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Catalytic alkylation of benzylic C–H bonds with 1,3-dicarbonyl compounds utilizing oxygen as terminal oxidant

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ABSTRACT

The oxidative alkylation of benzylic C–H bonds with 1,3-dicarbonyl compounds was developed using oxygen as the terminal oxidant in the presence of catalytic amounts of $FeCl_2$, CuCl and NHPI.

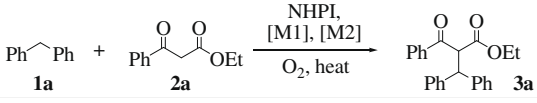
The recent emphasis on green and sustainable chemistry has fed a growing interest towards direct C–C bond formation through functionalization of C–H bonds.[1] One particular class of reactions in this respect is the transition metal-catalyzed functionalization of sp^3 C–H bonds.[2] Due to their usefulness, there is a wide interest in the benzylation of 1,3-dicarbonyl compounds and much of the research in this area centers on the metal-catalyzed[3] or Bronsted-acid catalyzed[4] alkylation of the benzylic alcohol. However, all these reactions use functionalized alcohols as substrates. In our effort to seek novel reactions of C–H bonds, we envisioned the alkylation through the direct oxidative reactions of both the 1,3-dicarbonyl and benzylic C–H bonds.

Previous reports by us and Powell have described the metal-catalyzed oxidative alkylation of benzylic C–H bonds in the presence of excess peroxide.[5] As part of our interest in finding more environmentally friendly and economical alternatives we turned our attention to utilizing oxygen as the terminal oxidant. Previous work reported by us and others have described the use of molecular oxygen for reactions with the C–H bond adjacent to nitrogen.[6] More recently we have shown that, with the use of *N*-hydroxyphthalimide (NHPI) and metal catalysts, cyclic benzylic ethers could be oxidatively alkylated.[7] In the presence of oxygen, NHPI is capable of oxidizing benzylic C–H bonds through a radical mechanism.[8,9] To the best of our knowledge, oxidative C–C formation involving benzylic C–H bonds using oxygen as terminal oxidant has not yet been reported.

Herein, we describe an efficient oxidative alkylation of benzylic C–H bonds with 1,3-dicarbonyls in the presence of catalytic amounts of NHPI, $FeCl_2$, and CuCl, utilizing oxygen as the terminal oxidant.

We first started our investigation using the reaction conditions reported in our previous publication for the oxidative alkylation of benzylic ethers and ketones.[7] We were happy to note that these conditions provided the expected product (**3a**) in 75% NMR yield (Table 1, entry 1). From our previous work we are aware that $FeCl_2$ mediates the alkylation in the presence of peroxide,[5a] we therefore replaced the indium catalyst with $FeCl_2$ and increased the temperature and were pleased to obtain the product in 84% yield (entry 2). Rare earth metals[10] are known to act as Lewis acids and are able to generate benzylic cations from benzylic alcohols, therefore we speculated that if benzhydrol was produced in situ, $Sc(OTf)_3$ would be able to aid in the alkylation; however its addition affected the

Table 1
Optimization of the reaction conditions[a]



Entry	$[M_1]$ (mol %)	$[M_2]$ (mol %)	*T* (°C)	Yield[b] (%)
1	$Cu(OTf)_2$ (5)	$InCl_3$ (5)	75	75
2	$Cu(OTf)_2$ (5)	$FeCl_2$ (5)	105	84
3	$Sc(OTf)_3$ (5)	$FeCl_2$ (5)	105	73
4	**CuCl (5)**	**$FeCl_2$ (5)**	**105**	**94**
5[c]	CuCl (5)	$FeCl_2$ (5)	105	42
6	—	$FeCl_2$ (5)	105	68
7[d]	CuCl (5)	$FeCl_2$ (5)	105	82
8[e]	CuCl (5)	$FeCl_2$ (5)	105	78
9	CuCl (10)	$FeCl_2$ (5)	105	85
10[f]	CuCl (5)	$FeCl_2$ (5)	105	18
11	CuCl (5)	—	105	17
12[g]	CuCl (5)	$FeCl_2$ (5)	105	72

[a] Reaction conditions: **2a** (0.2 mmol, 35 μL), **1a** (5 equiv, 0.17 mL), and 20 mol % NHPI under oxygen at 105 °C overnight unless otherwise noted.
[b] H NMR yields obtained using mesitylene as the internal standard.
[c] Reaction carried out in air.
[d] 10 mol % NHPI.
[e] 30 mol % NHPI.
[f] No NHPI added.
[g] 2.5 equiv **1a** used.

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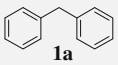
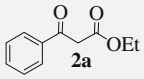
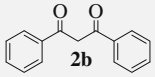
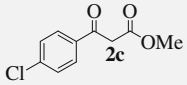
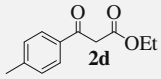
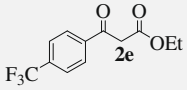
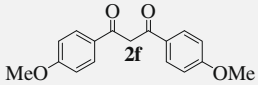
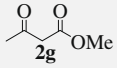
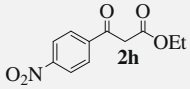
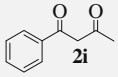
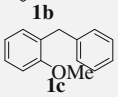
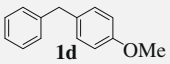
yield negatively (entry 3). We were able to increase the yield even further by replacing $Cu(OTf)_2$ with CuCl (entry 4). A dramatic decrease in yield was observed when either NHPI or $FeCl_2$ was removed which is indicative of their importance in the reaction (entries 10 and 11). The removal of CuCl or running the reaction in air also caused a decrease in yield although not as dramatic compared to NHPI and $FeCl_2$. Neither increasing the amount of CuCl (entry 9) nor changing the amount of NHPI (entries 7 and 8) in the system was favorable. An excess of diarylmethane is needed in this reaction due to the oxidation of **1a** to benzophenone and 5 equiv of the diarylmethane was found to be optimal.

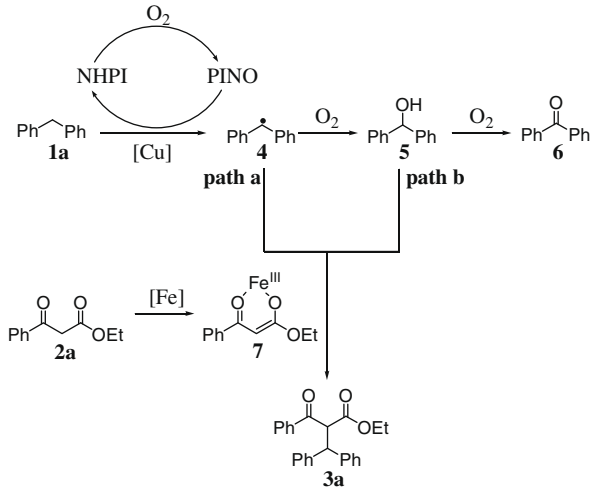
With our optimized conditions in hand (Table 1, entry 4) we then turned to the scope of the alkylation reaction (Table 2). Both aromatic β-ketoesters and 1,3-diketones were good substrates affording moderate to high yields. 1,3-Dicarbonyl substrates with aliphatic groups such as benzoyl acetone (entry 9) and methyl acetoacetate (entry 7) are more difficult to enolize and thus gave low to moderate yields. Diethyl malonate also reacted with diphenyl methane to afford the product albeit in low yield which was difficult to isolate. Electron donation on the phenyl ring of the 4-methoxybenzylanisole better activated the C–H bond and afforded the product in high yield (entry 12). Although 2-methoxybenzylanisole (entry 11) is more activated than diphenylmethane, the lower yield can be attributed to the steric bulk of the *ortho*-methoxy group. The reaction also proceeded smoothly for the less activated cyclic benzylic substrate (entry 10) although in low yield.

We propose two possible pathways that the reaction may be occurring through (Scheme 1). In oxygen, NHPI generates the phthalimide *N*-oxyl (PINO) radical which can then abstract a hydrogen radical from diphenylmethane producing a benzyl radical (**4**). The benzyl radical can either directly add to the iron-enolate intermediate (**7**) via **path a,** or it can be oxidized to benzhydrol (**5**). A third possibility exists where the benzyl radical can be trapped by dioxygen to form the peroxide radical. This peroxide radical can abstract hydrogen from diphenylmethane effectively in a chain propagation step which produces more benzyl radical (**4**). The diphenylmethyl peroxide radical in the presence of iron can then disproportionate into alcohol (**5**) and ketone (**6**) similar to the mechanism we proposed for isochroman.[7,11] Benzhydrol[3d,e] also has the ability to add to the iron-enolate (**path b**). We do not know the exact role of the copper in the reaction but it may aid in the formation of the diphenylmethane radical. Recently Chang reported a CuCl facilitated C–O formation between NHPI and benzylic compounds where they proposed copper was involved in the formation of the PINO radical.[12] The presence of benzophenone (**6**) in the crude reaction mixture is due to the oxidation of benzhydrol or disproportionation of the diphenylmethyl peroxide. We further investigated the mechanism (Scheme 2) by subjecting benzhydrol to the optimized reaction con-

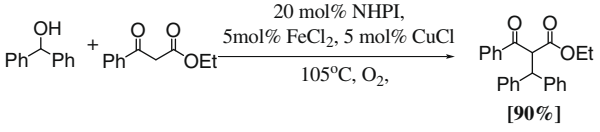
Table 2
Scope for the oxidative alkylation reaction[a]

Entry	Benzylic substrate	1,3-Dicarbonyl substrate	Product	Yield[b] (%)
1	 **1a**	 **2a**	**3a**	79
2	**1a**	 **2b**	**3b**	79
3	**1a**	 **2c**	**3c**	69
4	**1a**	 **2d**	**3d**	66
5	**1a**	 **2e**	**3e**	60
6	**1a**	 **2f**	**3f**	60
7	**1a**	 **2g**	**3g**	55
8	**1a**	 **2h**	**3h**	84
9	**1a**	 **2i**	**3i**	41
10	 **1b**	**2b**	**3j**	27
11	 **1c**	**2b**	**3k**	71
12	 **1d**	**2b**	**3l**	83

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.2 mmol), 5 mol % CuCl, 5 mol % $FeCl_2$, and 20 mol % NHPI under O_2 at 105 °C overnight.
[b] Isolated yields.



Scheme 1. Proposed reaction pathways.



Scheme 2. Reaction of benzhydrol with ethyl benzoyl acetate.

ditions and found that the reaction gave the C–C coupling product in 90% (NMR yield). Furthermore, this reaction also gives the product in 83% NMR yield when run in the absence of NHPI and under nitrogen, both of which supports **path b**.[13]

In summary, we have developed an efficient method for the construction of new C–C bonds through the alkylation of benzylic C–H bonds with 1,3-dicarbonyl compounds. Furthermore, with the addition of catalytic amounts of $FeCl_2$, CuCl, and NHPI we were able to utilize oxygen as the terminal oxidant. Further investigation into the mechanism, scope, and application of this chemistry is in progress.

Procedural information: 2-benzyl anisole **1c** and 4-benzyl anisole **1d** were synthesized according to earlier methods.[5a] Compounds **3a–3c**, **3g**, and **3i–3l** are known compounds and their ^{1}H NMR and ^{13}C NMR spectra corresponded to the literature.[5a,3d] **1a** (1.0 mmol, 0.17 mL) and **2a** (0.2 mmol, 35 μL) were placed in a sealable tube with a magnetic stir bar, to this CuCl (5 mol %, 1.0 mg), $FeCl_2$ (5 mol %, 1.3 mg) and NHPI (20 mol %, 6.5 mg) were added. The tube was flushed with oxygen and a balloon of oxygen was attached, after which it was placed in an oil bath at 105 °C overnight. The mixture was allowed to cool then flushed through a short column of silica gel in a pasture pipette with ethyl acetate and, after rotary evaporation, the compound was isolated by flash column chromatography on silica gel (hexane/ethyl acetate 5:1, R_f = 0.4). Off-white solid **3a** was obtained (56.3 mg, 79%).[14]

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References and notes

1. For recent reviews, see: (a) Bergman, R. G. *Nature* **2007**, *446*, 391; (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; (c) Ritleng, V.; Sirlin, C.; Pfeffer, M.. *Chem. Rev.* **2002**, *102*, 1731; (d) Dyker, G. *Handbook of C–H Transformations*; Wiley-VCH: Weinheim, 2005; (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 76; (f) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041; (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (h) Herrerias, C.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546; (i) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
2. For recent example see: (a) intramolecular reactions: (i) Watanabe, T. Oishi, T. S.; Fujii, S. N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759; (ii) Zhang, C.; Zhao, Y.; Li, B.; Song, H.; Xu, S.; Wang, B. *Dalton Trans.* **2009**, *26*, 5182; (iii) Xu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Organometallics* **2009**, *28*, 4438; (b) Examples of C–H bonds near nitrogen: (i) Zhao, L.; Basle, O.; Li, C.-J. *PNAS* **2009**, *106*, 4106; (ii) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56; (iii) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935; (iv) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242; (c) For recent examples of alkane functionalization: (i) Deng, G.; Chen, W.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 353; (ii) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171; (iii) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278; (d) Examples of sp3 C–H activation by Ru and Rh: (i) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Shi, L.; Cao, K.; Zhang, E. *Chem. Eur. J.* **2008**, *14*, 10201; (ii) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220; (iii) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836.
3. For examples of metal catalyzed alkylation of benzylic C–H bonds, see: (a) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793; (b) Kischel, J.; Mertins, K.; Michalik, D.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 865; (c) Babu, S. A.; Yasuda, M.; Tsukahara, Y.; Yamauchi, T.; Wada, Y.; Baba, A. *Synthesis* **2008**, 1717; (d) Yuan, Y.; Shi, Z.; Feng, X.; Liu, X. *Appl. Organomet. Chem.* **2007**, *21*, 958; (e) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065.
4. For recent examples of Bronsted acid catalyzed alkylation of benzylic C–H bonds see: (a) Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 2027; (b) Yadav, J. S.; Subba Reddy, B. V.; Pandurangam, T.; Raghavendra Rao, K. V.; Praneeth, K.; Narayana Kumar, G. G. K. S.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 4296.
5. (a) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505; (b) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822.
6. (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; (b) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047; (c) Basle, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661; (d) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005; (e) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C. C. *Chem. Commun.* **2009**, 953; (f) Singhal, S.; Jain, S.; Suman, L.; Sain, B. *Chem. Commun.* **2009**, 2371.
7. Yoo, W.-J.; Correia, C. A.; Zhang, Y.; Li, C.-J. *Synlett* **2009**, 138.
8. For reviews, see: (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393; (b) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051; (c) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800; (d) Galli, C.; Gentili, P.; Lanzalunga, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 4790.
9. For the oxidation of C–H bonds using NHPI in oxygen, see: (a) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934; (b) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520; (c) Kato, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 222; (d) Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 222; (e) Hara, T.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 6425; (f) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1120; (g) Sheldon, R. A.; Arends, I. W. C. E. *J. Mol. Catal. A: Chem.* **2006**, *251*, 200; (h) Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747.
10. (a) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825; (b) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033; Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161.
11. Jones, C. W. *Application of Hydrogen Peroxide and Derivatives*; The Royal Society of Chemistry: Cambridge, 1999.
12. Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824.
13. The production of **3a** in the absence of oxygen and NHPI suggest a diphenylmethane carbocation intermediate and subsequent attack by the iron enolate. This carbocation formation could be assisted by the Lewis acids in the mixture.
14. (a) Characterization of unknown compounds: *Ethyl 2-(4-methylbenzoyl)-3,3-diphenylpropanoate* (**3d**): Mp 148.5–151.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.95 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 7.3 Hz, 2H), 7.31–7.21 (m, 6H), 7.20–7.15 (m, 3H), 7.07 (t, J = 7.3 Hz, 1H), 5.41 (d, J = 11.8 Hz, 1H), 5.10 (d, J = 11.7 Hz, 1H), 3.98–3.87 (m, 2H), 2.41 (s, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 192.2, 167.9, 144.6, 141.8, 134.1, 129.4, 128.9, 128.6, 128.5, 128.3, 127.7, 126.8, 126.5, 61.5, 59.2, 50.8, 21.7, 12.7; HRMS (ESI): m/z: $[M+Na]^+$ calcd for $C_{25}H_{24}O_3Na$: 395.1623; found: 395.1614. *Ethyl 3,3-diphenyl-2-(4-(trifluoromethyl)benzoyl)propanoate* (**3e**): Mp 118.0–120.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.11 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.27–7.16 (m, 5H), 7.1–7.07 (t, J = 7.4 Hz, 1H), 5.42 (d, J = 11.8 Hz, 1H), 5.09 (d, J = 11.8 Hz, 1H), 3.99–3.92 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 192.3, 167.3, 141.4, 141.3, 139.2, 134.9, 134.6, 129.0, 128.7, 128.6, 128.1, 127.7, 127.0, 126.8, 125.8, 125.8, 125.7, 125.7, 61.9, 59.9, 50.9, 13.7; HRMS (ESI): m/z: $[M+Na]^+$ calcd for $C_{25}H_{21}O_3F_3Na$: 449.1340; found: 449.1332. *2-Benzhydryl-1,3-bis(4-methoxyphenyl)- propane-1,3-dione* (**3f**): Mp 182.0–183.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.88 (d, J = 8.8 Hz, 4H), 7.26 (d, J = 7.6 Hz, 4H), 7.16 (t, J = 7.6 Hz, 4H), 7.06 (t, J = 7.4 Hz, 2H), 6.82 (d, J = 9 Hz, 4H), 6.22 (d, J = 11.5 Hz, 1H), 5.33 (d,

J = 11.8 Hz, 1H), 3.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 192.6, 163.6, 142.0, 131.1, 130.0, 128.5, 128.2, 126.5, 113.8, 62.2, 55.4, 52.2; HRMS (ESI): m/z: $[M+Na]^+$ calcd for $C_{30}H_{26}O_4Na$: 473.1729; found: 473.1719. *Ethyl 2-(4-nitrobenzoyl)-3,3-diphenylpropanoate* (**3h**): Mp 104.5–107.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.27 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.27–7,22 (m, 3H), 7.17 (t, J = 7.6 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H) 5.42 (d, J = 11.9 Hz, 1H), 5.08 (d, J = 11.8 Hz, 1H), 4.12–3.93 (m, 2H) 0.974 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 192.9, 167.1, 150.4, 141.2, 141.1, 141.0, 129.6, 128.8, 128.7, 128.0, 127.7, 127.1, 126.9, 123.9, 62.1, 60.2, 51.1, 13.7; HRMS (ESI): m/z: $[M+Na]^+$ calcd for $C_{24}H_{21}O_5NNa$: 426.1317; found: 426.1310.