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Graphical Abstract

Metal-Free Radical Cascade Dichloromethylation of Activated Alkenes Using CH_2Cl_2: Highly Selective Activation of the C-H Bond

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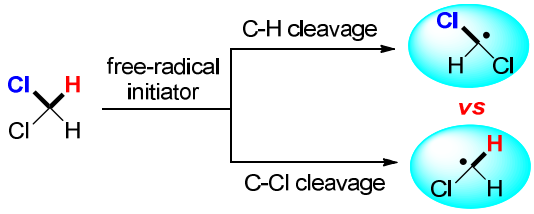

A dicumyl peroxide-initiated highly selective activation of the (sp^3)C-H bond in dichloromethane (DCM, CH_2Cl_2) has been achieved, which allows efficient access to dichloronated oxindoles via a free-radical cascade process.

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ARTICLE TYPE

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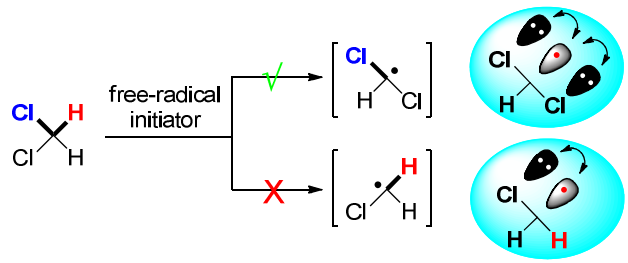
A dicumyl peroxide-initiated highly selective activation of the (sp^3)C-H bond in dichloromethane (DCM, CH_2Cl_2) has been achieved, which allows efficient access to dichloronated oxindoles via a free-radical cascade process.

Dichloromethane (CH_2Cl_2, DCM) is one of the most common compounds in chemistry, usually used as solvent. However, it seems that the DCM could only be used as solvent. The DCM involved chemical reactions have very rarely been reported in the past decades.[1] Of particular interests in the free-radical-initiated C-H bond functionalization, we have focused on selective activation of inert C-H bond in small molecules for years.[2] Encouraged by our previous studies on C-C bond formation via radical-promoted selective activation of the α-hydroxyl C-H bond of alcohol, [2a, 2f, 2h, 2i] we began to question whether the C-H bond of DCM could be selectively activated. Since the enthalpy of formation of dichloromethyl radical ($CHCl_2$ radical: ΔH_f^0 = 22.3 ± 1.0 kcal/mol) is lower than that of chloromethyl radical (CH_2Cl radical: ΔH_f^0 = 28.0 ± 0.7 kcal/mol),[3] the C-H bond cleavage would happen prior to the C-Cl bond cleavage under free-radical-initiated conditions (Scheme 1). Especially considering from the stereoelectronic effect,[4] the C-centered radical could be stabilized by the adjacent Cl-atom since electron delocalization would happen between the non-bonding orbital and the singly occupied molecular orbital (SOMO). Therefore, the dichloromethyl radical would be more stable than the chloromethyl radical.



Scheme 1. Free-Radical-Initiated C-H Bond Cleavage or C-Cl Bond Cleavage in DCM.

The *N*-arylacrylamide and its derivatives are proved to be excellent free radical acceptors, which are ready to undergo radical cascade reactions leading to a series of substituted oxindoles.[5] Very recently, we have developed an efficient strategy for synthesis of alkylated oxindoles via a free-radical addition/cyclization of *N*-arylacrylamides with simple alkanes.[2h] To test our hypothesis, *N*-methyl-*N*-phenylmethacrylamide and DCM were chosen as the model substrate to optimize the typical reaction conditions (Table 1). It can be seen from the table that the radical initiator and the temperature are the key factors affecting the reaction efficiency. The 3-(2,2-dichloroethyl)-1,3-dimethylindolin-2-one was isolated as the major product in nearly quantitative yield by using dicumyl peroxide (DCP) as the radical initiator, which is far more efficient than others such as *tert*-butyl hydroperoxide (TBHP), di- *tert*-butyl peroxide (DTBP), $K_2S_2O_8$, and benzoyl peroxide (BPO) etc (entries 1-6). Decrease or increase of the amount of DCP led to lower yield of the product than 3 equiv (entries 7 and 8). The desired product was obtained in 58% and 91% yields by using 2 mL and 4 mL of DCM as the solvent, respectively (entries 9 and 10). Only 33% yield of the corresponding oxindole was isolated while the reaction was conducted at 100 °C (entry 11). No product was observed when the temperature decreased to 90 °C (entry 12).

Table 1. Optimization of the typical reaction conditions. [a]

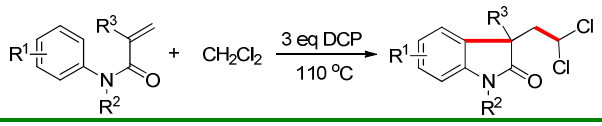
Entry	Radical Initiator (equiv)	DCM (mL)	T (°C)[b]	Yield (%)[c]
1	TBHP(3)[d]	3.5	110	-
2	TBHP(3)[e]	3.5	110	39
3	DTBP (3)	3.5	110	54
4	$K_2S_2O_8$(3)	3.5	110	-
5	BPO (3)	3.5	110	79
6	**DCP (3)**	**3.5**	**110**	**98**
7	DCP (2)	3.5	110	93

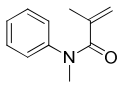
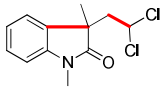
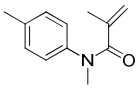
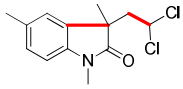
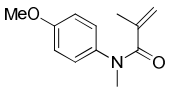
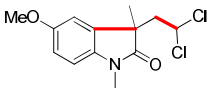
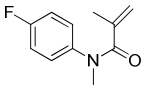
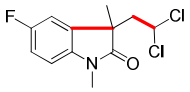
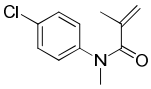
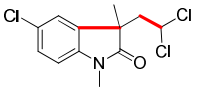
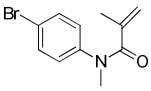
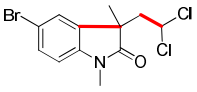
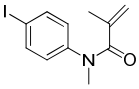
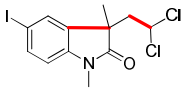
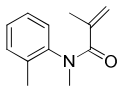
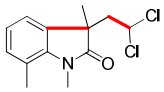
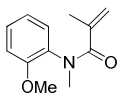
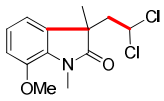
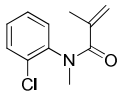
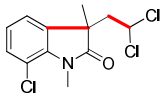
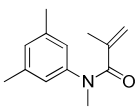
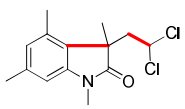
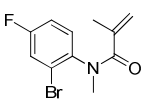
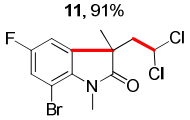
8	DCP (4)	3.5	110	51
9	DCP (3)	2.0	110	58
10	DCP (3)	4.0	110	91
11	DCP (3)	3.5	100	33
12	DCP (3)	3.5	90	-

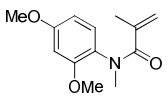
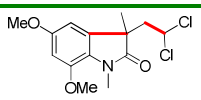
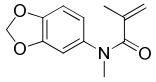
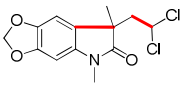
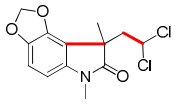
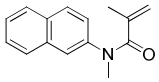
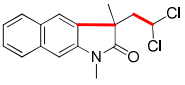
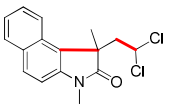
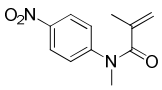
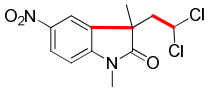
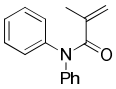
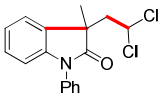
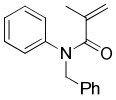
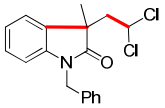
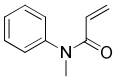
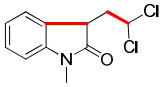
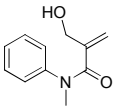
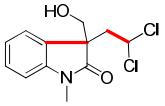
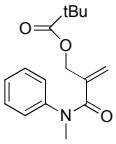
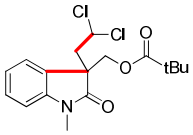
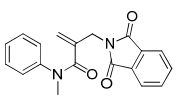
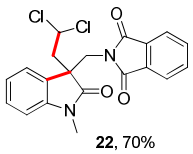
[a] Reaction conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), dichloromethane as solvent, sealed tube, 18 h. [b] Measured temperature of the oil bath. [c] Isolated yields. [d] TBHP (in decane). [e] TBHP (in water).

With the modified conditions in hand, we next pay attention to investigation of the substrate scope. It can be seen from the Table 2 that a wide range of substituted *N*-arylacrylamides are amenable to this reaction. The *N*-arylacrylamides with various substituents including alkyl and methoxyl groups, and halogen atoms located at the *para* position of the aromatic core all gave good to quantitative yield of the desired oxindoles (entries 1-7). The *ortho*-substituted *N*-arylacrylamides also led to the products in moderate to high yields (entries 8-10). Excellent yield of the products were isolated in the case of di-substituted *N*-arylacrylamides such as *N*-(3,5-dimethylphenyl)-*N*-methylmethacrylamide and *N*-(2-bromo-4-fluorophenyl) -*N*-methylmethacrylamide (entries 11 and 12). However, *N*-(2,4-dimethoxyphenyl)-*N*-methylmethacrylamide gave only 32% yield of the corresponding oxindole (entry 13). When *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-methylmethacrylamide and *N*-methyl-*N*- (naphthalen-2-yl)methacrylamide were used as the substrates in this system, a mixture of regio-selective isomers were obtained (entries 14 and 15). The ratio of the isomers indicated that cyclization occurred prior to the electron-rich site, which is reasonable because the possible secondary C-centered radical with an adjacent carbonyl group should be electrophilic. That is why no reaction occurred by using strongly electron-withdrawing groups such as NO_2 and CN substituted on the aromatic ring of the *N*-arylacrylamides (entry 16). In addition, the *N*,*N*-diphenylmethacrylamide and *N*-benzyl-*N*-phenylmethacrylamide as well as *N*-methyl-*N*-phenylacrylamide are effective substrates in this reaction (entries 17-19). Finally, the functional groups such as hydroxyl, ester, and lactam could be well survived in this system (entries 20-22).

Table 2. Free-Radical Cascade Reaction of *N*-arylacrylamide with DCM[a]

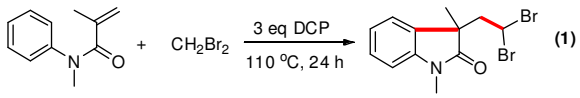


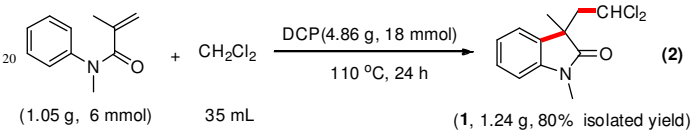
Entry	Substrate	Product, yield
1		 **1**, 98%[b]
2		 **2**, 81%
3		 **3**,[c] 87%
4		 **4**, 52%
5		 **5**, 99%
6		 **6**, 99%
7		 **7**, 81%
8		 **8**, 53%
9		 **9**,[c] 76%
10		 **10**, 77%
11		 **11**, 91%
12		 **12**, 97%

13		 **13**, 32% (rsm 40%)
14		 **14**,[d] 25%  **14'**,[d] 47%
15		 **15**,[d] 21%  **15'**,[d] 54%
16		 **16**, 0%
17		 **17**, 96%
18		 **18**, 72%
19		 **19**, 46% (rsm 38%)
20		 **20**, 75%
21		 **21**, 72%
22		 **22**, 70%

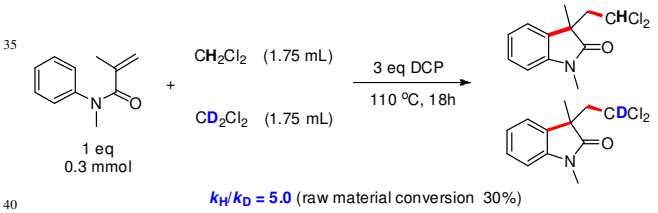
[a] Reaction conditions: *N*-arylacrylamide (1 equiv, 0.2 mmol), DCP (3 equiv, 0.6 mmol), dichloromethane (3.5 mL) as solvent, sealed tube, 110 °C (measured temperature of the oil bath), 18 h, unless otherwise noted. [b] Isolated yields. [c] Cu_2O (10 mol%, 0.02 mmol) was added. [d] DCP (4 equiv, 0.8 mmol).

Furthermore, the desired dibromomethylated oxindole **23** can be isolated in 22% yield by reaction of *N*-methyl-*N*-phenylmethacrylamide with dibromomethane under the typical conditions (equation **1**). It is also noteworthy that this reaction can be easily scaled-up to gram level (equation **2**), which indicates that it might be potentially applied in chemical industry.



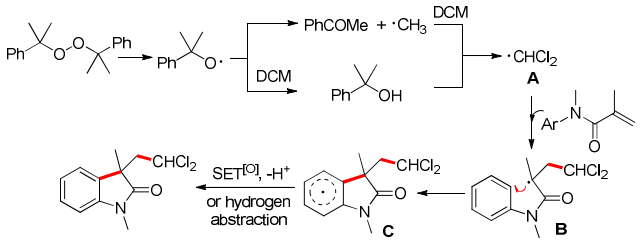


In order to investigate the mechanism for this reaction, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out. As demonstrated in Scheme 2, a significant KIE was observed with the k_H/k_D = 5.0 at a low conversion level. The results further confirm that the C-H bond even C-D bond would be cleaved prior to the C-Cl bond under free-radical-initiated conditions. Additionally, it also indicates that the cleavage of C–H bond would be involved in the rate-determining step of this procedure.



Scheme 2. KIE Experiment.

A free-radical addition/cyclization cascade mechanism for this process is proposed in Scheme 3. Homolysis of DCP forms cumyloxyl radical, which abstracts the H-atom from DCM leading to dichloromethyl radical **A** and 2-phenylpropan-2-ol which has been obtained as a byproduct. Alternatively, *β*-cleavage of the cumyloxyl radical would give the methyl radical and acetophenone which has also been isolated in this system. Methane and radical A would be formed via hydrogen abstraction of DCM by the methyl radical. Then addition of the radical **A** to *N*-arylacrylamide would generate a radical intermediate **B**, which cyclizes to the aromatic core giving radical **C**. Direct hydrogen abstraction or single-electron oxidation of radical **C** followed by deprotonation of the corresponding carbocation would form the final product.



Scheme 3. Proposed Mechanism.

In conclusion, a free-radical-initiated selectively functionalization of the C-H bond of DCM has been achieved, which allows efficient access to dichloromethylated oxindoles via radical addition/cyclization of *N*-arylacrylamides with DCM.[6] Though the bond dissociation energies (BDE) of C-H (97.3 ± 1.0 kcal/mol) in DCM is higher than that of C-Cl (80.8 kcal/mol),[3] the corresponding products via the dichloromethyl radical not the chloromethyl radical have been observed in this system. One could realize that the reactivities and/or selectivities of free-radical promoted C–H bond functionalization might be not due to the BDE of the C–H and C-X bonds, but the stability of the corresponding carbon centered radical.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) T. Yamashita, M. Yasuda, M. Watanabe, R. Kojima, K. Tanabe and K. Shima, *J. Org. Chem.* 1996, **61**, 6438; (b) G. W. Kabalka, N.-S. Li and S. Yu, *Organometallics* 1995, **14**, 1565; (c) J. B. Behr, D. Chavaria and R. Plantier-Royon, *J. Org. Chem.* 2013, **78**, 11477; (d) B. Maillard, A. Kharrat, F. Rakotomanana, E. Montaudon and C. Gardrat, *Tetrahedron* 1985, **41**, 4047; (e) M. Agorrody, M. Campagnole, E. Montaudon and B. Maillard, *Tetrahedron* 1987, **43**, 3429; (f) R. N. Haszeldine, R. Rowland, A. E. Tipping and G. Tyrrell, *J. Fluorine Chem.* 1982, **21**, 253; (g) E. Montaudon, M. Campagnole, F. Flies and B. Maillard, *J. Heterocycl.Chem.*1991, **28**, 459; (h) M. Agorrody, E. Montaudon and B. Maillard, *Can. J. Chem.* 1987, **65**, 2694.

2 (a) For our recent contributions on C-C bond formation/C-H bond activation, see: (a) Z.-Q. Liu, L. Sun, J. Wang, J. Han, Y. Zhao and B. Zhou, *Org. Lett.* 2009, **11**, 1437; (b) Z.-Q. Liu, Y. Zhang, L. Zhao, Z. Li, J. Wang, H. Li and L.-M. Wu, *Org. Lett.* 2011, **13**, 2208; (c) Z. Li, Y. Zhang and Z.-Q. Liu, *Org. Lett.* 2012, **14**, 74; (d) Y. Zhang, Z. Li and Z.-Q. Liu, *Org. Lett.* 2012, **14**, 226; (e) Y. Zhang, Z. Cui, Z. Li and Z.-Q. Liu, *Org. Lett.* 2012, **14**, 1838; (f) Z. Cui, X. Shang, X.-F. Shao and Z.-Q. Liu, *Chem. Sci.* 2012, **3**, 2853; (g) X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.* 2013, **42**, 3253; (h) Z. Li, Y. Zhang, L. Zhang and Z.-Q. Liu, *Org. Lett.* 2014, **16**, 382; (i) Z. Li, F. Fan, J. Yang and Z.-Q. Liu, *Org. Lett.* 2014, **16**, 3396.

3 Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, 2002.

4 (a) A. J. Kirby, *Stereoelectronic Effects*, Oxford University Press, Oxford, 1996; (b) K. Fukui, *Acc. Chem. Res.* 1971, **4**, 57.

5 (a) B. S. Jensen, *CNS Drug Rev.* 2002, **8**, 353; (b) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.* 2003, 2209; (c) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.* 2007, **46**, 8748. For selected recent examples to synthesis of oxindoles, see: (d) J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett.* 2010, **12**, 3446; (e) T. Wu, X. Mu and G.-S. Liu, *Angew. Chem. Int. Ed.* 2011, **50**, 12578; (f) X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo and G.-S. Liu *J. Am. Chem. Soc.* **2012**, *134*, 878; (g) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie and J.-H. Li, *Angew. Chem. Int. Ed.* 2013, **52**, 3638; (h) Y.-M. Li, M. Sun, H.-L. Wang, Q.-P. Tian and S.-D. Yang, *Angew. Chem., Int. Ed.*, 2013, **52**, 3972; (i) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng and J.-H. Li, *Chem. Sci.*, 2013, **4**, 2690; (j) X. Li, X. Xu, P. Hu, X. Xiao and C. Zhou, *J. Org. Chem.*, 2013, **78**, 7343; (k) K. Matcha, R. Narayan and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2013, **52**, 7985; (l) Y. Meng, L.-N. Guo, H. Wang and X.-H. Duan, *Chem. Commun.* 2013, **49**, 7540; (m) X. Wei, Y. Li, A. Zhou, T. Yang and S.-D. Yang, *Org. Lett.* 2013, **15**, 4158; (n) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng and C. Zhu, *Chem. Commun.* 2013, **49**, 5672; (o) H. Wang, L.-N. Guo and X.-H. Duan, *Chem. Commun.* 2013, **49**, 10370; (p) M.-B. Zhou, C.-Y. Wang, R.-J. Song, Y. Liu, W.-T. Wei and J.-H. Li, *Chem. Commun.* 2013, **49**, 10817; (q) T. Shen, Y. Yuan and N. Jiao, *Chem. Commun.* 2014, **50**, 554; (r) J.-Y. Wang, Y.-M. Su, F. Yin, Y. Bao, X. Zhang, Y.-M. Xu and X.-S. Wang, *Chem. Commun.* 2014, **50**, 4108; (s) D. C. Fabry, M. Stodulski, S. Hoerner and T. Gulder, *Chem. Eur. J.* 2012, **18**, 10834; (t) S.-L. Zhou, L.-N. Guo, H. Wang and X.-H. Duan, *Chem. Eur. J.* 2013, **19**, 12970; (u) J.-Y. Wang, X. Zhang, Y. Bao, Y.-M. Xu, X.-F. Cheng and X.-S. Wang, *Org. Biomol. Chem.* 2014, **12**, 5582; (v) H.-L. Wei, T. Piou, J. Dufour, L. Neuville and J. Zhu, *Org. Lett.* 2011, **13**, 2244; (w) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.* 2013, **15**, 5254; (x) F. Yin and X.-S. Wang, *Org. Lett.* 2014, **16**, 1128; (z) Z.-Z. Zhou, H.-L. Hua, J.-Y. Luo, Z.-S. Chen, P.-X. Zhou, X.-Y. Liu and Y.-M. Liang, *Tetrahedron* 2013, **69**, 10030.

6 When we are preparing the manuscript, an iron-catalyzed cascade carbochloromethylation of activated alkenes was reported, see: M.-Z. Lu and T.-P. Loh, *Org. Lett.* 2014, **16**, 4698.