbon atoms contribute to an aromatic sextet, constitute an important class of nitrogen-containing heterocyclic arenes.[11] The five-membered ring system is now well recognized as “electron-rich”, which is also referred to as “π-excessive”, due to delocalization of the two electrons from the nitrogen atom to other carbon members.[12] In particular relation to these properties, electrophilic aromatic substitution (S_{E}Ar) reaction of pyrroles has a long-standing history in synthetic organic chemistry, in terms of introduction of various functional groups onto the pyrrole ring.[13] As a distinct tendency, the S_{E}Ar reaction occurs predominantly at an α-carbon atom, the position adjacent to the nitrogen atom, because attack of an electrophile to the α-position leads to a more stable cation intermediate having three resonance forms, while reaction at a β-carbon atom gives a less stable cation with only two resonance forms (Scheme 1, electrophile = El).[2] Due to such electronic characteristics of pyrroles, regioselective functionalization at the β-position is still a challenging research issue in the field of organic chemistry.

Pyrroles having simple and functionalized alkyl chains at the β-position are important frameworks found in natural products[3] as well as functional organic materials[4] including, for instance, conducting polymers and gas-sensitive membranes. β-Alkylpyrroles are crucial also as building blocks for construction of porphyrins.[5] Developing a useful synthetic strategy for β-alkylpyrroles is thus of outstanding importance in a variety of aspects. Intra- and intermolecular ring-closing reactions are obvious candidates for the synthesis of β-alkylpyrroles,[5, 6] but, because of the sufficient aromaticity and π-excessive nature of pyrroles, direct installation of alkyl groups onto pyrroles by way of S_{E}Ar process seems to be more straightforward to access β-alkylpyrroles. However, as described in the previous paragraph, the preferential α-nucleophilicity of pyrroles actually makes the β-alkylation considerably difficult. In fact, a vast amount of research has thus far been devoted to exclusive or selective α-alkylation of pyrroles, in which various organic molecules such as alkynes,[7] alcohols,[8] allylic acetates,[9] ketones,[10] imines,[11] epoxides,[12] aziridines[12] and diazo compounds[13] have been the alkylating agents of choices. Under such situation, how do you alkylate pyrroles at the β-position regioselectively? In order to offer clear and valuable guidance to the query, this Concept article will focus on providing an overview with respect to “selective synthesis of β-alkylpyrroles from pyrroles” mainly through the S_{E}Ar route,[14] wherein our recent achievements will be also presented.

Use of Pyrroles with an Electron-Withdrawing Group at the α-Position

In the Friedel–Crafts reaction proceeding through S_{E}Ar process, it is well-known that electron-withdrawing groups (EWGs) such as carbonyl and cyano substituents on a benzene ring act as meta-directing groups for incoming electrophiles (Scheme 2).[15] The regiochemical nature concerning the meta-orientation extends also to pyrroles,[16] while, strictly, the terms ortho/meta/para cannot be applied to such five-membered situation. Thus, the strategic “trick” in this section is obstruction of electrophilic attack to the α-position, by controlling the electronic nature of the pyrrole ring with the aid of the EWG attached on the α-carbon (Scheme 2).

With respect to the S_{E}Ar reaction of pyrroles I, Rinkes reported the first example as nitration with HNO_{3} already in 1934, while its β-regioselectivity is moderate.[17] After 30 years since the pioneering study, Anderson and Hopkins first applied the strategy to Lewis acid-promoted β-alkylation using 2-propyl chloride as an alkylating agent.[18] The
The outline of the strategy is illustrated in Scheme 3. Although the key process is the second stage (1 to 2), two further steps for the introduction and removal of the EWG are, in practice, necessary to obtain desired β-alkylpyrroles 3.[19] The representative results for the β-2-propylation of 1 are collected in Table 1.

Table 1. Lewis acid-mediated β-2-propylation of pyrroles 1.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWG</th>
<th>Lewis acid</th>
<th>t [h]</th>
<th>Yield [%] of 4-6</th>
<th>4/5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>AlCl₃</td>
<td>2</td>
<td>&gt;99:1:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>GaCl₃</td>
<td>1</td>
<td>&gt;99:1:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>COMe</td>
<td>AlCl₃</td>
<td>4</td>
<td>93:3:4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CO₂Me</td>
<td>AlCl₃</td>
<td>18</td>
<td>56:19:25</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
<td>GaCl₃</td>
<td>1</td>
<td>85:10:5</td>
<td></td>
</tr>
</tbody>
</table>

[a] The reaction was performed in CS₂ (50 mL) at 50°C using 1 (10 mmol), 2-propyl chloride (10 mmol) and a Lewis acid (12 mmol). [b] Performed with AlCl₃ (24 mmol).

The EWG on the pyrrole α-position certainly overrides the intrinsic pyrrole regiochemistry, and hence the substitution selectively takes place at the C4. However, both the β-selectivity and yield depend on not only the EWG but also the Lewis acid. As Table 1 indicates, 1 having CHO appears to be the most reactive (entries 1 and 2) and is converted exclusively to 4-(prop-2-yl)pyrrole 4. In contrast, the use of the acetyl and ester derivatives results in the lower β-selectivities and, in addition, contamination with disubstituted pyrroles 6 (entries 3–5). For the formation of 5, rearrangement of the iPr group from the C4 to the C5 rather than direct alkylation at the C5 is proposed to be suitable, on the basis of some experimental observations.

Anderson and co-workers also reported tert-butylation of 1 under essentially the identical conditions as above (Table 2).[20] Due to much more facile rearrangement of the tBu group, prudent choices of both the EWG and Lewis acid are required for high β-selectivity, which is thus attained in the use of 1 with the CN group and of GaCl₃ as a Lewis acid (entry 4). No di-tert-butylation occurs here in any cases.

Table 2. Lewis acid-mediated β-tert-butylation of pyrroles 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWG</th>
<th>Lewis acid</th>
<th>T [°C]</th>
<th>t [min]</th>
<th>Yield [%] of 7 8</th>
<th>7/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂Me</td>
<td>AlCl₃</td>
<td>20</td>
<td>40</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CO₂Me</td>
<td>GaCl₃</td>
<td>40</td>
<td>40</td>
<td>91</td>
<td>62:38</td>
</tr>
<tr>
<td>3</td>
<td>CN</td>
<td>AlCl₃</td>
<td>40</td>
<td>30</td>
<td>95</td>
<td>87:13</td>
</tr>
<tr>
<td>4</td>
<td>CN</td>
<td>GaCl₃</td>
<td>40</td>
<td>30</td>
<td>&gt;97:&lt;3</td>
<td>7/8</td>
</tr>
</tbody>
</table>

[a] AlCl₃ (2.2 equiv to 1) was used. [b] The Lewis acid (1.1 equiv to 1) was used.

Now, actually, it is unnecessary to pre-synthesize pyrroles 1 (EWG = CHO, COMe, CO₂Me, CN) that have appeared in this section, because they are available as commercial sources, in contrast to the 1960s and early 70s. Accordingly, total efficiency of the method relies on facility of removing the EWG.[21] In most cases, decarboxylation of the carboxyl group is adopted as a final step (Scheme 4). When EWGs are CO₂Me and CN, they are removable readily in one-pot, by the hydrolysis-decarboxylation sequences.[20b] Removal of CHO from a pyrrole ring is achieved in two steps, which
are oxidation of the CHO to CO₂H and then decarboxylation.[22]

The β-directing effect of the EWG can be utilized also for synthesis of β-n-alkylpyrroles, though no direct alkylation of pyrrole rings is involved. As Scheme 5 indicates, the method disclosed by Anderson and co-workers consists of the following three steps:[20b,23] 1) the introduction of the thioester group onto the pyrrole α-carbon, 2) the regioselective β-acylation of 9 via S-EAr reaction, and 3) the synthesis of β-n-alkylpyrroles 11 by the combination of the Wolff–Kishner reduction of the carbonyl moiety and the removal of the thioester group by the hydrolysis and decarboxylation. The acylation of 9 giving 10a-c seems to proceed in a complete β-regioselective manner (Scheme 6).

Acylation and/or nitration of N-Ps–pyrrole (12a), disclosed independently by Anderson’s and Rokach’s groups in 1981, are the first examples utilizing the β-directing effect of the As group.[24] In almost all the reactions, remarkable β-selectivities are recorded. Two years later, Anderson and colleagues again first demonstrated direct alkylation of 12a (strategy A), but only the tert-butylation proceeds in a regioselective manner (Scheme 8, 12a to 13a).[25] Treatment of 13a with KOH in aqueous MeOH then gives β-tert-butylpyrrole (14a). In contrast to the tert-butylation, other alkylation with 2-propyl chloride or ethyl bromide results in much lower β-selectivity and yield of the product. Thus, the major inconvenience of the strategy A is that an alkyl group to be installed successfully to the β-position of 12 must be bulky in size.

Scheme 7. Schematic outline for synthesis of β-alkylpyrroles 14 with pyrroles 12 as starting substrates.

Kakushima and co-workers have reported the synthesis of β-alkylpyrrole 14b as the first performance of the strategy B, which, in detail, includes the following four steps: 1) the AlCl₃-mediated β-selective acetylation, 2) the transformation mediated by thallium nitrate,[26] 3) the hydrolysis of the ester part, and 4) the removal of the Ps group (Scheme 9).[27] The last two steps, both of which use bases, can be combined into a single operation (see, step b in Scheme 10). In contrast to the β-selective acylation observed in the first step, alteration of AlCl₃ into BF₃·OEt₂ drastically changes the orientation, thus leading to α-selective acylation.[27,28] A proper

Scheme 8. Synthesis of β-alkylpyrrole 14a based on strategy A.
A choice of a Lewis acid is thus highly important for the strategy to obtain \( \beta \)-acylpyrroles \( 15 \) selectively. The strategy is effective, especially for the synthesis of \( \beta \)-alkylpyrroles \( 14c-f \) bearing carboxyl, hydroxy and ester groups (Scheme 10).\(^{29}\)

Havinga and co-workers have reported a different approach of the strategy by means of more simple reaction sequences, which are the reduction of the carbonyl (the Clemmensen reduction in this case) following the \( \beta \)-acylation, and then the final desulfonylation, whereas the method includes the transformation of Cl to \( \text{SO}_3\text{Na} \). Unfortunately, details of the reaction conditions of as well as yield of the each step are not specified (Scheme 11).\(^{30}\)

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After the publication of the Havinga’s report, Rühr and co-workers refined the method by replacing toxic and acidic Zn–Hg/HCl with \( \text{NaAlH}_4(\text{OCH}_3)_3 \) (Red-Al), and thus synthesized several \( \beta \)-alkylpyrroles \( 14h \) with different lengths of alkyl chains, while the reduction of the carbonyl and the desulfonylation are performed in the reverse order, compared to the original Havinga’s method (Scheme 12).\(^{31}\)

Due to the reliability of the strategy reported by Havinga’s and Rühr’s groups, it has so far been utilized widely for preparing monomers directed towards poly(\( \beta \)-alkylpyrrole)s that are significant as conducting polymers, gas sensitive resistors, DNA sensors, and wool coating textiles.\(^{32,33}\) In other reports, reducing systems other than Red-Al and Zn–Hg/HCl are often selected.\(^{33}\)

Although a reasonable explanation why \( N \)-As–pyrroles \( 12 \) react with acylating agents selectively at the \( \beta \)-position should remain to be discussed further, its possible interpretation has recently been provided by Huffman and co-workers.\(^{34}\) In the \( \text{AlCl}_3 \)-mediated acylation of \( N \)-Ts–pyrrole \( (12b) \), they describe that high \( \beta \)-selectivities are ascribed to higher reactivity of in situ formed \( \beta \)-pyrrolyl–aluminum o-complex rather than that of \( \alpha \)-16 (Scheme 13). The formation of \( \alpha \)-16 and \( \beta \)-16 can be confirmed by D\textsubscript{2}O quenching of the reaction mixture, resulting in the incorporation of the D atom at the C2 and C3. They propose that the lower reactivity of \( \alpha \)-16 may be attributed to the following two aspects:

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Selective Synthesis of β-Alkylpyrroles

Use of Pyrroles with a Bulky Group on the Nitrogen Atom

A bulky group on a pyrrole nitrogen atom has a pronounced steric effect in S$_2$Ar reaction. A key “trick” in this section is thus to interfere with access of electrophiles to pyrrole α-positions, on the basis of steric shielding from the bulky substituent. For this purpose, groups such as triisopropylsilyl (TIPS) have been used as bulky substituents. Among them, the TIPS group is expected to be the most practical in terms of selectivity as well as ease of removable.

N-TIPS-β-bromopyrrole (20), derived selectively from the N-TIPS-β-alkylpyrroles 22, thus resulting from the bromine-lithium exchange followed by trapping of in situ formed pyrrolylium-lithium 21 with alkyl halides or aldehydes, while this idea includes no direct S$_2$Ar alkylation of pyrroles (Scheme 15).

Use of N-Metal–Pyrrole and Pyrrole–Metal Complexes

N-Metal–pyrrole species often undergo attack of electrophiles at the β-position. As the first example on this topic, in 1969, Castro and co-workers have reported that N-MgCl-pyrrole (24) in THF reacts with ethylene oxide to give 2-(pyrrol-3-yl)ethanol (25) exclusively, albeit in a low yield (Scheme 17).

By Harman and co-workers, β-selective alkylation of η$_1$-pyrrole–osmium(II) complex 29 has been achieved upon treatment with a range of alkylating agents (Scheme 18).

\[ \text{N}-\text{TIPS-β-bromopyrrole (20), derived selectively from the N-TIPS-β-alkylpyrroles 22,} \]

\[ \text{Use of N-Metal–Pyrrole and Pyrrole–Metal Complexes} \]

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\[ \text{CONCEPT} \]

\[ \text{Scheme 15. Synthesis of N-TIPS-β-alkylpyrrole 22.} \]

\[ \text{Scheme 16. Palladium-catalyzed synthesis of N-TIPS-β-alkylpyrroles 23.} \]

\[ \text{dpff = 1,1-bis(diphenylphosphino)ferrocene.} \]

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\[ \text{By Harman and co-workers, β-selective alkylation of η$_1$-pyrrole–osmium(II) complex 29 has been achieved upon treatment with a range of alkylating agents (Scheme 18).} \]

\[ \text{The complex (29) is readily prepared from [Os}^{\text{III}}\text{-}2\text{Cl}^+\text{-(NH$_3$)$_3$OT}]\text{OTF} (\text{TF} = \text{SO$_2$CF$_3$})\text{ and N-methylpyrrole in the presence of magnesium metal. The η$_1$ coordination disrupts delocalization of π electrons in the pyrrole ligand, thereby inducing enamine character to the pyrrole. This aspect, which is thus the “trick” in this system, effectively affects the β-alkylation toward the pyrrole ring. Alkylation agents include aldehydes, ketones, Michael acceptors, acetal} \]
and alkyl triflates. When these alkylating agents are used, 3H-pyrrolium species 30–35 are quite stable, and moderate external bases such as amines must be used to achieve re-aromatization (e.g., 35 to 37). Due to the stability of these 3H-pyrrolium systems, these reactions are negative to such undesired reactions as multiple alkylation and polymerization. In the use of a hard electrophile like methyl triflate, the alkylation at the nitrogen atom is competitive with the β-alkylation (35 vs 36). The β-alkylated pyrrole can be removed from the osmium metal simply by heating. With this chemistry, selective β-alkylation of an osmium–nitrogen-unsubstituted pyrrole complex is difficult since the alkylation is most likely to occur at the nitrogen atom. An asymmetric variant with the same strategy has been reported also by the Harman’s group.49b

Use of Simple Pyrroles: Indium-Catalyzed Reductive Alkylation with Alkynes or Carbonyl Compounds as Alkyl Group Suppliers

Recently, we have established a conceptually new strategy to introduce diverse alkyl groups onto pyrroles with perfect β-selectivity. Under indium catalysis, the strategy can be performed readily by a simple mixing of N-substituted pyrroles 39, EtSiH and either alkynes 3852 or carbonyl compounds (see below).53 The alkylne-based reaction, which has been developed prior to the reaction of carbonyl compounds, is the first example of catalytic β-alkylation of pyrroles in a single step. At first, we present the details of the alkyne-based reaction. The origin of the “trick” for the reaction is in our own previous research, which is the indium-catalyzed double addition of 39 to 38.54 Our original idea proposed as the working hypothesis is shown in Scheme 19. The important aspect is that β,β'-adducts 41 are formed selectively over other two isomers, that is, αβ-adducts 40 and α,α'-adducts in the double addition reaction.55 This interesting and unusual selectivity is responsible for the thermodynamic stability of 41, whose steric repulsion between the two pyrrolyl groups is the least among the three isomers, as shown at the bottom in Scheme 19. During the course of the mechanistic studies on the isomerization between 40 and 41, we envisaged that in sui trapping of cationic intermediate 42 with a hydride reagent would allow to develop an innovative one-step strategy for synthesizing β-alkylpyrroles 43.
The results acquired by applying our concept are summarized in Scheme 20. The β-alkylation can be performed by either method A or B, depending on the structure of $R^1$ and $R^2$. Method A is the simple procedure allowing the simultaneous treatment of $38$, $39$ and $Et_3SiH$ with the indium catalyst. In method B, $38$ and $39$ are pretreated with the catalyst before the reduction with $Et_3SiH$. With these two procedures, regiospecific β-alkylation by various combinations of substrates is feasible. The internal alkyne, 4-octyne, is also available, albeit requiring higher loadings of the pyrrole and indium catalyst at the higher temperature, compared to the standard conditions (Scheme 21). It is definitely worth noting that all of the reactions proceed with perfect β-selectivity.

![Scheme 21](image)

Scheme 21. Indium-catalyzed reductive β-alkylation of N-substituted pyrroles with 4-octyne. 4-Octyne (0.500 mmol), $R^2$-alkylpyrrole (1.50 mmol), $Et_3SiH$ (0.750 mmol), $InX_3$ (0.125–0.150 mmol, 25–30 mol%), 1,4-dioxane (1.0 mL). See ref. [52] and its Supporting Information for further details.

$R^1$: Method A is the simple procedure allowing the simultaneous treatment of $38$, $39$ and $Et_3SiH$ with the indium catalyst. In method B, $38$ and $39$ are pretreated with the catalyst before the reduction with $Et_3SiH$. With these two procedures, regiospecific β-alkylation by various combinations of substrates is feasible. The internal alkyne, 4-octyne, is also available, albeit requiring higher loadings of the pyrrole and indium catalyst at the higher temperature, compared to the standard conditions (Scheme 21). It is definitely worth noting that all of the reactions proceed with perfect β-selectivity.

![Scheme 22](image)

Scheme 22. Synthesis of nitrogen-unsubstituted β-alkylpyrroles 44. a) $TiCl_3$ (2.0 equiv), Li (13 equiv), $I_2$ (1.0 equiv), THF, RT, 16 h.

46 are slightly co-produced in the reaction of $N$-methylpyrrole with 2-methylfuran, the selectivity can be improved entirely by replacing $N$-methylpyrrole with pyrroles bearing the bulkier substituent ($R^2 = Bn$, $Bu$, $Ph$) on the nitrogen atom. Scheme 23 shows only the benzyl case. The synthetic reaction of the furylpyrrolylalkane can be regarded as substrate-selective double addition in which each one molecule of a pyrrole and a furan adds to an alkyne. This is the first example of the assembly of alkyne and two different heterocyclic arenes.

![Scheme 23](image)

Scheme 23. Indium-catalyzed synthesis of β-alkylpyrroles 45 incorporating carbon nucleophiles $[Nu(C) = 2$-methylfuran, $Me_3SiCN]$. $38$ (0.750 mmol), $39$ (1.00 mmol), $Nu(C)$ (0.750 or 1.00 mmol), $In(OTf)_3$ (62.5 mol%), 1,4-dioxane (0.7 or 2.0 mL). See ref. [56] and its Supporting Information for further details.

In spite of the outstanding simplicity of the alkyne-based β-alkylation, the scope of alkynes $38$ is restricted mainly to terminal alkynes, the terminal carbon of which is inevitably incorporated just as the methyl group into product 43. We therefore envisioned that replacing $38$ with carbonyl compounds 47 would drastically extend the diversity of alkyl groups installable onto $39$, giving 48 (Scheme 24). Moreover, it was expected that the use of 47, which is cheaper in general than 38, would make the process highly attractive and practical.

The one-step strategy does not work well for pyrrole ($R^2 = H$ in 39). However, a two-step strategy is reliable in this situation. Thus, the first step is the β-alkylation of $N$-benzylpyrrole $39a$ by method A or B. With the desired alkyl group in place, the benzyl group is removed with a low-valent titanium reagent, giving nitrogen-unsubstituted β-alkylpyrroles 44 (Scheme 22).

Besides the hydride nucleophile, 2-methylfuran and $Me_3SiCN$ can be used as carbon nucleophiles $[Nu(C)]$ for extension of a carbon–carbon bond, where method B using $In(OTf)_3$ as a catalyst is effective. The representative results are collected in Scheme 23. Although α-alkylpyrroles...
the primary alkyl group that is impossible to handle in the alkynyl variant. The carbon nucleophiles such as Me₃SiCN, 2,3-dimethylthiophene and 4-vinylanisole also participate well in this reaction (Scheme 26). Using these nucleophiles enables installation of the tertiary alkyl unit onto the β-position of 39. Worthy of note is that regioselectivities on pyrrole rings are perfectly controlled in all the cases.

Nitrogen-unsubstituted β-alkylpyrroles 50 are easily accessible also in this case, by employing the same procedure presented in Scheme 27. As can be seen from Schemes 25–27, the special emphasis in this research is that the indium-catalyzed β-alkylation combined with the de-benzylation can offer all six variations consisting of nitrogen-substituted and -unsubstituted β-alkylpyrroles 48–50 with primary, secondary and tertiary alkyl groups.

Despite that α,β- dipropyrylalkanes 51, which possibly lead to α-alkylpyrroles 55 by the elimination of the β-pyrrolyl ring, exist in the reaction mixture before the trapping with nucleophiles 48–52, a natural question is why no 55 is formed in this strategy. On the basis of experimental results, we can provide the most plausible interpretation for the question. In both the methods with alkynes and carbonyl compounds, the first step surely affords an isomeric mixture of dipropyrylalkanes, among which β,β'-isomers 52 predominate. After this stage, the exclusive generation of β-alkylpyrroles 56 is ascribed to two synergistic effects as shown in Scheme 28,

Scheme 24. Indium-catalyzed reductive β-alkylation of N-substituted pyrroles: Alkynes versus carbonyl compounds as sources of alkyl groups.

Scheme 25. Indium-catalyzed reductive β-alkylation of N-substituted pyrroles with carbonyl compounds and Et₂SiH. 47 (0.30 mmol), 39 (0.90–1.2 mmol), Et₂SiH (0.45 mmol), InX₃ (30–75 μmol, 10–25 mol%), 1,4-dioxane (0.50 mL). See ref. [53] and its Supporting Information for further details. [B] = B(pinacolate). Cumyl = 2-phenylisopropyl.

Scheme 26. Indium-catalyzed synthesis of β-alkylpyrroles 49 incorporating carbon nucleophiles [Nu(C) = Me₃SiCN, 2,3-dimethylthiophene, 4-vinylanisole]. 47 (0.250 mmol), 39 (1.00 mmol), Nu(C) (0.375 or 0.750 mmol), In(NTf₂)₃ (37.5–50.0 μmol), 1,4-dioxane (0.25 mL).

Scheme 27. Synthesis of nitrogen-unsubstituted β-alkylpyrroles 50. a) TiCl₃ (2.0 equiv), Li (13 equiv), I₂ (1.0 equiv), THF, RT, 16 h.

Scheme 28. Possible routes from 51 and 52 to products 55 and 56. [In] = indium(III) salt. Nu = nucleophile.
where the possible routes from 51 and 52 are depicted. The first significant effect is the dominant formation of 54 being much more stable than alternative cationic species 53, which have 1,3-allylic-type strain between R² and R¹. The second is higher leaving ability of the α-pyrrolyl group to the β-pyrrolyl group. Since 52 with two β-pyrrolyl groups inevitably leads to only 56, the above two effects play crucial roles especially in the process of the transformation of 51. The plausible reaction mechanism is thus provided in Scheme 29.

**Scheme 29. A plausible reaction route.** [In] = indium(III) salt. Nu = nucleophile. In the use of 38 as starting substrates, R¹ in the intermediate and product is Me. [a] In the use of 47 as starting substrates, H₂O is formed.

The indium(III) salt [[In]] first assembles alkynes 38 or carbonyl compounds 47 and pyroles 39 into dipyrrolylalkanes 57, one pyrrolyl group in which coordinates to the [In] and then eliminates to give cationic species 54 exclusively, via the C(sp³)–C(pyrrolyl) bond cleavage. The trapping of 54 with nucleophiles (Nu) leads to final products 56.

### Summary and Outlook

In summary, it was found that the strategies on β-alkylation of pyroles via the S_pAr process can be classified into five major categories. In each strategy, the unique “trick” operates nicely to direct electrophiles toward the β-site of pyroles. Prior to disclosing our new system in 2009, the methodology starting with the β-acylation of N-As-pyroles seems to have been the primary contributor to offer β-alkylpyroles, probably due to its reliability of providing the target structure and moderate scope of substrates. However, requiring the multi-step as well as the stoichiometric amount of promoters has remained issues to be improved. In contrast to such classical approaches including others, we have achieved, for the first time, the catalytic synthesis of β-alkylpyroles in a single step with the aid of an indium salt. This conceptually novel strategy includes the following salient features: 1) broad scope of substrates, 2) remarkable functional group compatibility, and 3) perfect β-selectivities. With carbonyl compounds as alkyl group suppliers, all variations, that is, primary, secondary and tertiary alkyl units can be installed in place onto the pyrrole ring. Although the de-benzylazation and de-cumulation guide us to nitrogen-unsubstituted β-alkylpyroles, at present, their direct synthesis with high yields and β-selectivities unfortunately appears to be beyond the scope of our strategy. Accordingly, elegant catalytic one-step synthesis of nitrogen-unsubstituted β-alkylpyroles from pyrrole remains a challenge for the future.

Finally, I hope that this Concept article will help stimulate the relevant research in this field so that innovative findings with practicality and simplicity are made in the coming years.

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J. W. Huffman, V. I. Smith, L. W. Padgett, "Tetrahedron 2008, 64, 2104–2112. For other mechanistic considerations, see reference [27], and references therein.


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For selected β-alkylation of N-Bu-pyrrole upon treatment with ethyl diazoacetate in the presence of a copper catalyst, see: B. E. Maryanoff, "J. Org. Chem. 1979, 44, 4410–4419.


Selective Synthesis of \( \beta \)-Alkylpyrroles

[55] For example, upon treatment of 1-octyne and \( N \)-methylpyrrole with \( \text{In}^{3+} (\text{OTf})_3 \) (10 mol%), a 85:15 mixture of the corresponding \( \beta \)- and \( \alpha,\beta' \)-adducts is produced. No \( \alpha,\alpha' \)-isomer is thus formed. Use of pyrroles with bulkier substituents on the nitrogen atom leads to higher selectivity of 41. For further details, see reference [54].

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