Small-Ring Compounds

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Copper-Catalyzed (2+1) Annulation of Acetophenones with Maleimides: Direct Synthesis of Cyclopropanes**

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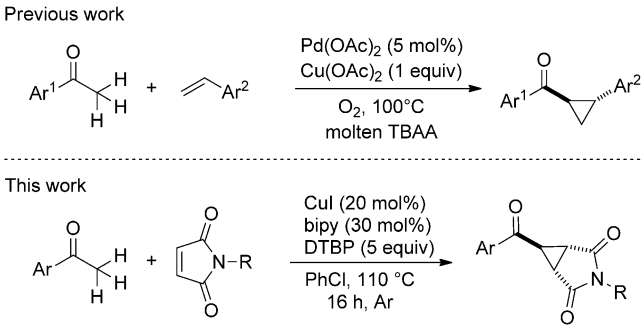
Abstract: *A practical copper-catalyzed direct oxidative cyclopropanation of electron-deficient alkenes with acetophenone derivatives is reported. The dehydrogenative annulation involves a double C–H bond functionalization at the α-position of the ketone using di-tert-butyl peroxide as oxidant. The broad scope of the reaction and excellent functional-group tolerance is demonstrated for the stereoselective synthesis of fused cyclopropanes. The developed transformation revealed an unprecedented reactivity for copper-catalyzed processes.*

Cyclopropanes represent versatile synthons with unique reactivity in organic synthesis. Strained carbocycles are present in many natural, and biologically and medicinally important products.[1] The synthesis of the cyclopropane moiety has evoked considerable interest and resulted in the development of different synthetic strategies. Cyclopropanation of alkenes with carbenes, carbenoids, and ylides is a widely used transformation.[2] The Simmon–Smith reaction[3] and Michael-initiated ring closure[4] have found applications in the synthesis of cyclopropanes. Furthermore, methods based on the transformation of compounds with active methylene groups[5] and photochemical approaches[6] were used for the preparation of cyclopropanes. These methods require the application of reactive prefunctionalized reagents. Therefore, the development of novel and practical methods for the straightforward synthesis of strained cyclopropanes using nonfunctionalized materials remains a considerable challenge and their elaboration is highly desired.

Recently, Cotugno et al. reported an elegant palladium(II)-catalyzed direct cyclopropanation of alkenes with acetophenones (Scheme 1).[7] The reaction is limited to styrenes and requires the use of stoichiometric amounts of a copper salt as a co-oxidant and an ionic liquid as the reaction medium. Herein, we report the first direct oxidative[8] copper-catalyzed stereoselective annulation of alkenes with acetophenone derivatives (Scheme 1).



Scheme 1. Metal-catalyzed annulation. TBAA = tetrabutylammonium acetate.

Our group has been involved in the development of novel methods for the synthesis[9] and functionalization[10] of heterocyclic compounds using direct C–H bond transformations. We were interested in investigating direct approaches for the synthesis of 3-azabicyclo[3.1.0]hexane derivatives.[11] Initially, *N*-methylmaleimide (**1a**) and 2-acetylnaphthalene (**2a**) were selected to identify optimal reaction conditions for the direct 3-azabicyclo[3.1.0]hexane synthesis (Table 1). We began our studies of cyclopropanation by using CuI (20 mol%) and 1,10-phenanthroline (**L1**, 10 mol%) in the presence of di-*tert*-butylperoxide (DTBP) as the oxidant in chlorobenzene at 100 °C under argon. Notably, the product **3a** was obtained in 52% yield after 24 hours (Table 1, entry 1). Inspired by the initial result, we first tested different ligands. We found that the copper-catalyzed cyclopropanation occurs with a higher yield of **3a** when using 2,2′-bipyridine (**L3**, 63% yield) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L4**, 64% yield) as ligands, while the use of other ligands was less efficient (Table 1, entries 1–5 and see the Supporting Information). Afterwards, various oxidants were tested in direct cyclopropanation, and DTBP was found to be the best oxidant. We did not observe the desired product when either *tert*-BuOOH, H_2O_2, or $PhI(OAc)_2$ were employed as oxidants (see the Supporting Information). The formation of **3a** was inhibited in the presence of oxygen. When the reaction was carried out at different temperatures, the yield of **3a** was decreased to 63% at 90 °C. The best yield (72%) of **3a** was obtained at 110 °C (entries 7–9). Various copper salts were used as precatalysts, however, the yields were slightly reduced when using CuBr or CuCl. When copper(II) diacetate was used, a yield of only 35% of **3a** was achieved (entries 10–12). An increase of the loading of the oxidant led to an improved yield of 83% for **3a**. Chlorobenzene was found to be the best solvent (see the Supporting Information).

With optimized reaction conditions in hand, we investigated the scope of the cyclopropanation using different

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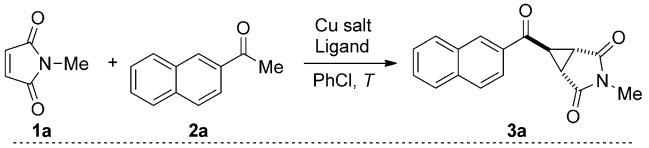
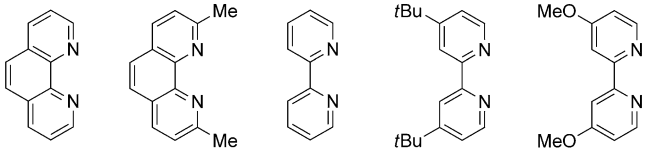
Table 1: Screening of reaction conditions.[a]



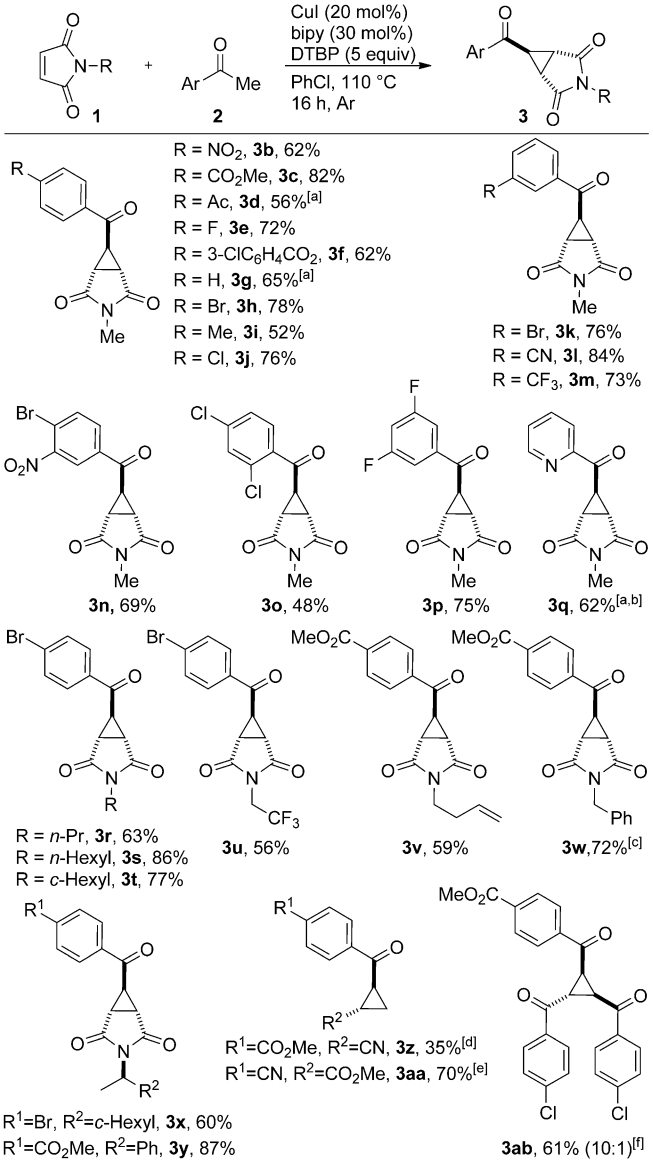


Entry	Cu salt (mol%)	Ligand (mol%)	T [°C]	DTBP (equiv)	Yield [%]
1	CuI (20)	**L1** (10)	100	3	52
2	CuI (20)	**L2** (10)	100	3	trace
3	CuI (20)	**L3** (10)	100	3	63
4	CuI (20)	**L4** (10)	100	3	64
5	CuI (20)	**L5** (10)	100	3	49
6[b]	CuI (20)	**L3** (10)	100	3	trace
7	CuI (20)	**L3** (30)	100	3	65
8	CuI (20)	**L3** (30)	110	3	72
9	CuI (20)	**L3** (30)	120	3	68
10	CuBr (20)	**L3** (30)	110	3	65
11	CuCl (20)	**L3** (30)	110	3	62
12	$Cu(OAc)_2$ (20)	**L3** (30)	110	3	35
13	CuI (20)	**L3** (30)	110	5	83

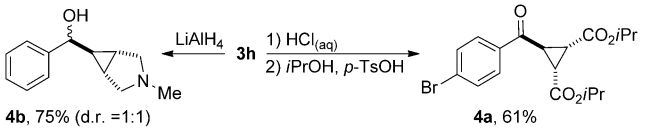
[a] Reaction conditions: **1a** (0.25 mmol) and **2a** (0.5 mmol), in solvent (2.0 mL) for 24 h under argon. [b] Reaction carried out under O_2.

acetophenone derivatives with *N*-methyl maleimide. Various functional groups on the acetophenone were tolerated without any difficulty under the reaction conditions (Scheme 2, products **3b**–**p**). The application of polysubstituted acetophenones provided the desired products (**3n**–**p**) as well. The developed method was employed for heterocyclic derivatives. For example, the cyclopropanation with 2-acetylpyridine delivered the desired product **3q** in 62% yield. Notably, all desired products were obtained as single isomers. Encouraged by those results, we further explored the scope of the copper-catalyzed cyclopropanation with a series of N-substituted maleimides (**3r**—**y**). A variety of alkyl-substituted maleimides allowed formation of the target products. The application of *N*-benzylmaleimide provided the product **3w** in 72% yield without over-oxidation of the activated benzylic position. Importantly, a maleimide substituted with a terminal alkene was tolerated under the radical reaction conditions and gave the desired product **3v** in 59% yield. Furthermore, by employing chiral maleimides in the annulation, the desired products **3x** and **3y** were obtained diastereoselectively. Acrylic acid derivatives were applicable and stereoselectively delivered the *trans*-substituted cyclopropanes **3z** and **3aa**. Moreover, the product **3ab** was obtained in yield 61% and good diastereomeric ratio through the annulation of *trans*-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione .

Afterwards, we investigated additional transformations of the obtained products (Scheme 3). The product **3h** was transformed into the cyclopropane **4a** by hydrolysis and subsequent diesterification. By using an excess of $LiAlH_4$, **3h** was smoothly reduced to 3-azabicyclo[3.1.0]hexane derivative **4b**.

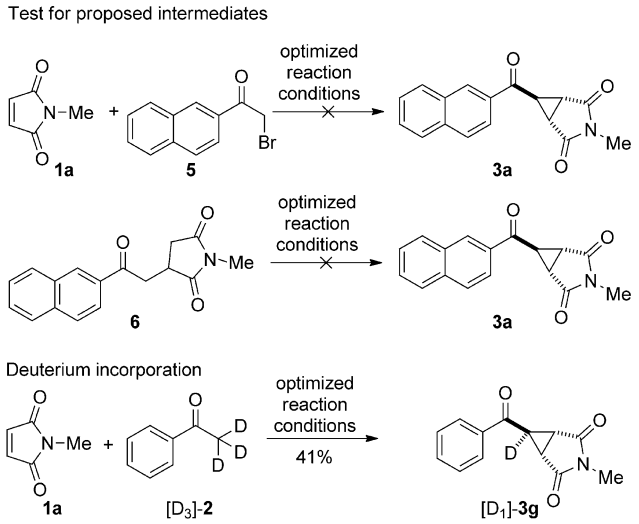


Scheme 2. Scope of annulation. Reaction conditions: **2** (0.25 mmol), **1** (0.5 mmol), DTBP (5 equiv), CuI (20 mol%), and **L3** (30 mol%) in PhCl (2.0 mL) at 110°C for 16 h under argon. All products were formed with a d.r. > 20:1. [a] **1** (0.25 mmol) and **2** (3 equiv) were used. [b] **L1** (10 mol%) and 4 equiv DTBP were used. [c] Reaction time was 12 h. [d] Acrylonitrile (4 equiv) was used. [e] Using CuI (10 mol%), **L4** (20 mol%), DTBP (3 equiv) methyl acrylate (10 equiv). [f] At 100°C, major isomer is shown.



Scheme 3. Transformations of **3h**. Ts = 4-toluenesulfonyl.

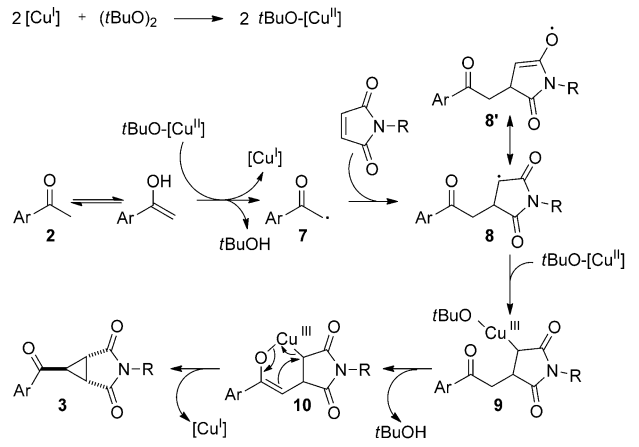
Next we turned our attention to understanding the mechanism of the copper-catalyzed reaction. Initially, we



Scheme 4. Mechanistic experiments.

wondered whether the cyclopropanation reaction proceeds by in situ formation of α-haloacetophenone. The reaction of **5** under the optimized reaction conditions did not yield the desired product (Scheme 4). The desired product **3a** was also not obtained from the Michael adduct **6**, which could be obtained by addition of **2a** to **1a**. The formation of **3a** was suppressed in the presence of TEMPO, thus indicating that cyclopropanation occurs through a radical process. Interestingly, when using deuterated acetophenone ([D_3]-**2g**) in the cyclopropanation, [D_1]-**3g** was obtained in 41% yield (Scheme 4). Incorporation of deuterium was greater than 95%. Therefore, the high diastereoselectivity of the reaction is not a result of epimerization through a keto-enol mechanism. The kinetic isotopic effect was equal to 2.45. Therefore, the abstraction of both hydrogen atoms is not the rate-determining step in the developed cyclopropanation.

On the basis of these observations and literature reports, a plausible mechanism is proposed for the cyclopropanation of maleimides with acetophenones (Scheme 5). First, copper(I) is oxidized to a copper(II) species by DTBP. Warren and co-workers reported that the oxidation of copper(I) with DTBP occurs with a fast reaction rate and quantitative conversion into [Cu^{II}]-O*t*Bu.[12] In the following step, acetophenone is oxidized by the copper(II) species to the radical **7**. In a control experiment using the optimized reaction conditions for **3a** but in the absence of the copper catalyst, the product **3a** and intermediate **6** were not formed (see the Supporting Information).[13] The formation of **7** from the enol by oxidation with high-valent metals is known in oxidative coupling.[8] The radical **7** then adds to maleimide to produce the radical **8**, which can be stabilized through resonance. Addition of **8** to the copper(II) species generated the intermediate **9**. Enolization of the keto group leads to ligand exchange and yields the cyclic intermediate **10** and *tert*-butanol. The formation of **10** is the stereodetermining step of the developed annulation. Reductive elimination of copper(I) from **10** gives the final product **3**, and the copper(II) catalyst is regenerated by oxidation of copper(I) with DTBP.



Scheme 5. Plausible mechanism.

In conclusion, we have developed a novel copper-catalyzed cyclopropanation of maleimides with acetophenone derivatives with broad scope. This reaction represents an unprecedented example of a copper-catalyzed stereoselective synthesis of annulated cyclopropanes. Mechanistic studies revealed a novel reactivity for copper-catalyzed radical reactions. The developed reaction is highly practical because diverse and readily available starting materials can be used without preliminary functionalization.

Keywords: annulation · copper · heterocycles · small-ring compounds · synthetic methods

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[1] a) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; *Angew. Chem.* **2014**, *126*, 5608–5628; b) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, 979–1029; c) P. Tang, Y. Qin, *Synthesis* **2012**, 2969–2984; d) D. Y. K. Chen, R. H. Pouwer, J. A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642; e) Z. H. Zhang, J. B. Wang, *Tetrahedron* **2008**, *64*, 6577–6605; f) J. Salaün, *Top. Curr. Chem.* **2000**, *207*, 1–67.

[2] a) D. H. Ringger, P. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 4686–4689; *Angew. Chem.* **2013**, *125*, 4784–4787; b) Z. Y. Cao, X. M. Wang, C. Tan, X. L. Zhao, J. Zhou, K. L. Ding, *J. Am. Chem. Soc.* **2013**, *135*, 8197–8200; c) B. Morandi, E. M. Carreira, *Science* **2012**, *335*, 1471–1474; d) J. Li, S. H. Liao, H. Xiong, Y. Y. Zhou, X. L. Sun, Y. Zhang, X. G. Zhou, Y. Tang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8838–8841; *Angew. Chem.* **2012**, *124*, 8968–8971; e) T. Piou, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 11292–11295.

[3] a) J. A. Bull, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1895–1902; b) S. R. Goudreau, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15633–15635; c) Z. L. Song, T. Lu, R. P. Hsung, Z. F. Al-Rashid, C. H. Ko, Y. Tang, *Angew. Chem. Int. Ed.* **2007**, *46*, 4069–4072; *Angew. Chem.* **2007**, *119*, 4147–4150; d) J. Long, Y. Yuan, Y. Shi, *J. Am. Chem. Soc.* **2003**, *125*, 13632–13633.

[4] a) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894; b) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2006**, *45*, 6024–6028; *Angew. Chem.* **2006**, *118*, 6170–6175; c) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241; d) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2004**, *43*, 2681–2684; *Angew. Chem.* **2004**, *116*, 2735–2738.

[5] a) A. Yoshimura, T. N. Jones, M. S. Yusubov, V. V. Zhdankin, *Adv. Synth. Catal.* **2014**, *356*, 3336 – 3340; b) B. Jin, J. Shen, R. F. Peng, R. Z. Zheng, S. J. Chu, *Tetrahedron Lett.* **2014**, *55*, 5007 – 5010; c) R. H. Fan, Y. Ye, W. X. Li, L. F. Wang, *Adv. Synth. Catal.* **2008**, *350*, 2488 – 2492.

[6] a) O. Muehling, P. Wessig, *Chem. Eur. J.* **2008**, *14*, 7951 – 7960; b) P. Wessig, O. Muhling, *Angew. Chem. Int. Ed.* **2005**, *44*, 6778 – 6781; *Angew. Chem.* **2005**, *117*, 6936 – 6940; c) P. Wessig, O. Muhling, *Helv. Chim. Acta* **2003**, *86*, 865 – 893.

[7] P. Cotugno, A. Monopoli, F. Ciminale, A. Milella, A. Nacci, *Angew. Chem. Int. Ed.* **2014**, *53*, 13563 – 13567; *Angew. Chem.* **2014**, *126*, 13781 – 13785.

[8] a) F. H. Guo, M. D. Clift, R. J. Thomson, *Eur. J. Org. Chem.* **2012**, 4881 – 4896; b) H. Q. Do, T. V. Hung, O. Daugulis, *Organometallics* **2012**, *31*, 7816 – 7818; c) B. M. Casey, R. A. Flowers, *J. Am. Chem. Soc.* **2011**, *133*, 11492 – 11495; d) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546 – 11560; e) A. G. Csákÿ, J. Plumet, *Chem. Soc. Rev.* **2001**, *30*, 313 – 320; f) Y. Ito, T. Konoike, T. Harada, T. Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 1487 – 1493; g) Y. Ito, T. Konoike, T. Saegusa, *J. Am. Chem. Soc.* **1975**, *97*, 2912 – 2914.

[9] a) R. Samanta, R. Narayan, J. O. Bauer, C. Strohmann, S. Sievers, A. P. Antonchick, *Chem. Commun.* **2015**, *51*, 925 – 928; b) R. Narayan, A. P. Antonchick, *Chem. Eur. J.* **2014**, *20*, 4568 – 4572; c) K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 11960 – 11964; *Angew. Chem.* **2014**, *126*, 12154 – 12158; d) S. Manna, K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 8163 – 8166; *Angew. Chem.* **2014**, *126*, 8302 – 8305; e) S. Manna, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 7324 – 7327; *Angew. Chem.* **2014**, *126*, 7452 – 7455; f) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 7985 – 7989; *Angew. Chem.* **2013**, *125*, 8143 – 8147.

[10] a) Z. Q. Song, R. Samanta, A. P. Antonchick, *Org. Lett.* **2013**, *15*, 5662 – 5665; b) K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2013**, *52*, 2082 – 2086; *Angew. Chem.* **2013**, *125*, 2136 – 2140; c) A. P. Antonchick, L. Burgmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3267 – 3271; *Angew. Chem.* **2013**, *125*, 3349 – 3353; d) R. Samanta, R. Narayan, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 6108 – 6111; e) R. Samanta, J. Lategahn, A. P. Antonchick, *Chem. Commun.* **2012**, *48*, 3194 – 3196; f) R. Samanta, J. O. Bauer, C. Strohmann, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 5518 – 5521.

[11] a) K. K. Toh, A. Biswas, Y. F. Wang, Y. Y. Tan, S. Chiba, *J. Am. Chem. Soc.* **2014**, *136*, 6011 – 6020; b) K. K. Toh, Y. F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942 – 13945.

[12] R. T. Gephart, C. L. McMullin, N. G. Sapiezynski, E. S. Jang, M. J. B. Aguila, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2012**, *134*, 17350 – 17353.

[13] An alternative mechanism: the reaction of $Cu^{I}X$ with DTBP occurs by electron transfer, thereby generating tBuO$Cu^{II}X$ along with the *tert*-butoxyl radical. The *tert*-butoxyl radical may react with **2** to generate the radical **7** by H-abstraction.

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