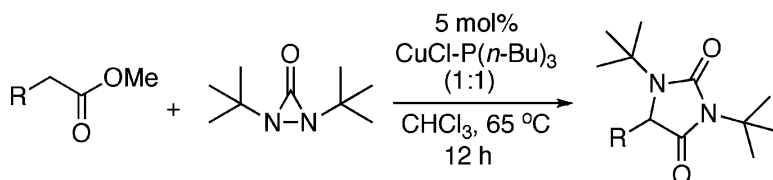


A Cu(I)-Catalyzed C#H #-Amination of Esters. Direct Synthesis of Hydantoins

Baoguo Zhao, Haifeng Du, and Yian Shi

J. Am. Chem. Soc., **2008**, 130 (23), 7220-7221 • DOI: 10.1021/ja802242h • Publication Date (Web): 13 May 2008

Downloaded from <http://pubs.acs.org> on February 8, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



A Cu(I)-Catalyzed C–H α -Amination of Esters. Direct Synthesis of Hydantoin

Baoguo Zhao, Haifeng Du, and Yian Shi*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received March 26, 2008; E-mail: yian@lamar.colostate.edu

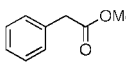
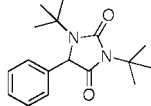
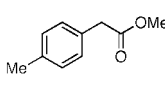
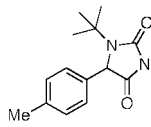
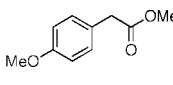
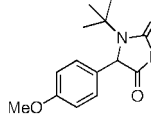
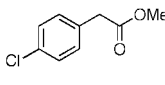
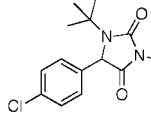
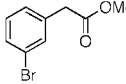
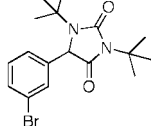
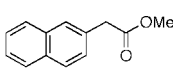
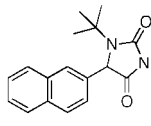
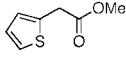
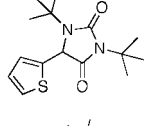
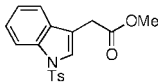
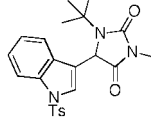
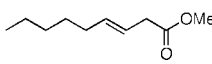
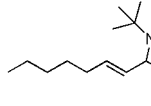
Amines and their derivatives are very important functional moieties present in a wide variety of biologically and chemically significant molecules. The C–N bond formation represents one of very important synthetic transformations. Various effective methods have been developed for the construction of C–N bonds.¹ Converting C–H bonds to C–N bonds by direct amination is also an attractive strategy to introduce nitrogens to molecules. Significant progress has been made in this area.^{2,3} During our studies on amination with diaziridinones,^{4,5} we found that ester **1** can be aminated at the α position using di-*tert*-butyldiaziridinone (**2**)^{6,7} as a nitrogen source and CuCl as a catalyst, leading to a direct formation of hydantoin (**3**) (Scheme 1). Herein we wish to report our preliminary results on this subject.

Treating methyl phenylacetate (**1a**) with di-*tert*-butyldiaziridinone (**2**) and 10 mol % of CuCl-P(*n*-Bu)₃ (1:1) in CDCl₃ at 65 °C in an NMR tube for 12 h gave hydantoin **3a** with 54% conversion (Scheme 1). Lower conversions were obtained with the corresponding ethyl ester (44%) and *tert*-butyl ester (25%) under the same reaction conditions, suggesting that the bulkier esters are less effective toward the amination. Further studies show that the reaction can be improved by slow addition of di-*tert*-butyldiaziridinone over 8 h. Under this protocol, hydantoin **3a** was obtained in 79% yield using 5 mol % of CuCl-P(*n*-Bu)₃ (1:1) as catalyst (Table 1, entry 1) (the X-ray structure of **3a** is shown in Figure 1). As shown in Table 1, various methyl arylacetates were efficiently α -aminated to give the corresponding hydantoin derivatives in good yields (Table 1, entries 1–6). Heteroaryl and β,γ -unsaturated methyl esters were also α -aminated to give the corresponding hydantoin derivatives with somewhat lower yields (Table 1, entries 7–9). However, aliphatic methyl esters such as methyl octanoate are not effective substrates under the current reaction conditions.

The deprotection of the resulting hydantoin derivatives was investigated with compound **3a**. Both *tert*-butyl groups were smoothly removed with CH₃SO₃H in hexane (1:10, v/v) at 65 °C for 3.5 h to give compound **4** in 92% yield. However, when the deprotection was carried out at room temperature, one *tert*-butyl group was selectively removed to give compound **5** in 96% yield (Scheme 2). The structure of compound **5** was determined by the X-ray structure of its acetyl derivative **5a** (Scheme 2) (Figure 1). The ability of selective removal of the protection groups provides opportunities to introduce different groups on the two nitrogen atoms of hydantoin derivatives if it is desired.

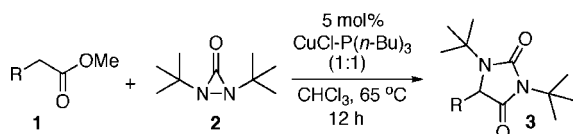
While an exact reaction mechanism awaits further study, a plausible catalytic cycle is shown in Scheme 3. The CuCl probably first reduces the N–N bond to form species **6**^{4c,8–11} or

Table 1. Cu(I)-Catalyzed α -Amination of Esters^a

Entry	Substrate (1)	Product (3)	Yield (%) ^b
1			79
2			62
3			73
4			78
5			68
6			61
7			57
8			49
9			54

^a All reactions were carried out with ester (**1**) (0.4 mmol), di-*tert*-butyldiaziridinone (**2**) (0.8 mmol), CuCl-P(*n*-Bu)₃ (1:1) (0.02 mmol) in CHCl₃ (0.05 mL) at 65 °C under argon for 12 h unless otherwise stated. For entry 7, the reaction scale was doubled. For entries 1 and 3, the reaction scale was doubled except CHCl₃ (0.05 mL).
^b Isolated yield based on ester.

Scheme 1



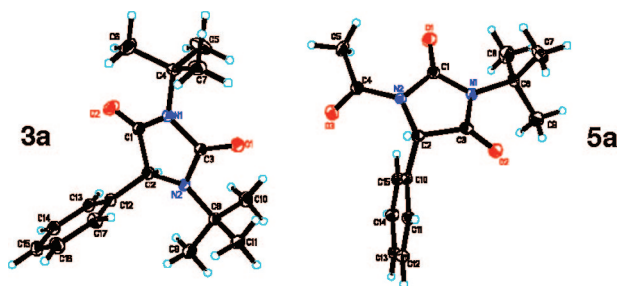
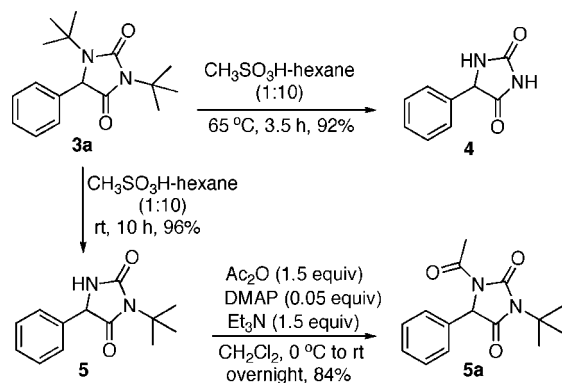
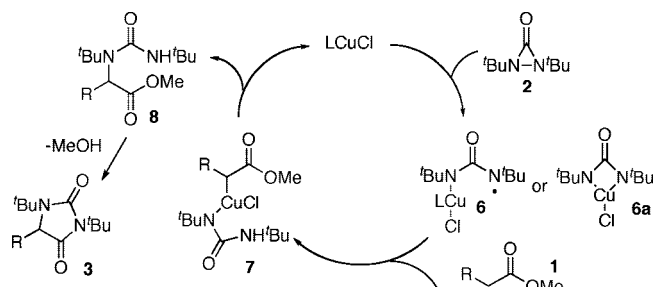


Figure 1. The X-ray structure of hydantoin 3a and 5a.

Scheme 2



Scheme 3. A Proposed Catalytic Cycle for the α -Amination



6a, which reacts with ester **1** to form **7** possibly via a hydrogen abstraction or deprotonation. The reductive elimination of **7** gives compound **8** and regenerates CuCl catalyst.^{12,13} Compound **8** cyclizes to form hydantoin **3** by loss of MeOH. This mechanism is also consistent with the fact that esters, such as methyl octanoate, without groups that can facilitate the α -hydrogen abstraction or deprotonation are not effective substrates under the reaction conditions.

In summary, a variety of methyl arylacetates and β,γ -unsaturated methyl ester can be effectively α -aminated using CuCl as catalyst and di-*tert*-butyldiaziridinone (**2**) as nitrogen source under mild reaction conditions. The current α -amination process provides direct access to various hydantoin which are present in various biologically active compounds.¹⁴ Further studies on the reaction mechanism, exploration of different catalysts and nitrogen sources, and expansion of the substrate scope as well as development of asymmetric process are currently underway.

Acknowledgment. This paper is dedicated to the memory of Professor Albert I. Meyers. We are grateful for the generous financial support from the Camille and Henry Dreyfus Foundation.

Supporting Information Available: Complete ref 14c, the amination and deprotection procedures, the characterization of amination products, and the X-ray data of compounds **3a** and **5a** along with the ¹H and ¹³C NMR spectra of amination products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For recent leading reviews, see: (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (b) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (f) Hultsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (g) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (h) Kottli, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug. Des.* **2006**, *67*, 101. (i) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (j) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (k) Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.
- (2) For leading reviews, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 17. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.
- (3) For recent leading references on sp³ C-H amination, see: (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Leung, S. K.-Y.; Huang, J.-S.; Liang, J.-L.; Che, C.-M.; Zhou, Z.-Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 340. (c) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078. (d) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (e) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (f) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (g) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639. (h) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184. (i) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. (j) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158. (k) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316.
- (4) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (c) Yuan, W.; Du, H.; Zhao, B.; Shi, Y. *Org. Lett.* **2007**, *9*, 2589. (d) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688.
- (5) For a leading review on diaziridinones, see: Heine, H. W. In *The Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley & Sons, Inc: New York, 1983; p 547.
- (6) Greene, F. D.; Stowell, J. C.; Bergmark, W. R. *J. Org. Chem.* **1969**, *34*, 2254.
- (7) For leading references on the reaction of diaziridines with ketenes, see: (a) Shevtsov, A. V.; Petukhova, V. Yu.; Strelenko, Yu. A.; Lyssenko, K. A.; Makhova, N. N.; Tartakovsky, V. A. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 1021. (b) Shevtsov, A. V.; Ananikov, V. P.; Makhova, N. N. *Russ. J. Org. Chem.* **2007**, *43*, 1101.
- (8) For a leading review on metal-promoted radical reactions, see: Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.
- (9) (a) For leading reviews on CuX-catalyzed atom transfer reactions see: Patten, T. E.; Matyjaszewski, K. *Acc. Chem. Res.* **1999**, *32*, 895. (b) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1.
- (10) For leading references on nitrogen-centered radicals, see: (a) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407. (b) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.
- (11) For leading references on Cu(I)-catalyzed homolytic cleavage of N–O bonds of oxaziridines, see: (a) Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466. (b) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269. (c) Black, D. StC.; Edwards, G. L.; Laaman, S. M. *Tetrahedron Lett.* **1998**, *39*, 5853. (d) Black, D. StC.; Edwards, G. L.; Laaman, S. M. *Synthesis* **2006**, 1981.
- (12) For leading references on Cu(II)-promoted oxidative couplings of carbonyl compounds, see: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857.
- (13) For a leading review on organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
- (14) For leading references, see: (a) Rizzi, J. P.; Schnur, R. C.; Hutson, N. J.; Kraus, K. G.; Kelbaugh, P. R. *J. Med. Chem.* **1989**, *32*, 1208. (b) Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klingler, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158. (c) Kim, D.; et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3099. (d) Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417. (e) Sheppeck, J. E., II; Gilmore, J. L.; Tebben, A.; Xue, C.-B.; Liu, R.-Q.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2769.

JA802242H