ORGANIC LETTERS

2012
Vol. 14, No. 15
3982–3985

Copper Catalyzed Oxidative Esterification of Aldehydes with Alkylbenzenes via Cross Dehydrogenative Coupling‡

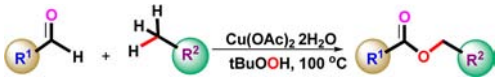
Saroj Kumar Rout, Srimanta Guin, Krishna Kanta Ghara, Arghya Banerjee, and Bhisma K. Patel*

Department of Chemistry, Indian Institution of Technology, Guwahati, Guwahati 781 039, India

patel@iitg.ernet.in

Received June 27, 2012

ABSTRACT



Copper(II) as the catalyst in a cross dehydrogenative coupling (CDC) reaction has been demonstrated for the synthesis of benzylic esters using aldehydes and alkylbenzenes as coupling partners.

The upsurge in interest in the transition metal catalyzed reactions via the cleavage of an ubiquitous C−H bond has been creating a renaissance in the construction of a diverse array of C−C and C−X (X = heteroatom) bonds.[1] The two most popular approaches are chelation assisted C−H bond functionalization[2] and the cross dehydrogenative coupling (CDC).[3] This field of synthesis has advanced to such an extent that even the otherwise inert sp^3 C−H bonds could now be functionalized.[3,4] The CDC approach is attractive because it does not require substrate prefunctionalization and it is atom economic.[1d,5] As evident from the literature, CDC has been widely investigated for the formation of C−C bonds[3a,6] albeit the concept has rarely been explored regarding C−O bond formation. The relevance of C−O bonds in organic chemistry has resulted in the emergence of various transition metal based methodologies via C−H bond activation.[7] In this regard the ester functionality has been the common target. Some recent metal catalyzed CDC based transformations for the synthesis of esters involve acid and cyclic ethers where the functionalization occurs selectively at the sp^3 carbon atom α to the ethereal oxygen.[8] Focusing on the protocols for the synthesis of benzylic esters, besides the traditional methods, a number of CDC based approaches employing metal catalysts such as Ru,[9] Rh,[10] Ir,[11] and Pd[12] have been developed.

‡ Dedicated to Prof. Bijay Kumar Mishra on the occasion of his 60th Birthday.

(1) (a) *Handbook of C−H transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005. (b) Shilov, A. E.; Shulpin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(2) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(3) (a) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335 and references therein. (b) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827. (c) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (d) Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384.

(4) (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Kreutzer, J. S.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (c) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(5) (a) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436. (b) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

(6) (a) Han, W.; Mayer, P.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2178. (b) Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (c) Deng, G.; Zhao, L.; Li, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (d) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 4455. (e) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (f) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (g) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822.

(7) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (c) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (e) Ye, Z.; Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 3974.

(8) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Lei, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085.

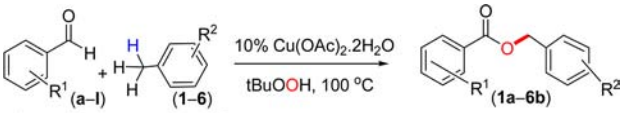
(9) (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840. (b) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Milstein, D. *Dalton Trans.* **2007**, *107*, 113. (c) Gunanathan, C.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2009**, *131*, 3146. (d) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624.

10.1021/ol301756y
Published on Web 07/20/2012

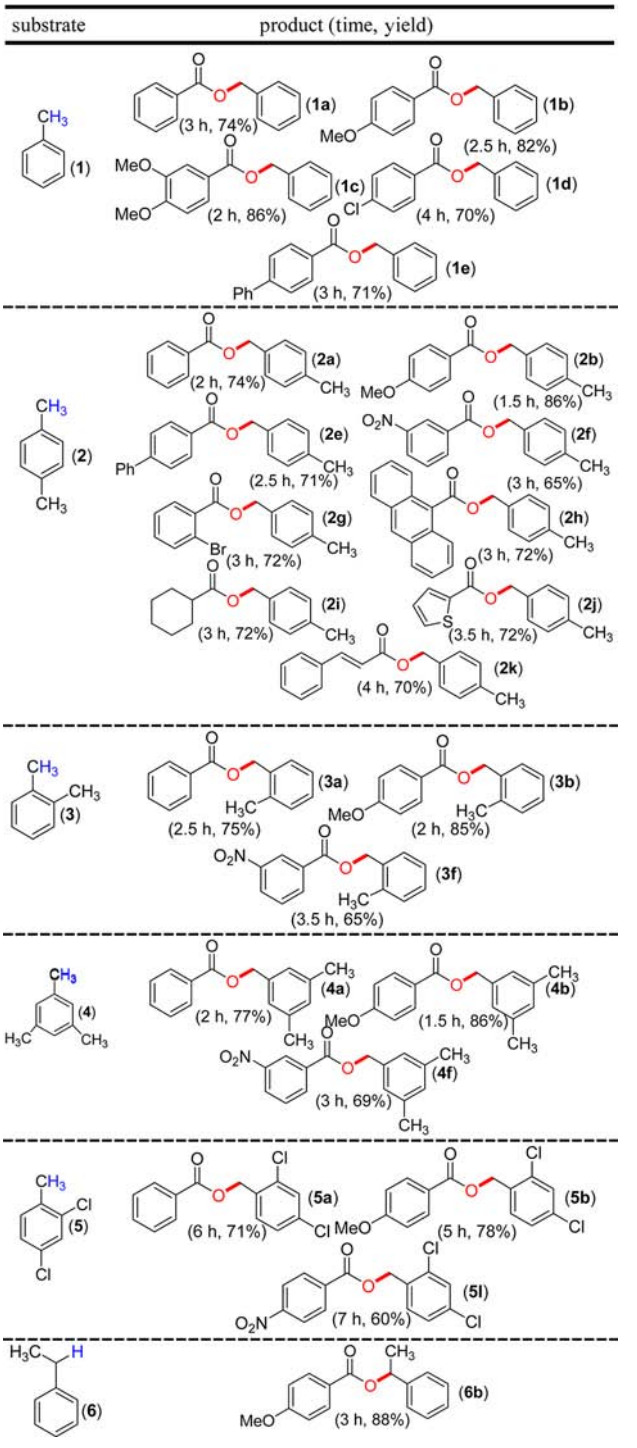
Most of these transition metal catalyzed formations of benzylic esters invoke the concept of a hydrogen borrowing[13] or hydrogen autotransfer process[14] where benzylic alcohols serve as a precursor. The other methodology that has recently been developed uses the advantage of metal-free conditions for the synthesis of benzylic esters via oxidative C−O bond formation at the sp^3 benzylic carbon of various alkylbenzenes with carboxylic acids.[15]

Extensive use and exploration of copper in C−H activation is a promising area in organic synthesis because of its high efficiency as a catalyst.[16] The use of various copper salts in combination with peroxides as an oxidant is known to work effectively in facilitating functionalizations at the relatively inert sp^3 carbon.[3a,17] However, most of these methodologies concentrate on C−H bond functionalization at the sp^3 carbon atom α to heteroatoms. A direct functionalization at the relatively nonactivated alkylbenzenes has rarely been explored. To date, there is no precedence of copper catalyzed methodology with alkylbenzenes and aldehydes as precursors for the synthesis of benzylic esters via a CDC approach. With this motivation we initiated our investigation by reacting benzaldehyde (1 equiv) (**a**) with toluene (5 equiv) (**1**) in the presence copper(I) bromide (20 mol %) and aqueous TBHP (1 equiv) at 80 °C which provided the expected (**1b**) ester but in a mere yield of 22%. The hydrated copper(II) acetate provided a superior yield (48%) compared to other Cu salts such as $CuBr_2$, CuCl, $CuCl_2$, and $Cu(OTf)_2$ tested. The use of a decane solution of TBHP instead of aqueous TBHP improved the yield up to 65%. Interestingly, an identical yield was observed using 10 mol % of the catalyst when TBHP in decane (5−6 M) was used. A complete disappearance of the substrate (**1a**) was observed with an isolated yield of 74% when the oxidant quantity was increased by 2-fold at a temperature of 100 °C. A further decrease in catalyst loading (5 mol %) had an adverse effect on product yield. No desired product was obtained when oxidant H_2O_2 was used instead of TBHP. The control experiments carried out with either a copper

Table 1. Substrate Scope for Benzylic Esters[a,b]



R^1 = H, Ph, OMe, Cl, NO_2; R^2 = H, CH_3, Cl



[a] Reaction conditions: aldehyde (1 mmol), alkylbenzene (5 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (0.1 mmol), TBHP (2 mmol), 100 °C, time 1.5−7 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

(10) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559.

(11) (a) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, *68*, 1601. (b) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem.—Eur. J.* **2010**, *16*, 6820. (c) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667. (d) Shimizu, K. -i.; Ohshima, K.; Satsuma, A. *Chem.—Eur. J.* **2009**, *15*, 9977.

(12) (a) Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5139. (b) Liu, C.; Wang, J.; Meng, L.; Deng, Y.; Li, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5144. (c) Liu, C.; Tang, S.; Zheng, L.; Liu, D.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5662.

(13) (a) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. (b) Lamb, G. W.; Williams, J. M. J. *Chim. Oggi.* **2008**, *26*, 17. (c) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.

(14) Ramon, J.; Yus, M.; Guillena, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.

(15) Feng, J.; Liang, S.; Chen, S.-Y.; Zhang, J.; Fu, S.-S.; Yu, X.-Q. *Adv. Synth. Catal.* **2012**, *354*, 1287.

(16) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (b) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (c) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (d) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075.

(17) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

catalyst or TBHP alone did not serve the purpose, as no desired product could be detected.

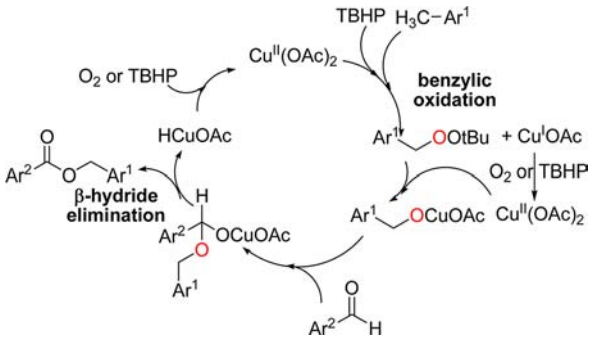
Encouraged by the outcome of the above experiments, the suitability of this protocol was examined toward the synthesis of benzylic esters employing various alkylbenzenes with a set of aldehydes as coupling partners. The optimized conditions were initially applied to the coupling of toluene (**1**, Table 1) with a set of aromatic aldehydes (**a**−**e**, Table 1) having both electron-donating (**b** and **c**) and electron-withdrawing (**d**) substituents. It was observed that, under the present conditions, toluene smoothly underwent reactions with various aldehydes to afford the desired benzylic esters (**1a**−**1d**) in good to excellent yields as shown in Table 1. Reaction with *p*-phenyl benzaldehyde (**e**) gave a fairly good yield of the corresponding benzylic ester (**1e**). As evident from the results in Table 1, the electronic effects of the substituent in the aryl ring bearing the aldehyde functionality played a role in controlling the product yields. With electron-donating substituents (**b**−**c**, Table 1), high yields of the benzylic esters (**1b**−**1c**, Table 1) were obtained in a shorter span while those with electron-withdrawing substituents (**d**, Table 1) proceeded a bit sluggishly providing moderate yields. To further unravel the potentiality of this approach, other target alkylbenzenes, viz. *p*-xylene (**2**), *o*-xylene (**3**), and mesitylene (**4**) (Table 1), were examined, all of which possess more than one benzylic carbon. A query arises as to whether their reactions would provide mono, bis, or tri esters. However, the most appealing outcome in all their reactions were the selective formation of the corresponding monoester with the other alkyl (methyl) groups remaining intact besides undergoing a smooth reaction with their corresponding coupling aldehyde partners. Specifically, the reaction of *p*-xylene (**2**) when treated with a diverse array of aldehydes, viz. aromatic (**a**−**b**, **e**−**h**, Table 1) aliphatic (**i**), heteroatomic (**j**), and α−β unsaturated (**k**), provided satisfactory results (Table 1). The formations of the benzylic esters (**2a**−**2k**, Table 1) were unaffected by the influence of any groups present within the aldehydic moiety. This methodology was also equally successful toward the monoesterification of *o*-xylene (**3**) and mesitylene (**4**) with various aldehydes as shown in Table 1. Noteworthy, the reactivity trends observed for these di- or trialkylatedbenzenes with aromatic aldehydes were the same as was observed with toluene (**1**). Next we turned our attention to study the reactivity of benzylic C−H of 2,4-dichloromethylbenzene (**5**, Table 1) with aromatic aldehydes (**a**, **b**, and **l**, Table 1). In all these cases the reactions proceeded rather sluggishly to afford the desired products (**5a**, **5b**, and **5l**) in moderate to good yields depending on the substituent present in the aldehydes. The slow reactivity of 2,4-dichloromethylbenzene (**5**) could be attributed to the reluctance of the methyl group toward the C−O bond formation with Cu/TBHP. The reaction of ethylbenzene (**6**, Table 1) with *p*-methoxybenzaldehyde (**b**) proceeded smoothly to form the C−O bond selectively at the 2° benzylic carbon to form the corresponding benzylic ester (**6b**, Table 1). This observation shows that benzylic carbon is more susceptible toward an oxidative C−O bond formation rather than another alkyl (1°) position. The use of benzylic alcohols such as *p*-methoxybenzyl and *p*-nitrobenzyl alcohols (as latent aldehydic functionality) with alkylbenzenes is expected to give the aforementioned unsymmetrical esters. However, when *p*-methoxybenzyl and *p*-nitrobenzyl alcohols were treated separately with toluene (**1**) under the present experimental conditions, only self-coupled symmetrical benzylic esters, viz. 4-nitrobenzyl-4-nitrobenzoate and 4-methoxybenzyl-4-methoxybenzoate, were obtained and no traces of unsymmetrical esters benzyl-4-nitrobenzoate and benzyl-4-methoxybenzoate could be found. Thus, the present methodology is most suitable for the preparation of unsymmetrical esters.

Scheme 1. A Crossover Experiment

To probe the mechanism of the reaction, several control experiments were performed. During the reaction of benzaldehyde (**a**) with *p*-xylene (**2**), along with the desired product (**2a**), formation of *p*-methylbenzyl alcohol was observed with a trace amount of benzoic acid (oxidation of benzaldehyde). *p*-Methylbenzyl alcohol formed by the oxidation of a combination of *p*-xylene (**2**) with Cu/TBHP.[18] Thus ambiguity appears in whether the esterification occurred via a reaction of *in situ* generated benzyl alcohol with benzaldehyde (**a**) by an oxidative process[19] or by the radical coupling of the *in situ* generated benzoic acid (from benzaldehyde) with *p*-xylene (**2**) as has been reported.[15] To ascertain the exact coupling partners a crossover experiment was performed in which *p*-methoxybenzaldehyde (**b**) and benzoic acid were reacted with *p*-xylene (**2**) under the present experimental conditions (Scheme 1). No formation of 4-methylbenzyl benzoate (**2a**) and exclusive formation of 4-methylbenzyl-4-methoxy benzoate (**2b**) ruled out the usual esterification of acid and alcohol (generated *in situ* from *p*-xylene) or the radical pathway between acid and alkylbenzene.[15] This reaction, rather, occurs via the coupling of aldehyde and the *in situ* generated alcohol (from alkylbenzene) via a hemiacetal intermediate[12,19] as shown in Scheme 2. No kinetic isotope effect ($K_H/K_D \sim 1$) was observed when the reaction of deuterated benzaldehyde was carried out with toluene (**1**) suggesting that hydride transfer is not the rate-determining step. Considerable rate retardation associated with the poor yield of product in the presence of a radical scavenger such as 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) suggests inhibition of oxidation at the benzylic carbon leading to the formation of alcohol which is possibly the rate-determining step.[18]

(18) Rothenberg, G.; Feldberg, L.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin. Trans. 2* **1998**, 2429.
(19) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577.

Scheme 2. Proposed Mechanism of the Oxidative Esterification



In conclusion we have developed a new and efficient catalytic approach for the synthesis of benzylic ester from aldehydes and alkylbenzenes. This reaction proceeds via benzylic sp^3 C–H bond activation of alkylbenzenes in the presence of an inexpensive copper catalyst and TBHP combination. Exclusive formation of monoesters was observed for polyalkylated benzenes indicating a high degree of selectivity. This methodology provides an avenue to the synthesis of various unsymmetrical benzylic esters from diverse alkylbenzenes and aldehydes. Hence this protocol is yet another novel addition to the existing methods.

Acknowledgment. B.K.P. acknowledges the support of this research by the Department of Science and Technology (DST) (SR/S1/OC-79/2009), New Delhi, and the Council of Scientific and Industrial Research (CSIR) (01(2270)/08/EMR-II). S.K.R., S.G., and A.B. thank CSIR for fellowships. Thanks are due to Central Instruments Facility (CIF) IIT Guwahati for NMR spectra.

Supporting Information Available. General information, experimental procedures, spectral data, and copies of ^1H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.