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# Exclusive Synthesis of β-Alkylpyrroles under Indium Catalysis: Carbonyl Compounds as Sources of Alkyl Groups

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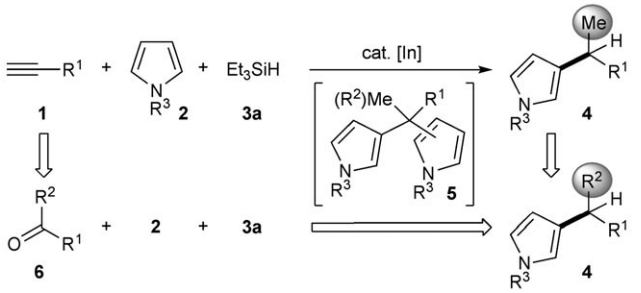
*Dedicated to Professor Tamejiro Hiyama in commemoration of his retirement from Kyoto University*

Introduction of alkyl groups onto aromatic rings is among the most important transformations in organic synthesis. Transition-metal-catalyzed cross-coupling must be a leading option to make alkyl–aryl bonds at desired positions.[1] However, pre-activation of both fragments with halides and electropositive metals is required to secure the regioselectivities. A realistic candidate to reduce our dependence on the pre-activation would be electrophilic aromatic substitution (EAS), that is, the Friedel–Crafts alkylation that replaces the pre-activated arenes with simple arenes, while the simple arenes for the EAS generally cause non-regioselective reaction, and, in addition, their reaction sites are narrowed to more nucleophilic positions.[2] Therefore, development of EAS enabling regioselective alkylation at desired sites on arenes would be useful over the cross-coupling. In this context, we recently reported the regiospecific β-alkylation of pyrroles through EAS, by the simple assembly of alkynes **1**, pyrroles **2**, and $Et_3SiH$ (**3a**) under indium catalysis (Scheme 1).[3] β-Alkylpyrroles are structural motifs found in many natural products[4] and functional organic materials,[5] but β-alkylation of pyrroles by EAS has been a challenging issue, due to dominant α-nucleophilicity of pyrroles.[6] Despite such characteristics of pyrroles, our recent finding, which is the first example of catalytic β-alkylation of pyrroles in one-step, showed that β-alkylpyrroles **4** are formed exclusively, via formation of dipyrrolylalkanes **5** as crucial intermediates.[7,8] However, the scope of **1** has been restricted mainly to terminal alkynes, the terminal carbon atom of which is inevitably incorporated as a methyl group into **4**.[9] We envisioned that replacing **1** with carbonyl compounds **6** would drastically extend the diversity of alkyl groups installable onto **2**.[10] Moreover, the use of **6**, which is cheaper in general than **1**, would make the process highly attractive and practical. Herein we disclose a new method for synthesis of β-alkylpyrroles **4** using **6** as alkyl group suppliers.[11]




Scheme 1. Indium-catalyzed reductive β-alkylation of pyrroles: alkynes versus carbonyl compounds as sources of alkyl groups ([In] = indium salt).

Due to the potent activity of $In(NTf_2)_3$ ($Tf = SO_2CF_3$) found in our preceding research,[3] research on this topic began with its testing in the reaction of 2-decanone (**6a**) and *N*-methylpyrrole (**2a**) with $Et_3SiH$ (**3a**), by the procedure shown as method A: simultaneous treatment of **6**, **2**, **3** and $In(NTf_2)_3$ (Table 1). Thus, the reaction with $In(NTf_2)_3$ (10 mol%) in 1,4-dioxane at 85 °C for 3 h gave 3-(decan-2-yl)-*N*-methylpyrrole (**4a**) as a single isomer in 92% yield (entry 1). The absence of formation of its α-isomer is particularly noteworthy. Another important aspect is that the use of **6a** allowed to reduce the catalyst loading, compared with reaction of the corresponding alkyne, 1-decyne, requiring 25 mol% of $In(NTf_2)_3$.[3] The 5-nonyl group, which is difficult to install regioselectively when an unsymmetrical alkyne (4-nonyne) is used, is readily available from 5-nonanone (entry 2). The cyclic structures that are inaccessible from alkynes can be treated with ease (entries 3–5), while 2-adamantanol (15% yield), resulting from direct reduction of

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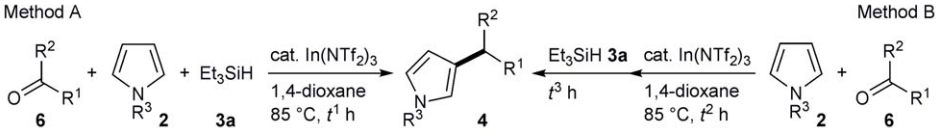
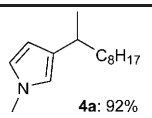
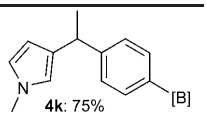
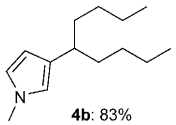
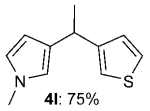
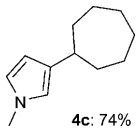
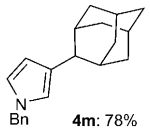
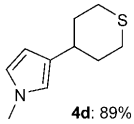
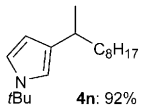
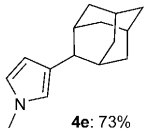
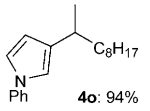
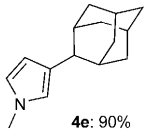
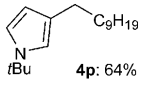
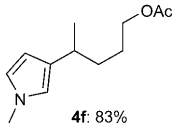
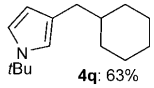
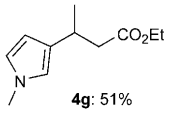
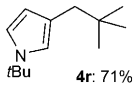
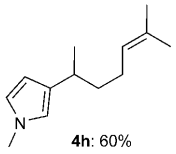
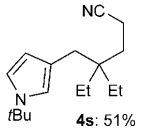
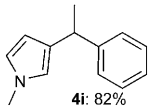
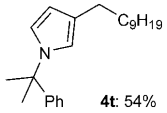
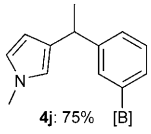
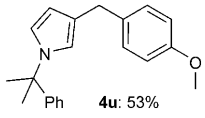
Table 1. Indium-catalyzed reductive β-alkylation of pyrroles with carbonyl compounds and $Et_3SiH$.[a]




| Entry | Method | $t$ [h] | Product, yield[b] | Entry | Method | $t$ [h] | Product, yield[b] |
|---|---|---|---|---|---|---|---|
| 1 | A | $t^1=3$ |  **4a**: 92% | 12[d,e] | B | $t^2=1$<br>$t^3=5$ |  **4k**: 75% |
| 2 | A | $t^1=7$ |  **4b**: 83% | 13[e] | B | $t^2=1$<br>$t^3=5$ |  **4l**: 75% |
| 3 | A | $t^1=3$ |  **4c**: 74% | 14 | B | $t^2=20$<br>$t^3=1$ |  **4m**: 78% |
| 4 | A | $t^1=3$ |  **4d**: 89% | 15 | A | $t^1=3$ |  **4n**: 92% |
| 5 | A | $t^1=3$ |  **4e**: 73% | 16 | B | $t^2=1$<br>$t^3=3$ |  **4o**: 94% |
| 6 | B | $t^2=20$<br>$t^3=1$ |  **4e**: 90% | 17 | A | $t^1=7$ |  **4p**: 64% |
| 7 | A | $t^1=7$ |  **4f**: 83% | 18 | A | $t^1=3$ |  **4q**: 63% |
| 8 | B | $t^2=1$<br>$t^3=20$ |  **4g**: 51% | 19 | A | $t^1=3$ |  **4r**: 71% |
| 9[c] | A | $t^1=7$ |  **4h**: 60% | 20[f] | A | $t^1=24$ |  **4s**: 51% |
| 10 | B | $t^2=1$<br>$t^3=4$ |  **4i**: 82% | 21 | A | $t^1=10$ |  **4t**: 54% |
| 11[d] | B | $t^2=1$<br>$t^3=3$ |  **4j**: 75% [B] | 22[c] | A | $t^1=20$ |  **4u**: 53% |

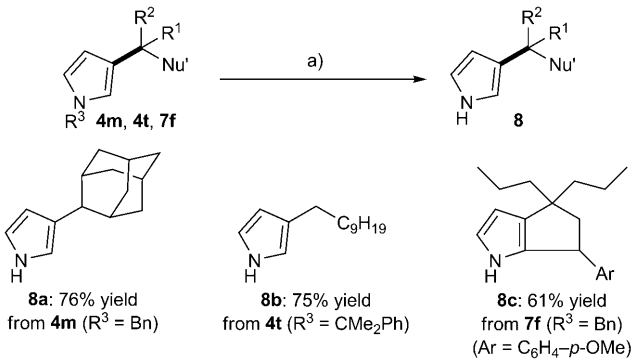
[a] Reagents (unless otherwise specified): **6** (0.30 mmol), **2** (0.90–1.2 mmol), **3a** (0.45 mmol), $In(NTf_2)_3$ (0.030–0.075 mmol) for entries 1–16 or $In(ONf)_3$ (0.030–0.075 mmol) for entries 17–22, 1,4-dioxane (0.5 mL). See Supporting Information for further details. [b] Isolated yield based on **6**. [c] Performed at 60 °C. [d] Carried out in the presence of $MgSO_4$ (3.0 equiv). [e] The process after the addition of **3a** was performed at 100 °C. [f] **3a** (2.4 mmol) was used.

2-adamantanone by **3a**, was contaminated in the case of entry 5. The undesired reduction was suppressed entirely by the simple alteration of method A to method B, in which **3** is added after consumption of **6**, leading to in situ formation of dipyrrolylalkanes **5** as intermediates (entry 6).[12] A range of functional groups, sulfide, ester, alkenyl, boryl {[B]= B(pinacolate)}, cyano, and alkoxy, are compatible with the strategy (entries 4, 7–9, 11, 12, 20, and 22). For aryl and heteroaryl ketones, method B is valid to exclude α-alkylation (entries 10–13).[13] Pyrroles bearing a benzyl (Bn), *t*Bu, Ph, or cumyl (2-phenylisopropyl) group on the nitrogen atom also participated well in this protocol (entries 14–22). One of the major highlights is to ensure access to primary alkyl groups that are impossible to handle in our previous system,[3] since terminal alkynes **1** accept **2** at the internal carbon of the C≡C bond.[11c] In fact, linear and α-branched aliphatic aldehydes as well as an aromatic one reacted with **2** and **3a** over $In(ONf)_3$ ($Nf=SO_2C_4F_9$) as a catalyst to give β-alkylpyrroles **4p**–**4u** exclusively (entries 17–22). Here the bulkiness on the nitrogen atom of **2** is crucial for complete β-selectivities and also high conversion of intermediates **5**. In these cases, $In(NTf_2)_3$ is less effective, due mainly to lower conversion of **5**. Utility of the strategy can be demonstrated by performing scale up synthesis. For example, **4m** (667 mg, 76% yield) and **4t** (520 mg, 53% yield) can be prepared in virtually the same yield, compared to those obtained in entries 14 and 21 of Table 1, by tenfold scale-up reaction.

Besides hydride nucleophile **3a**, carbon nucleophiles [Nu(*C*)] **3**, such as $Me_3SiCN$ (**3b**), 2,3-dimethylthiophene (**3c**) and 4-vinylanisole (**3d**), can be adopted for extension of a carbon–carbon bond (Scheme 2).[11f] Their use enables installation of tertiary alkyl units onto **2**, here again in a perfect β-selective manner in all cases. In the cases of **3d**, the bicyclic ring was formed at once through regioselective three carbon–carbon bond-forming cascades, in which a benzylic cation generated after nucleophilic attack of the C=C bond of **3d** is likely to accept the α-carbon of the pyrrolyl group.

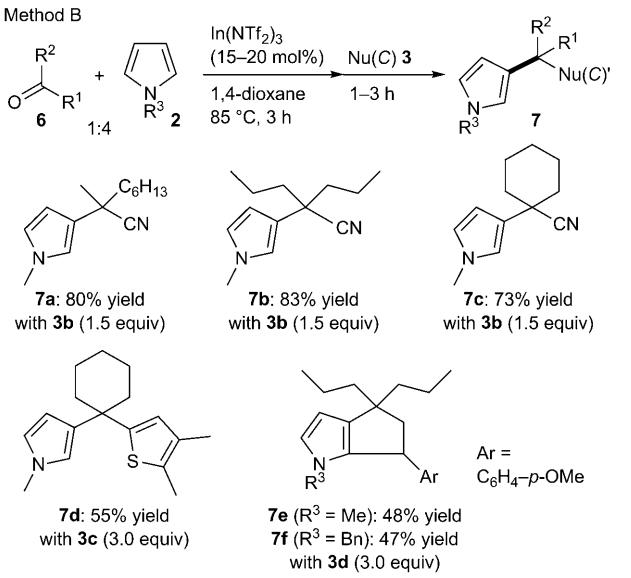
Nitrogen-unsubstituted β-alkylpyrroles also are easily accessible by the removal of the benzyl or cumyl group in β-alkylpyrroles synthesized thus far (Scheme 3).[14] For example,



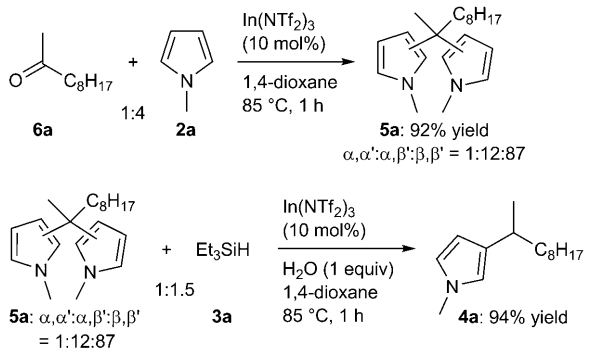

Scheme 3. Synthesis of nitrogen-unsubstituted β-alkylpyrroles **8a**–**8c**. Reagents and conditions: a) $TiCl_3$ (2.0 equiv), Li (13 equiv), $I_2$ (1.0 equiv), THF, RT, 16 h.

the treatment of **4m**, **4t**, or **7f** with $TiCl_3/Li/I_2$ in THF at room temperature gave **8a**, **8b**, or **8c**, respectively,[15] indicating that the debenzylation and decumylation allow us to gain nitrogen-unsubstituted β-alkylpyrroles with all types of alkyl groups, that is, primary, secondary and tertiary ones.

We next performed some reactions to get insight into the reaction mechanism (Scheme 4). Thus, the indium-catalyzed reaction of **6a** with **2a**, but without **3**, gave an isomeric mixture of **5a**, as already observed in the reactions using method B (vide supra). Subsequently, treating **5a**, **3a**, and $H_2O$ with $In(NTf_2)_3$ (10 mol%) provided β-(decan-2-yl)pyrrole **4a** exclusively.[16] These results indicate that dipyrrolylalkanes **5** are intermediates in the three-component reaction using **6**, **2**, and **3**. On the basis of these results and our previ-



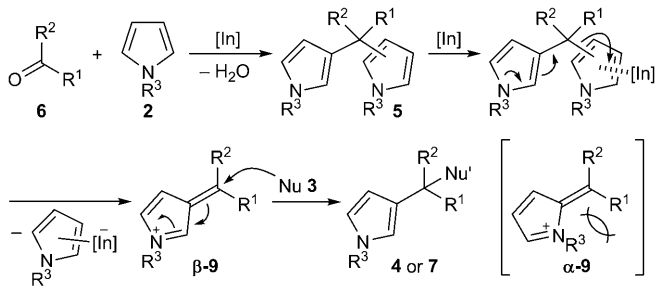

Scheme 2. Indium-catalyzed β-alkylation of pyrroles with carbonyl compounds and carbon nucleophiles (**3b**: $Me_3SiCN$, **3c**: 2,3-dimethylthiophene, **3d**: 4-vinylanisole).




Scheme 4. Indium-catalyzed synthesis of dipyrrolyldecanes **5a**, and indium-catalyzed synthesis of β-(decan-2-yl)pyrrole **4a** starting from **5a**.

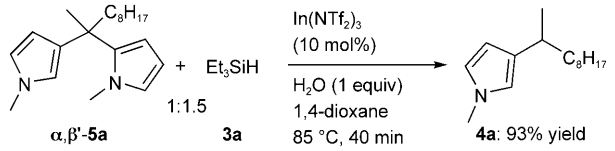
  

ous ones,[3,11f] a plausible mechanism is depicted in Scheme 5, in which one pyrrolyl ring in **5** is fixed as the β-pyrrolyl ring, due actually to no formation of α-alkylpyrroles




Scheme 5. A plausible reaction mechanism.

derived inevitably from **α,α′-5**. The indium salt [In] first assembles **6** and **2** into **5**,[17] one pyrrolyl group of which coordinates to the indium salt and then eliminates to give cationic species **β-9** by way of the C($sp^3$)–C(pyrrolyl) bond cleavage. The trapping of **β-9** by nucleophile (Nu) **3** affords final product **4** or **7**. The origin of the perfect β-selectivities is attributed to the following two synergistic effects, as previously noted:[3,11f] 1) dominant formation of **β-9** being much more stable than alternative cationic species **α-9** (Scheme 5), which has 1,3-allylic-type strain between $R^1$ and $R^3$,[18] and 2) superior leaving ability of an α-pyrrolyl group to a β-pyrrolyl group. In fact, only **4a** is produced, even from **α,β′-5a**, which is a possible precursor for **4a** and its α-isomer (Scheme 6).




Scheme 6. Indium-catalyzed reaction of **α,β′-5a** with **3a**.

In conclusion, we have disclosed a new robust and simple synthetic method for β-alkylpyrroles by the choice of carbonyl compounds as alkyl group sources, through tandem C=O and C–C bond activations under indium catalysis. The regioselectivities on both pyrrole rings and alkyl units are perfectly controlled. The striking feature is that the indium-catalyzed β-alkylation in combination with the debenzylation offers all six variations including nitrogen-substituted and -unsubstituted β-alkylpyrroles with primary, secondary, and tertiary alkyl groups. Application of the strategy to an asymmetric variant is currently underway, and the result will be reported in due course.

## Experimental Section

**Synthesis of 4a (Table 1, entry 1)**: $In(NTf_2)_3$ (28.7 mg, 30.0 μmol) was heated in a 20 mL Schlenk tube at 150 °C in vacuo for 2 h. Under argon, 1,4-dioxane (0.5 mL), 2-decanone (46.9 mg, 0.300 mmol), *N*-methylpyrrole (73.0 mg, 0.900 mmol) and $Et_3SiH$ (52.3 mg, 0.450 mmol) were added to the Schlenk tube. The mixture was stirred at 85 °C for 3 h, and then a saturated $NaHCO_3$ aqueous solution (0.3 mL) was added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layer was washed with brine (1 mL) and then dried over anhydrous $Na_2SO_4$. Filtration and evaporation of the solvent followed by column chromatography on silica gel (hexane/EtOAc = 60:1) gave 3-(decan-2-yl)-*N*-methylpyrrole (**4a**) (61.1 mg, 92% yield).

## Acknowledgements

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**Keywords:** aldehydes · C–C activation · indium · ketones · nucleophilic substitution

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[10] Carbonyl compounds have much higher skeletal and substitutional diversities than alkynes as commercial sources. See, for example, SIGMA-ALDRICH Product Catalog at http://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16273490.

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[12] Disappearance of **6** followed by formation of **5** can be confirmed by GC analysis.

[13] For example, the reaction of acetophenone ($R^1$=Ph, $R^2$=Me), **2a** and **3a** by using method A gives a 98:2 mixture of β- and α-(1-phenylethyl)pyrroles in 88% yield (see entry 10).

[14] Unfortunately, application of the strategy to pyrrole ($R^3$=H) resulted in low yield and β-selectivity: treatment of **6a**, pyrrole, **3a** (1:3:1.5) and $In(NTf_2)_3$ (10 mol%) at 85°C for 20 h by using method A gives a 54:46 mixture of β- and α-(decan-2-yl)pyrroles in 28% yield.

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[16] The process of the indium-catalyzed reaction of **6a** with **2a** produces one molar equivalent of $H_2O$ along with **5a**. Accordingly, the reaction was carried out in the presence of $H_2O$ (1 equiv).

[17] Synthesis of dipyrrolylalkanes upon treatment of carbonyl compounds and pyrroles with acid catalysts is a well-established reaction, especially in porphyrin chemistry. For a recent review, see: J. S. Lindsey, *Acc. Chem. Res.* **2010**, *43*, 300–311, and references therein.

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