JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Decarboxylative Allylation of Amino Alkanoic Acids and Esters via Dual Catalysis

Simon B. Lang, Kathryn M. O'Nele, and Jon A. Tunge*

Department of Chemistry, The University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

Supporting Information

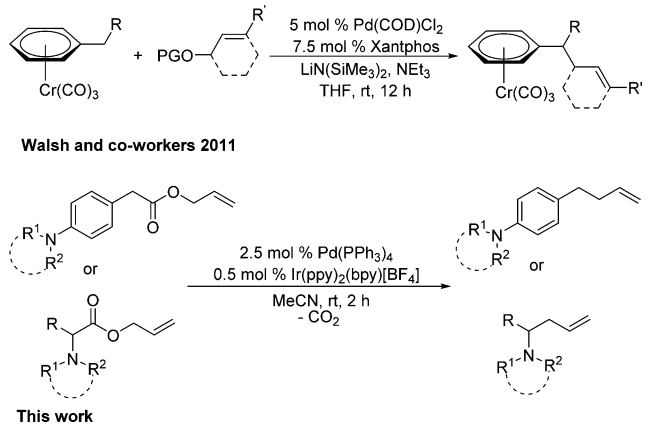
ABSTRACT: A combination of photoredox and palladium catalysis has been employed to facilitate the room temperature decarboxylative allylation of recalcitrant α-amino and phenylacetic allyl esters. This operationally simple process produces CO_2 as the only byproduct and provides direct access to allylated alkanes. After photochemical oxidation, the carboxylate undergoes radical decarboxylation to site-specifically generate radical intermediates which undergo allylation. A radical dual catalysis mechanism is proposed. Free phenylacetic acids were also allylated utilizing similar reactions conditions.

The site-specific generation of reactive intermediates from easily accessible carboxylic acids while producing CO_2 as the only stochiometric byproduct is an attractive hallmark of decarboxylative coupling reactions.[1] One limiting factor of these transformations is that the rate of decarboxylation qualitatively tracks with the pK_a of the resulting anion.[1a] Thus, decarboxylations to generate alkyl anion equivalents with pK_a's > 25 require high temperatures or do not occur at all. We sought to overcome this limitation by taking advantage of the facile radical decarboxylation of alkanoates as opposed to the recalcitrance of more common anionic decarboxylation. Ultimately, we hypothesized that photoredox decarboxylation could be combined with Pd-catalysis to effect the allylation of alkyl species that do not undergo anionic decarboxylation.[2]

The radical decarboxylation of various aryl acetic and α-amino acids following photo-[3] and electrochemical[4] oxidation has been studied for many decades. We were interested in beginning our investigation with (aminoaryl)acetic acids given that the nitrogen lone pair is more prone to oxidation than carboxylates and the resulting radical has been trapped post-decarboxylation.[3h,5] For example, photoredox catalysis[6] has been utilized for the decarboxylative radical addition of aminoarylacetic acids to electron-deficient alkenes by Nishibayashi[7] and for the arylation of α-amino acid derivatives by MacMillan.[8]

Palladium-catalyzed benzylic allylation is especially challenging because benzyl nucleophiles have pK_a's > 40, which limits their accessibility under mild conditions.[9] In 2011 the Walsh group disclosed the use of $Cr(CO)_3$ to increase the acidity of the benzylic C−H bonds, which allowed for their deprotonation and use in Pd-catalyzed allylic substitution reactions (Scheme 1).[10] While this was a significant advancement in the allylation of benzylic nucleophiles, the approach requires the use of a stoichiometric base and chromium and suffers from the need to preform the organometallic complex and remove chromium after the reaction. We hypothesized that a combination of photoredox and palladium catalysis may allow for the direct allylation of benzyl species without the need for a stoichiometric base or activating agents.

Scheme 1. Benzylic Allylation

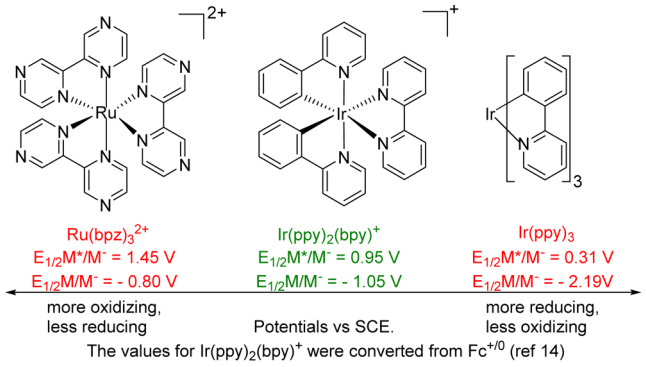


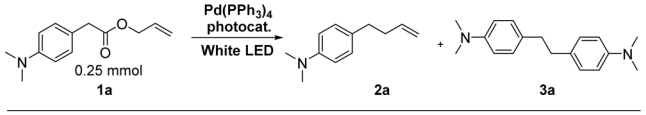
We began by screening conditions for the decarboxylative coupling of allyl ester **1a** by combining $Pd(PPh_3)_4$ with various visible-light-mediated photoredox catalysts and monitoring the conversion to **2a**/**3a** by GC/MS (Table 1). A solvent screen revealed that a polar aprotic solvent was required for reactivity and that acetonitrile gave the best conversion. After 9 h good conversion of starting material to desired product **2a** and homocoupled benzylic radical product **3a** was observed when 1 mol % of $Ru(bpy)_3[BF_4]_2$ was used as the photocatalyst (entry 1). Employing more oxidizing[11] ruthenium based photocatalysts led to extremely low conversions, even after extended reactions times (entries 5, 6). Decreased conversion was also observed when strongly reducing[12] tris-cyclometalated iridium photocatalysts were used (entries 2, 4). In contrast, complete conversion was observed when $Ir(ppy)_2(bpy)[BF_4]$, which possesses intermediate photoredox properties,[13,14] was employed (entry 3). Additional optimization revealed that the reaction reached full conversion in just 1 h (entry 7) and that both the palladium and photocatalyst loading could be reduced at the expense of a slightly longer reaction time (entry 8). No conversion was detected when the reaction was run in the

Received: August 13, 2014
Published: September 17, 2014

   dx.doi.org/10.1021/ja508317j | J. Am. Chem. Soc. 2014, 136, 13606−13609

Table 1. Screening of Photocatalysts[a]





entry	$Pd(PPh_3)_4$	photocat.	time	conversion	(2a/3a)[b]
1	5 mol%	1 mol% $Ru(bpy)_3[BF_4]_2$	9h	95%	67:33[c]
2	5 mol%	1 mol% $Ir(ppy)_3$	9h	32%	nd
3	5 mol%	1 mol% $Ir(ppy)_2(bpy)[BF_4]$	9h	100%	64:36
4	5 mol%	1 mol% $Ir(dFppy)_3$	9h	41%	nd
5	5 mol%	1 mol% $Ru(bpm)_3[PF_6]_2$	15h	trace	nd
6	5 mol%	1 mol% $Ru(bpz)_3[PF_6]_2$	15h	trace	nd
7	5 mol%	1 mol% $Ir(ppy)_2(bpy)[BF_4]$	1h	100%	66:34
8	**2.5 mol%**	**0.5 mol% $Ir(ppy)_2(bpy)[BF_4]$**	**2h**	**100%**	66:34[d]
9	5 mol%	-	1h	none	nd
10	-	1 mol% $Ir(ppy)(bpy)_2[BF_4]$	1h	none	nd
11	2.5 mol%	0.5 mol% $Ir(ppy)_2(bpy)[BF_4]$	2h	none[e]	nd

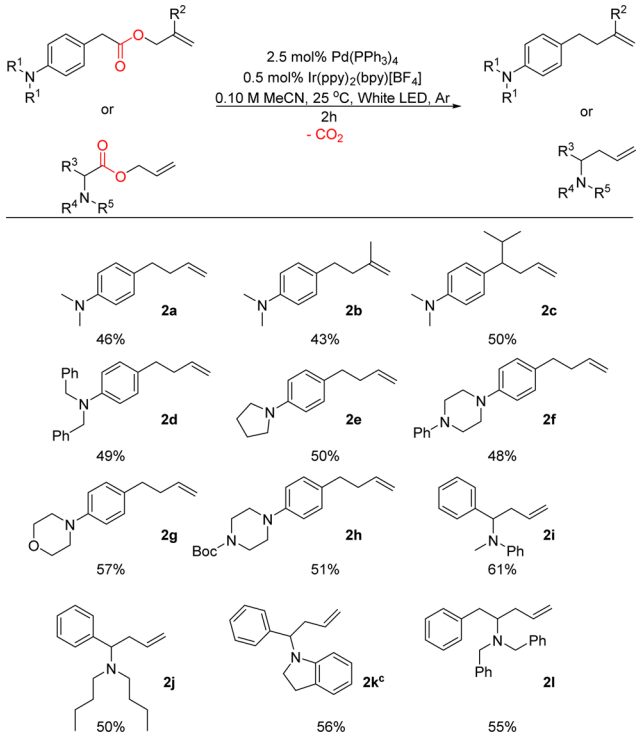
[a]0.25 mmol of **1a** in 2.5 mL of MeCN was stirred under Ar with $Pd(PPh_3)_4$ and photocatalyst for the indicated time in front of a white LED. The crude reaction mixture was analyzed by GC/MS. [b]GC/MS ratios [c]32% isolated yield of **2a**. [d]Isolated 44% **2a**; 0.052 mmol, 41% **3a**. [e]In the absence of light.

absence of light, photocatalyst, $Pd(PPh_3)_4$, or in the presence of 2 equiv of the radical scavenger TEMPO (entries 9, 10, and 11).

Next, different reaction concentrations, temperatures, and palladium sources/ligands were examined in an attempt to control the ratio of **2a** and **3a**. Despite an extensive screen (see Supporting Information), the ratio of desired allylation product to benzylic homodimerization adduct did not appreciably change from 2:1 in reactions that reached complete conversion. This observation led us to hypothesize that both benzyl and allyl radicals were being produced during the reaction leading to a statistical mixture of products.[15] Importantly, monitoring the reaction via ^{1}H NMR spectroscopy revealed the formation of an allyl−allyl coupling product (1,5-hexadiene) and bibenzyl (**3a**) in a 1:1 ratio. While the nature of the radical coupling limits the maximum yield of the coupling, this disadvantage is far outweighed by the operational simplicity of accessing allylated alkane products without any stoichiometric additives.

With these conditions in hand, we began evaluating decarboxylative couplings of *para*-amino substituted phenylacetic acid allyl esters (Scheme 2, **2a**−**2h**). Both cyclic and acyclic tertiary amines underwent radical decarboxylation to

Scheme 2. Scope of Amino Alkanoic Esters[a,b]



[a]Reactions performed on a 0.25 mmol scale. [b] Isolated yields. [c] ~95% pure see SI for more information.

provide the desired product. Steric bulk about the benzyl radical did not dramatically improve the yield by decreasing the amount of homodimerization (**2c**). Substrates with an additional heteroatom that could undergo oxidation without participating in direct resonance with the carboxylate (**2f**−**2h**) were also successfully allylated. Importantly, no allylation was observed at the remote benzylic positions [$-N(CH_2Ph)_2$] of substrate **1d**, which suggests that decarboxylation allows the site-specific generation and reaction of radicals.

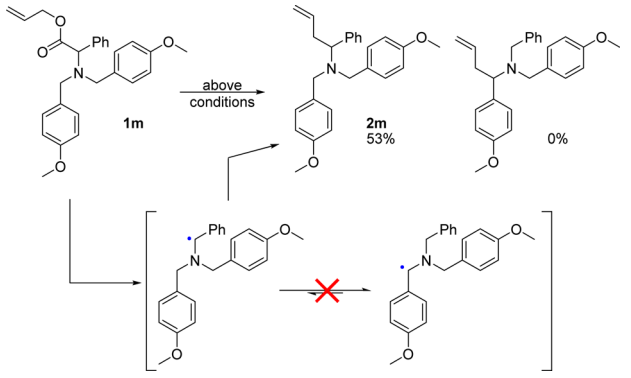
Next, α-amino substituted phenyl acetic acid allyl esters were evaluated (**2i**−**2m**). Tertiary amines with benzyl (**2l**, **2m**), aryl (**2i**, **2k**), and alkyl (**2j**) substituents were all compatible with the standard reaction conditions. In addition, the successful coupling of a phenylalanine derivative to provide **2l** shows that radical formation is not strictly limited to benzylic positions.

To further test the site-specificity of radical coupling, substrate **1m** was synthesized and subjected to decarboxylative allylation conditions (Scheme 3). Indeed, only allylation at the site of the carboxylate was observed. Thus, photochemical decarboxylation allows the generation of the thermodynamically less favored radical, and that radical does not isomerize to the more stabilized radical under the reaction conditions.

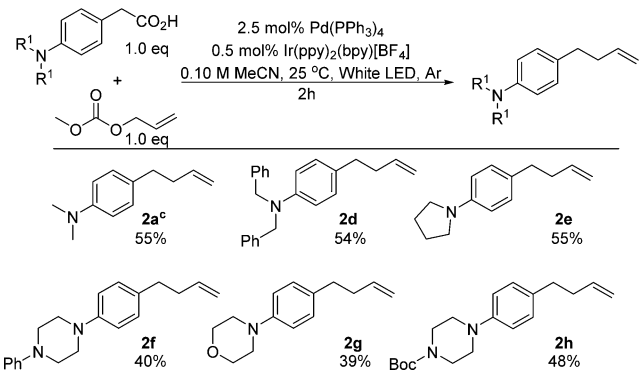
Lastly, avoiding the preformation of allyl esters by generating the same reactive species *in situ* from phenylacetic acids and an allyl source such as allyl methyl carbonate was pursued. We hypothesized that oxidative addition to Pd(0) would generate a Pd-π-allyl species along with methyl carbonate which provides a base capable of generating the requisite carboxylate anion. Indeed, employing the previously optimized conditions to a 1:1 ratio of *para*-amino substituted phenyl acetic acid with allyl methyl carbonate resulted in the generation of the desired allylation products in comparable yields to those from the intramolecular process (Scheme 4).

dx.doi.org/10.1021/ja508317j | J. Am. Chem. Soc. 2014, 136, 13606−13609

Scheme 3. Regiospecific Allylation



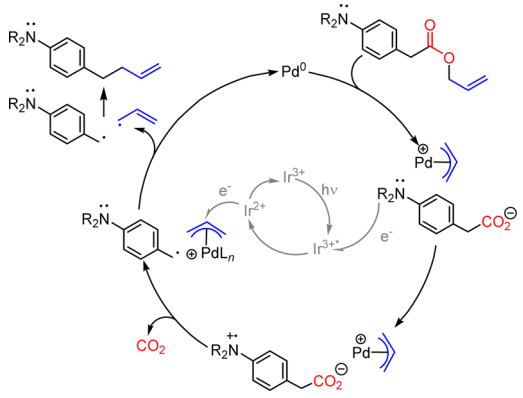
Scheme 4. Allylation of Amino Alkanoic Acids[a,b]



[a]Reactions performed on a 0.25 mmol scale. [b] Isolated yields. [c] The ratio of **2a**/**3a** was measured by GC/MS to be 2:1.

On the basis of the observed experimental results, we tentatively propose a dual catalysis mechanism (Scheme 5).

Scheme 5. A Plausible Mechanism



First, oxidative addition of the allyl ester to Pd(0) forms a Pd-π-allyl species and the carboxylate counterion. This carboxylate can be oxidized by the photoactivated iridium catalyst which triggers radical decarboxylation. Next, the Ir^{II} species may reduce the Pd(allyl) species by one electron,[16] resulting in homolysis to provide an allyl radical and regenerate the active Pd(0) and Ir^{III} catalysts. Alternatively, it is possible that the benzyl radical adds to the Pd(allyl) complex to generate a Pd(III)-allyl species that undergoes reduction by the photocatalyst and reductive elimination.[2a,g,17] In either case, it is noteworthy that the photocatalyst performs both the oxidation of the carboxylate and reduction of the Pd(allyl) complex. This electron shuttling mechanism avoids the need for stoichiometric sacrificial oxidants or reductants that are commonly required in photocatalysis. Additionally, the need to perform both oxidation and reduction is consistent with our observation that a photocatalyst with intermediate redox properties performs better in the decarboxylative allylation reaction.

In conclusion, we have developed an additive-free method for the allylation of alkanes that cannot undergo standard anionic decarboxylative allylation. The dual catalytic coupling proceeds by the site-specific generation of radicals and has the potential to greatly expand the scope of decarboxylative allylation chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H, ^{13}C NMR spectra, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

tunge@ku.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding for this research was provided by the National Science Foundation (CHE-1058855). Support for the NMR instrumentation was provided by NSF Academic Research Infrastructure Grant No. 9512331, NIH Shared Instrumentation Grant No. S10RR024664, and NSF Major Research Instrumentation Grant No. 0320648.

■ REFERENCES

(1) For recent reviews, see: (a) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (b) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (c) Dzik, W. I.; Lange, P. P.; Goossen, L. J. *Chem. Sci.* **2012**, *3*, 2671.

(2) For examples of dual catalytic systems containing photoredox catalysts, see: (a) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (c) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem.—Eur. J.* **2012**, *18*, 5170. (d) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505. (e) Shu, X.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844. (f) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science.* **2014**, *345*, 433. (g) Zuo, Z.; Ahneman, D.; Chu, L.; Terrett, J.; Doyle, A. G.; MacMillan, D. W. C. *Science.* **2014**, *345*, 437.

(3) (a) Joschek, H.-I.; Grossweiner, L. I. *J. Am. Chem. Soc.* **1966**, *88*, 3261. (b) Davidson, R. S.; Steiner, P. R. *J. Chem. Soc. C* **1971**, 1682. (c) Davidson, R. S.; Steiner, P. R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1357. (d) Meiggs, T. O.; Grossweiner, L. I.; Miller, S. I. *J. Am. Chem. Soc.* **1972**, *94*, 7981. (e) Battacharyya, S. N.; Das, P. K. *J. Chem. Soc., Faraday Trans. 2* **1984**, *80*, 1107. (f) D'Alessandro, N.; Albini, A.; Mariano, P. S. *J. Org. Chem.* **1993**, *58*, 937. (g) H. Habibi, M.; Farhadi, S. *J. Chem. Res. (S)* **1998**, 776. (h) Su, Z.; Mariano, P. S.; Falvey, D. E.; Yoon, U. C.; Oh, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 10676. (i) Xu, M.; Wan, P. *Chem. Commun.* **2000**, 2147. (j) Gould, I. R.; Lenhard, J. R.; Farid, S. *J. Phys. Chem. A* **2004**, *108*, 10949. (k) Poupko, R.; Rosenthal, I.; Elad, D. *Photochem. Photobiol.* **1973**, *17*, 395.

(4) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 2450. (b) Trahanovsky, W. S.; Cramer, J.; Brixius, D. W. *J. Am. Chem. Soc.* **1974**, *96*, 1077. (c) Dessau, R. M.; Heiba, E. I. *J. Org. Chem.* **1975**, *40*,

3647. (d) Linstead, R. P.; Shephard, B. R.; Weedon, B. C. L. *J. Chem. Soc.* **1951**, 1130.
(5) (a) Griesbeck, A. G.; Heinrich, T.; Oelgemöller, M.; Lex, J.; Molis, A. *J. Am. Chem. Soc.* **2002**, *124*, 10972. (b) Griesbeck, A. G.; Heinrich, T.; Oelgemöller, M.; Molis, A.; Heidtmann, A. *Helv. Chim. Acta* **2002**, *85*, 4561. (c) Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M. *Org. Lett.* **2009**, *11*, 4652. (d) Yoshimi, Y.; Kobayashi, K.; Kamakura, H.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Hatanaka, M. *Tetrahedron Lett.* **2010**, *51*, 2332. (e) Nishikawa, K.; Yoshimi, Y.; Maeda, K.; Morita, T.; Takahashi, I.; Itou, T.; Inagaki, S.; Hatanaka, M. *J. Org. Chem.* **2012**, *78*, 582. (f) Nishikawa, K.; Ando, T.; Maeda, K.; Morita, T.; Yoshimi, Y. *Org. Lett.* **2013**, *15*, 636.
(6) For recent reviews, see: (a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (c) Schultz, D. M.; Yoon, T. P. *Science.* **2014**, *343*, 985.
(7) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7854.
(8) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257.
(9) (a) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439. (b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. (c) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (d) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860.
(10) Zhang, J.; Stanciu, C.; Wang, B.; Hussain, M. M.; Da, C.-S.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 20552.
(11) (a) Crutchley, R. J.; Lever, A. B. P. *J. Am. Chem. Soc.* **1980**, *102*, 7128. (b) Rillema, D. P.; Allen, G.; Meyer, T. J.; Conrad, D. *Inorg. Chem.* **1983**, *22*, 1617.
(12) Tamayo, A. B.; Alleyne, B. D.; Djurovich, P. I.; Lamansky, S.; Tsyba, I.; Ho, N. N.; Bau, R.; Thompson, M. E. *J. Am. Chem. Soc.* **2003**, *125*, 7377.
(13) Garces, F. O.; King, K. A.; Watts, R. J. *Inorg. Chem.* **1988**, *27*, 3464.
(14) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.
(15) For a detailed analysis, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(16) Kunkely, H.; Vogler, A. *Inorg. Chim. Acta* **2003**, *344*, 262.
(17) Reid, S. J.; Baird, M. C. *Dalton Trans.* **2003**, 3975.