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Radical-Based Regioselective Cross-Coupling of Indoles and Cycloalkanes

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An investigation on regiochemistry of radical functionalization of indoles using cycloalkanes through di-*tert*-butyl peroxide (DTBP)promoted $C(sp^3)$ -H activation was conducted. A wide range of indoles bearing substituents at different position was functionalized directly with simple cycloalkanes in moderate to high regioselctivity. 2-, 4- and 7-position were mainly functionalized.



Scheme 1. Representative bioactive alkylindoles.

Regiocontrolled functionalization of indole rings has been an important subject because of the vital role of indole structural motif in many biologically active natural products (Scheme 1).^[1]Some cycloalkyl substituted indoles have exhibited better metabolic stability than their unsubstituted counterparts.^[2] Consequently, the development of new methods for synthesis of functionalized indoles including cycloalkyl substituted

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indoles are desirable for both organic synthesis and medicinal chemistry considerations.

There are numerous methods which have been developed for the preparation of cycloalkyl substituted indoles, including multicomponent coupling reaction,^[3] Friedel-Craft alkylation,^[4] arylation,^[5] and transition-metal catalyzed C-H activation cross-coupling reaction.^[6] The regioselectivity of these reactions has also been investigated over the years.^[7] A more attractive approach for cycloalkylation of indoles was a condensation of pre-halogenated indole with cyclanone followed by reduction with LiAlH₄.^[8] These strategies can obtain the target product in high regioselectivity, but they come with the multiple drawbacks including low atom utilization, use of toxic reagents and inconvenience of operations. Therefore, the development of direct functionalization methods for the selective modification of indoles remains an important practical goal.



Scheme 2. Di-tert-butyl peroxide (DTBP)-Mediated Oxidative Cross-Coupling reactions.

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During the last few decades, radical reactions have emerged as a powerful toolkit for the direct activation of simple alkanes such as cheap constituents of petroleum ether and nature gas.^[9] The metal-free C(sp³)-H bond functionalization progress for C - C (S) bond formation of disulfides, olefins, heteroaromatics and cycloalkanes promoted by di-tert-butyl peroxide (DTBP) has also been reported (Scheme 2).^[10] With this in mind and our continuous efforts to develop metal-free radical syntheses,^[11] we envisioned that the formation of cycloalkyl-substitued indoles in oxidative radical system could happen, which, if realized, would provide a simple and practical strategy for the synthesis of cycloalkylindole derivatives. To verify the feasibility of our proposed assumption, we started the investigation by selecting the reaction of indole 1a and cyclohexane 2a as the model reaction (Table 1).

Table 1. Optimization of reaction conditions.
 [a]

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$\begin{array}{c} & & & \\ & &$					>
Entry	Oxidant (equiv.)	Addi. (2 equiv.)	Temp. (°C)	Time (h)	Yield (%)
1	(cquiv.)		140	12	n. r.
2	DTBP(1.5)		140	12	74
3	$K_2S_2O_8(1.5)$		140	12	n. r.
4	TBHP(1.5)		140	12	n. r.
5	DTBP(3)		140	12	75
6	DTBP(1.5)		140	24	73
7	DTBP(1.5)		140	8	67
8	DTBP(1.5)		140	4	54
9	DTBP(1.5)		100	12	10
10	DTBP(1.5)		85	12	trace
11	DTBP(1.5)	CsCO ₃	140	12	73
12	DTBP(1.5)	^t BuOK	140	12	71
13	DTBP(1.5)	K_2CO_3	140	12	70
$14^{[b]}$	DTBP(1.5)		140	12	41
15 ^[c]	DTBP(1.5)		140	12	trace

[a] Reaction conditions: indole (1 mmol), cyclohexane (4 mL), under nitrogen. [b] Under air. [c] Indole (1 mmol), cyclohexane (3 mmol), acetonitrile (4 mL).

In the absence of radical initiator, the cyclohexyl substituted indole product was not detected (Table 1, entry 1). To our surprise, **3a**, was obtained in 74% yield in the presence of 1.5 equiv. of DTBP.

According to the reports in the literature, the direct functionalization of indoles mostly occurs at the 2- or 3-position.^[12] There is almost no report about directly C-H activation reaction on 4-position of indoles. In 1994, Katritzky et al. demonstrated aquathermolysis of indole and 2,3-dimethylindole in cyclo-hexane at 460 °C for 1 h, in which 4-substituted indole was detected as a significant product.^[13] Our group recently reported the reaction of isochroman with indoles using DTBP as oxidant provides facile access to 3-(isochroman-1-yl)-indoles.^[14] The unexpected 4-position

substituted product could be a harbinger of a new method for the preparation of indole derivatives with substituents on the benzene ring.

Afterwards, various oxidants were screened (Table 1, entries 2-4). The use of tert-butyl hydroperoxide (TBHP) and potassium persulfate instead of DTBP provided no access to the desired product 3a. Increasing the amount of DTBP did not lead to significant difference in the yield of 3a (Table 1, entry 5). Reaction temperature and time were also screened (Table 1, entries 6-10). The coupling occurred efficiently when heated to 140°C for 12 hours. There was nearly no reaction when the temperature was decreased to 85°C. Extension of reaction time may lead to more undesired byproducts. Then we carried out a screening of various additives, however, none of the screened additives gave better results (Table 1, entries 11-13). Furthermore, when the reaction was performed under air atmosphere, a lower yield was obtained (Table 1, entry 14). Finally, we used acetonitrile as the solvent with the aim of decreasing the amount of cyclohexane to 3 equiv., but the yield was decreased substantially (Table 1, entry 15).

With the above optimized conditions in hand, the scope of the reaction with respect to indole derivatives was tested and the results are listed in Table 2.

Table 2. Cross-coupling of Indoles (1) with Cyclohexane $(2a)^{laj\cdot lcj}$



[a] Reaction conditions: indoles (1 mmol), cyclohexane (4 mL), DTBP (1.5 mmol) at 140 $^{\circ}$ C for 12 h, under N₂. [b] Yield was given as a total yield of mixtures of products, and the structure was confirmed by NMR. [c] Regioselectivity ratio determined by GC-MS. [d] Detected by GC-MS.

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Indoles with substituents at 5-position were tested primarily, the reaction proceeded predominately at the 4-position in all cases (3b-3i), Structure of 3e was confirmed by X-ray crystal structure analysis (Scheme 3). Although the electrical properties of substituents could hardly give any influence on the regioselectivity, the yields of products (3g and 3h), by using electron-rich substrates such as 5-methylindole and 5methoxyindole were lower than that using electron-deficient indoles. Substitutes at other positions were also investigated. N-methylindole could obtained 2-cyclohexyl-1-methyl-1Hindole and 4-cyclohexyl-1-methyl-1H-indole with the ratio of 74% and 25% respectively. 2-methylindole reacted selectively at 4-position to give the corresponding products in moderate yields. With a substituent at 3 or 4-position, the 2cyclohexylindole becomes the major product (31, 3m). In the case of 6-substituted indole, the reaction displayed a stronger preference toward the 7-position than the 4-position selectivity (3n and 3o), compared with 3b and 3c. There was no significant difference between 2- and 4-position selectivity in terms of 7-substitued indole.



Scheme 3 X-ray crystal structure analysis of 3e

To expand the scope of the methodology, a range of cycloalkanes was examined afterwards (Table 3). In a similar manner to the reaction of **2a**, cyclopentane (**2b**), cycloheptane (**2c**) and cyclooctane (**2d**) reacted smoothly. **3s** was obtained in a lower yield when 1*H*-indole-5-carbonitrile was reacted with n-hexane under the conditions. Interestingly, when cyclododecane (**2e**) was used, the corresponding products were isolated in moderate yields.

Table 3. Cross-coupling of Indoles with Cycloalkanes.[a]-[b]



[a] Reaction conditions: indole (1 mmol), cycloalkane (4 mL) , DTBP (1.5 mmol) at 140 °C for 12 h, under N₂. [b] Yield was given for the main product, and the structure was confirmed by NMR.

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To gain insights into the reaction mechanism, several control experiments were carried out (Scheme 4). Addition of the radical-trapping reagents 2, 2, 6, 6-tetramethylpiperidine Noxide (TEMPO) could completely inhibit the reaction and 1-(cyclohexyloxy)-2, 2, 6, 6-tetramethylpiperidine was detected by GC-MS. Moreover, with the absence of 5-chloro-1*H*-indole, 1, 1'-bi (cy-clohexane) was detected by GC-MS as the main product under the reaction conditions. These results indicated that the transformation may proceed via a radical course.



Scheme 4. Insights into the mechanism.

As shown in table 2, indoles with substituents at different positions on benzene ring, reaction selectivities were quite different. Further document research on the selectivity was conducted. In 2011, Li and co-worker reported a direct paraselective oxidative cross-coupling of benzene derivatives with cycloalkanes catalyzed by ruthenium, overwhelming the effect of strongly ortho-directing of chelating substituents. [15] Different substituents also showed diverse ratio of ortho/meta/para product. They attributed the selectivity to the stability of resonance of a radical-charactered intermediate and the specific mechanism was not given. Similarly, we supposed that the position of substituent on the indoles might have an effect on the stability of the radial intermediates, thereby leading to selective functionalization. To test this hypothesis, relative radical stabilities of 1c and 1o were investigated using density functional theory (DFT) calculation employing the method B3LYP (Table 4). The activation energies of radical transition state (TS) varied with the Breaking bonds. In the case of 1c, the intermediate generated from breaking C-H⁴ have the lowest activation energy than C-H⁶ and C-H⁷. While breaking C-H⁴ and C-H⁷ could afford more stable radical transition state than C-H⁵ for **10**. The results of theoretic calculation were well coincident with those of tests.

Table 4	Theoretic	calculation	results	of 1c	and	10
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Compounds	Breaking bonds	Radical TS energies (hartree)	Activation energies (kJ/mol)
H ⁴ Cl⊾ ↓ _	C-H ⁴	-1058.6131	41.75
H ⁶	C-H ⁶	-1058.6105	48.57
⊡ 1c	C-H ⁷	-1058.6107	48.05
H ⁴ H€ ↓ _	C-H ⁴	-1058.6117	45.42
	C-H ⁵	-1058.6083	54.35
H′ 10	C-H ⁷	-1058.6121	44.63

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Moreover, Frank De Proft et al. reported an electrophilicity scale, global as well as local, and a nucleophilicity scale for 35 radicals in 2007.^[16] In their opinion, radicals can be regarded as electrophilic/nucleophilic, and the nature of the radical has an effect on which reactive sites in a substrate are more likely to be attacked. Quite recently, Fionn et al. carried out a systematic investigation of factors affecting the regiochemistry of radical functionalization of heterocycles using alkylsulfinate salts. These studies overthrew the stigma that direct radical functionalization processes are necessarily low yielding and regiochemically unpredictable.^[17] Based on these, we supposed that the present regioselectitvity may due to the nature of cyclohexane radicals, which is more nucleophilic than previously reported isochroman case.^[14] A hypothesis for the reaction pathway is depicted in Scheme 5. The tert-butoxyl radical is first generated by the thermal decomposition of ditert-butyl peroxide (DTBP). And then the tert-butoxyl radical abstracted hydrogen from the C(sp³)-H bond of cyclohexane to afford a cyclohexyl radical (A), which finally reacted with indole derivative to generate the most stable radical intermediate (B), affording the final target product 3.



Scheme 5. Proposed reaction mechanism.

Conclusions

In summary, we have conducted an regiochemistral investigation on the radical reaction of indoles and cycloalkanes through $C(sp^3)$ -H activation under metal-free conditions in the presence of *t*BuOOtBu. A wide range of indoles bearing substituents at different positions was functionalized directly with simple cycloalkanes in moderate to high regioselctivity. 2-, 4-, and 7-position were mainly functionalized. The detailed mechanism and full scope of present methodology are the focus of ongoing research efforts.

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Notes and references

[1] (a) Gopalan, B.; Manojit, P.; Shrikant, H. H. et al. Novel heterocyclic compounds, pharmaceutical compositions containing them and processes for their preparation: India, WO 2009115874 A2 [P], **2009**-01-29. (b) Zemolka, S.; Schunk, S.; Englberger, W.; Koegel, B. Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Graubaum, H.; Hinze, C. Preparation of cyclohexylindoles as opioid receptor-like 1 (ORL1) receptor inhibitors: Germany, WO 2008009415 A2 [P], **2008**-01-24. (c) Tanaka, T.; Konishi, Y.; Kubo, D.; Fujino, M.; Doi, I.; Nakagawa, D.; Murakami, T.; Yamakawa, T. Preparation of (hetero) arylamines having keratinocyte proliferation inhibitory activity: Japan, WO 2014069510 A1 [P], **2014**-05-08. (d) Muratake, H.and Natsume, M. *Heterocycles*, **1990**, 31, 683.

[2] Giuseppe, L. R.; Ruoli, B.; Whilelmina, M. R. et al. J. Med. Chem. 2013, 56, 123.

[3] (a) Lu, B. Z.; Wei, H. X.; Zhang, Y. D.; Zhao, W. Y.; Dufour, M.;
Li, G. S.; Farina, V.; Senanayake, C. H. *J. Org. Chem.* 2013, 78, 4558.
(b) Wang, Y. Z.; Ye, L. W.; Zhang, L. M. *Chem. Commun.*, 2011, 47, 7815.
(c) Chen, W. L.; Gao, Y. R.; Mao, S.; Zhang, Y. L.; Wang, Y. F.; Wang, Y. Q. *Org. Lett.*, 2012, 14, 5920.

[4] (a) Jiao, L.; Bach, T. J. Am. Chem. Soc. 2011, 133, 12990. (b) Zeng,
 M.; You, S. L. Synlett. 2010, 9, 1289. (c) Guo, X. W.; Pan, S. G.; Liu, J.
 H.; Li, Z. P. J. Org. Chem. 2009, 74, 8848.

[5] Ackermann, L.; Lygin, A. V. Org. Lett. 2011, 13, 3332.

[6] (a) Leskinen, M. V.; Yip, K. T.; Valkonen, A.; Pihko, P. M. J. Am. Chem. Soc. 2012, 134, 5750. (b) Nathalie, L.; Igor L. J. Am. Chem. Soc.
2008, 130, 2926. (c) Nadres, E. T.; Lazareva, A.; Daugulis, O. J. Org. Chem. 2011, 76, 471.

[7] Shathaverdhan, P.; Kyle C. P.; Serge I. G.; Andrew P.; Alexis P. L.; Brenton D. J. Am. Chem. Soc. 2010, 132, 14676.

[8] Zhang, X. M.; Lee, I.; Zhou, X.; Anthony, J. B. J. Am. Chem. Soc. 2006, 128, 143.

[9] (a) Curran, D. P.; Rakiewicz, D. M. J. Am. Chem. Soc., 1985, 107, 1448. (b) Chawla, R.; Singh, A. K.; Yadav, L. D. S. Eur. J. Org.Chem. 2014, 10, 2032.

[10] (a) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C. J. Chem. Eur. J. 2009, 15, 333.(b) Xia, R.; Niu, H. Y.; Qu, G. R.; Guo, H. M. Org. Lett. 2012, 14, 5546.(c) Zhao, J. C.; Fang, H., Han, J. L.; Pan, Y.; Li, G. G. Adv. Synth. Catal. 2014, 356, 2719.(d) Peng,H. B.; Yu, J. T.; Jiang, Y.; Yang, H.T.; Cheng, J. J. Org. Chem. 2014, 79, 9847.(e) Zhao, J. C.; Fang, H.; Song, R. C.; Zhou, J.; Han, J. L.; Pan, Y. Chem. Commun., 2015, 51, 599. (f) Guo, X. Y.; Li, C. J. Org. Lett. 2011, 13, 4977. (g) Deng, G. J.; Li, C. J. Org. Lett. 2009, 11, 1171. (h) Antonchick, A. P.; Burgmann, L. Angew. Chem. Int. Ed. 2013, 52, 3267. (i) Zhu,Y. F.; Wei,Y. Y. Chem. Sci. 2014, 5, 2379.

[11] (a) Zhu, Y.W.; Yi, W. B.; Qian, J. L. and Cai, C. ChemCatChem 2014, 6, 733. (b) Lin, Y. M.; Lu, G. P.; Cai, C.; Yi, W. B. Org. Lett. 2015, 17, 3310.

[12] (a) Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron*. 2001, 57, 975. (b)
Cao, L. L.; Wang, D. S.; Jiang, G. F.; Zhou, Y. G. *Tetrahedron Letters*.
2011, 52, 2837. (c) Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron Letters*,
2013, 54, 3394.

- [13] Katritzky, A. R.; Barcock, R. A. Energy & Fuels. 1994, 8, 990.
- [14] Jin, L.k.; Feng, J.; Lu, G. P.; Cai. C. Adv. Synth. Catal. 2015, 357, 2105.
- [15] Guo X. Y.; Li, C. J. Org. Lett., 2011, 13, 19, 4977.

[16] Freija, D. V.; Veronique, V. S.; Michel, W.;Paul, G.; Frank, D. P. *Org. Lett.*, **2007**, 9, 2721.

[17] Fionn O.; Donna G. B.; Phil S. B. J. Am. Chem. Soc. 2013, 135, 12122.

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[regioselective, simple, metal-,base-free, atom-economic]

An investigation on regiochemistry of radical functionalization of indoles using cycloalkanes through di-*tert*-butyl peroxide (DTBP)-promoted $C(sp^3)$ -H activation was conducted. A wide range of indoles bearing substituents at different position was functionalized directly with simple cycloalkanes in moderate to high regioselctivity. 2-, 4- and 7-position were mainly functionalized.