C–H Activation

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Synergistic Palladium-Catalyzed C(sp^3)–H Activation/C(sp^3)–O Bond Formation: A Direct, Step-Economical Route to Benzolactones**

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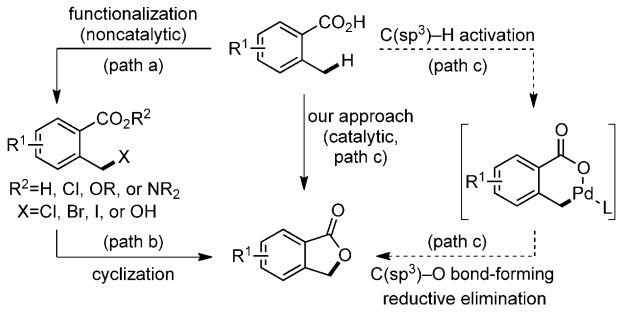
In the last decade, C–H bond-activation protocols have profoundly changed the landscape of organic synthesis through unconventional bond-disconnection strategies for the assembly of complex organic molecules.[1] Ideally, directing groups that are commonly employed in C–H activation processes should have a dual role by assisting chelation and subsequently promoting further functionalization. The use of benzoic acids holds great promise in this regard,[2] as illustrated by the recent work of Yu and co-workers,[3] and other research groups.[4] Despite the available background knowledge, the development of catalytic methods for activating C(sp^3)–H bonds is still in its infancy.[5] Indeed, it is highly desirable to design new synthetic pathways based on C(sp^3)–H activation[6] in order to dramatically increase molecular complexity while avoiding tedious functional group manipulation.

Benzolactones are a prominent structural motif of many bioactive natural products and pharmaceutically important compounds.[7] Classical methods for the synthesis of benzolactones include the cyclization of hydroxy acids or halolactonization processes (Scheme 1, path b).[8] Unfortunately, these methods require prefunctionalization steps, which limit the applicability because of the need for additional synthetic steps (Scheme 1, path a). The most attractive route toward benzolactones **2** would imply a direct catalytic conversion of benzoic acids **1**, thus drastically reducing the overall number of synthetic steps (Scheme 1, path c). Despite encouraging precedents,[9] particularly the pioneering and elegant work reported by Sames and co-workers when using Pt catalysts,[9a] this seemingly routine transformation is not yet efficient because of the low functional group tolerance, the high price of Pt,[10] and the limited substitution patterns that can be accessed, thus enforcing a change in strategy. As part of our ongoing interest in the synthesis of benzoic acids by Pd-catalyzed CO_2 activation,[11] it was anticipated that **1** might undergo a Pd^{II}-catalyzed activation of a proximal C(sp^3)–H bond, followed by a virtually unexplored reductive elimination of a Pd^{II} intermediate to form a C(sp^3)–O bond[12] (Scheme 1, path c).[13,14] This step would be rather challenging because of the large energy gap between the highest occupied molecular orbital (HOMO) of the Pd–O bond and the lowest unoccupied molecular orbital (LUMO) of the Pd–C bond, and the substantial ionic character of the Pd–O bond.[15,16] Overall, path c (Scheme 1) would constitute a direct, step-economical approach toward benzolactones **2**.[17] We hypothesized that the judicious choice of a supporting ligand and its appropriate fine-tuning might play an important, if not critical, role in the synthesis of **2**. Herein, we demonstrate that these two mechanistically distinct Pd-catalyzed processes can be drastically accelerated by the employment of an N-protected amino acid as the supporting ligand in the synthesis of highly functionalized benzolactones with a diverse set of substitution patterns that are beyond reach otherwise.



Scheme 1. Synthetic approaches to benzolactones.

We began our study with **1a** as the model substrate. After considerable optimization,[18] we found that the use of Pd-$(OAc)_2$, K_2HPO_4, and Ag_2CO_3 as the oxidant in chlorobenzene as the solvent afforded a remarkable level of activity (Table 1). As expected from our previous work in inert-bond activation,[11,19] a minor modification in the ligand backbone had a detrimental impact on the reaction outcome. Among the ligands examined, we noticed that the use of **L2** and **L3** was highly beneficial (Table 1, entries 2–3).[20] Subsequently, we found that commercially available N-protected amino acids **L4**–**L9** could be successfully employed as ligands (Table 1, entries 4–10). The beneficial effect of using N-protected amino acids for the activation of various C(sp^2)–H bonds has already been demonstrated by the pioneering work of Yu and co-workers;[21] however, the use of N-protected amino acids for the functionalization of C(sp^3)–H bonds has received much less attention.[22] To the best of our knowledge, N-protected amino acids have not been employed as ligands in Pd-catalyzed C(sp^3)–O bond-forming reactions. Ligand **L7** was particularly active; its use drastically reduced the yield of **3a** while the yield of **2a** was increased up to 95% (Table 1,

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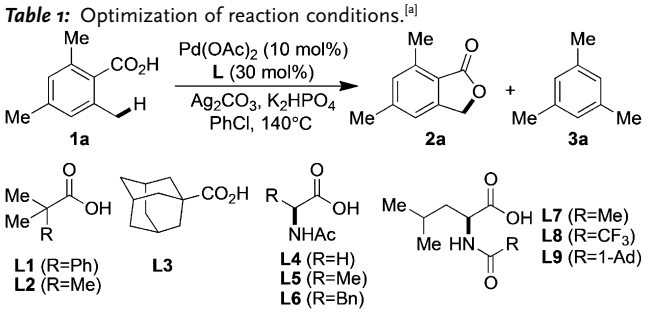
Table 1: Optimization of reaction conditions.[a]

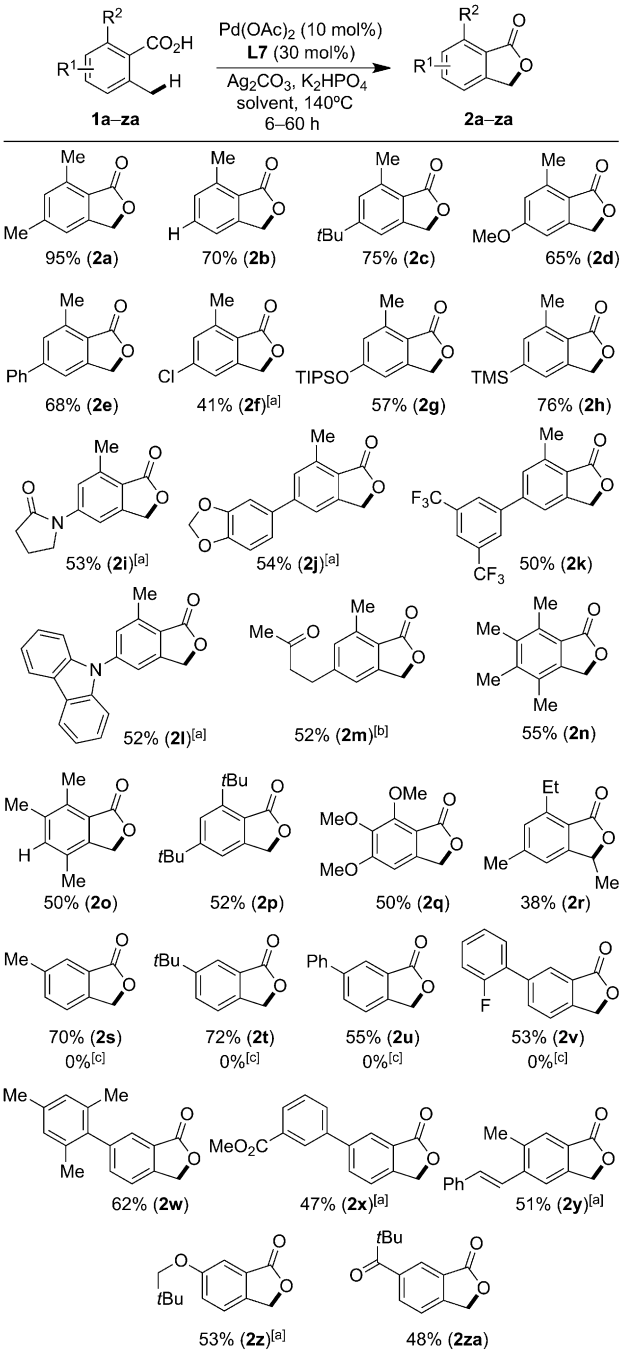


Entry	Ligand	Yield [%][b]	
		2a	**3a**
1	L1	22	17
2	L2	63[c]	1
3	L3	71[c]	13
4	L4	7	3
5	L5	74	12
6	L6	43	11
7	**L7**	**95**[c]	**1**
8	L7	80[c,d]	1
9	L8	36	32
10	L9	42	37
11[e]	–	22	14

[a] **1a** (0.50 mmol, 0.25 M in PhCl as the solvent), $Pd(OAc)_2$ (10 mol%), **L** (30 mol%), Ag_2CO_3 (3 equiv), K_2HPO_4 (2.50 equiv), 140°C. [b] Yield determined by gas chromatography using dodecane as the internal standard. [c] Yield of isolated product. [d] $Pd(OAc)_2$ (5 mol%) was used. [e] Conditions reported in Ref. [9] were used. The entry in bold represents the optimized reaction conditions. Bn = benzyl.

entry 7). Interestingly, this transformation could also be carried out at a lower catalyst loading with 80% yield (Table 1, entry 8). Intriguingly, the favourable profile when using **L7** can not be explained simply by electronic or steric effects, as **L8** or **L9** (Table 1, entries 9 and 10, respectively) are not particularly effective, thus showing the subtleties of our protocol. It is worth mentioning that, in contrast to the previous use of Ag^I salts for promoting decarboxylation,[23] our Ag^I-mediated protocol only afforded **2a**. In order to put these results into perspective, we compared our optimized reaction with the Pt-catalyzed process[9] (Table 1, entry 11) and demonstrated the superior activity of our catalytic system based on **L7**.

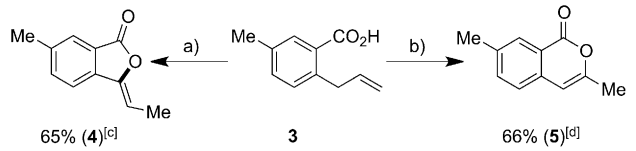
We next turned our attention to the scope of this transformation. As shown in Scheme 2, the chemoselectivity of our methodology was nicely illustrated by the fact that ethers (**2d**,**q**,**z**), silyl ethers (**2g**,**h**), amides (**2i**), ketones (**2m**,**za**), acetals (**2j**), esters (**2x**), alkenes (**2y**), and trifluoromethyl groups (**2k**) were all well accommodated, thus giving a direct access to benzolactones that are inaccessible by classical routes.[8,24] Moreover, the reaction could be conducted in the presence of aryl halides, thus allowing for further manipulation by conventional cross-coupling reactions (**2f**,**v**). Remarkably, compounds bearing nitrogen-containing heterocycles (**2l**) or keto groups with α-acidic protons (**2m**) remained unaffected, thus showing the potential of this transformation. More interestingly, our methodology allowed for the discrimination between different C–H bonds when substrates with substituents at the *meta* position of the



Scheme 2. Preparation of benzolactones. Reaction conditions as in Table 1 with ligand **L7** and, unless stated otherwise, with PhCl as solvent. Yields are those of isolated products (average of two independent runs). [a] A mixture of PhCl/NMP = 4:1 was used as solvent. [b] NMP was used as solvent. [c] Conditions reported in Ref. [9] were used. NMP = *N*-methylpyrrolidin-2-one, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

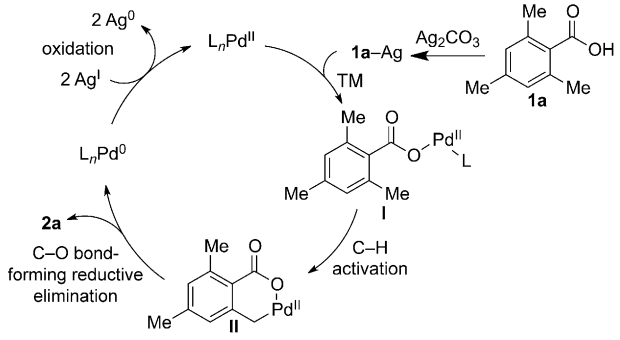
benzoic acid unit were employed (**2s**–**2z**). In these particular cases, selective $C(sp^3)$–H bond activation was observed.[25,26] These results are quite remarkable in light of the unsuccessful preparation of **2s**–**2v** under the same reaction conditions based on Pt catalysts.[9,27] The successful preparation of **2r** (albeit in lower yields) is equally instructive as it indicates that

our reaction is not limited to *ortho*-methyl benzoic acids as substrates. Notably, subtle solvent modification results in different **4**/**5** ratios, thus suggesting the intermediacy of Pd^{II}/π-allyl species[25] or styrene derivatives, respectively (Scheme 3).



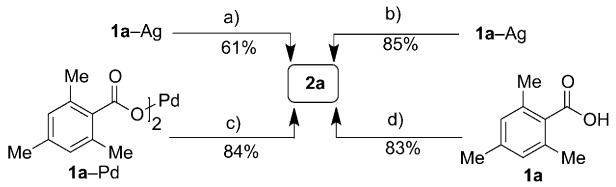
Scheme 3. Preparation of benzolactones **4** and **5**. Reaction conditions as in Table 1 with ligand **L7**, and a) NMP (**4**/**5** = 3.6:1) and b) PhCl/NMP = 4:1 (**5**/**4** = 5:1) as solvent.

A tentative mechanism for the synthesis of benzolactones is shown in Scheme 4. We propose a pathway consisting of a transmetalation of an initially generated silver salt **1a**–Ag



Scheme 4. Mechanistic hypothesis for the synthesis of benzolactones. TM = transmetallation.

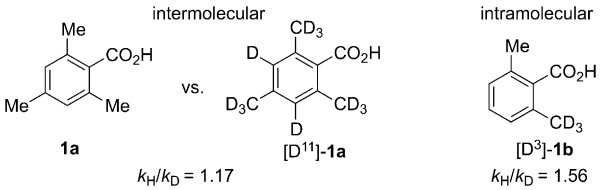
followed by C(sp^3)–H activation to give **II**. C(sp^3)–O bond-forming reductive elimination then delivers **2a** and Pd^0, which upon oxidation by Ag^I regenerates the catalytically active species. At present, we cannot rule out a mechanistic pathway consisting of the dissociation of the carboxylate ligand in **II** to generate a π-benzylic Pd intermediate, followed by an intramolecular Pd–O bond-forming reaction.[28] To support our mechanistic hypothesis, we decided to study the reactivity of some putative intermediates within the catalytic cycle (Scheme 5). Consistent with the proposed mechanism, **1a**–Ag was cleanly converted to **2a** when stoichiometric or catalytic



Scheme 5. Reactivity of the putative intermediates. a) $Pd(OAc)_2$ (1 equiv), **L7** (3 equiv), K_2HPO_4 (2.50 equiv); b) $Pd(OAc)_2$ (10 mol%), **L7** (30 mol%), Ag_2CO_3 (3 equiv), K_2HPO_4 (2.50 equiv); c) **L7** (3 equiv), K_2HPO_4 (2.50 equiv); d) **1a**–Pd (10 mol%), **L7** (30 mol%), Ag_2CO_3 (3 equiv), K_2HPO_4 (2.50 equiv).

amounts of $Pd(OAc)_2$ were used (Scheme 5, steps a and b, respectively).[18] Similarly, **1a**–Pd was shown to be both chemically and kinetically competent as an intermediate in the absence of Ag_2CO_3, and afforded **2a** in 84% yield (Scheme 5, step c).[18] Interestingly, the absence of K_2HPO_4 had a deleterious effect and led exclusively to **3a**. At present, we also cannot exclude the intermediacy of k^2-Pd^{II} complexes.[29] As expected, **1a**–Pd could also be used as a precatalyst and afforded **2a** in a comparable 83% yield (Scheme 5, step c).[18] Even though these experiments cannot be used as an ultimate proof, they provide evidence that a Pd^{II}/Pd^{IV} catalytic cycle[30] is highly unlikely, and support the notion that the Ag^I salts act with a dual role by recovering the catalytic species and participating in an early transmetalation step (Scheme 4).

We also conducted experiments with isotopically labeled substrates (Scheme 6). No significant kinetic isotope effect was observed in the competitive reaction of **1a** and [D_{11}]-**1a**;



Scheme 6. Kinetic isotope effects.

similar results were also found in the intramolecular cyclization of [D_3]-**1b**. The observed isotope effects suggest that the C(sp^3)–H bond cleavage might not be rate-determining, which is a rather peculiar observation as the vast majority of C–H activation processes possess high k_H/k_D values.[31] Although further investigations need to be conducted,[32] at present we support the hypothesis that the C(sp^3)–O bond-forming reductive elimination[12,13] is rate-limiting in our protocol. Overall, we believe our results are highly instructive, and advocate the notion that **L7** might play an important role in both the activation of the C(sp^3)–H bond and the reductive elimination to form the C(sp^3)–O bond.

In conclusion, we have developed a direct and operationally simple protocol to prepare benzolactones with a wide variety of functional groups and a diverse set of substitution patterns. We believe that our represents a significant step forward for truly applicable, yet active catalysts for a step-economical route to benzolactones. Future investigations are aimed at gaining further mechanistic evidence and the development of an asymmetric version of this route.

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[1] For selected reviews, see: a) C. S. Yeung, M. V. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; b) J. F. Hartwig, *Chem. Soc. Rev.*

2011, *40*, 1992 – 2002; c) L. McMurray, F. O'Hara, M. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885 – 1898; d) T. W. Lyons, M. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169; e) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976 – 10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792 – 9826011; f) X. Chen, K. M. Engle, D. H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196 – 5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094 – 5115.

[2] T. Satoh, M. Miura, *Synthesis* **2010**, 3395 – 3409.

[3] For selected references, see: a) D. H. Wang, J. Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767 – 5769; b) D. H. Wang, K. M. Engle, B. F. Shi, J. Q. Yu, *Science* **2010**, *327*, 315 – 319; c) Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 14654 – 14655.

[4] For selected references, see: a) C. L. Sun, J. Liu, Y. Wang, X. Zhou, B.-J. Li, Z.-J. Shi, *Synlett* **2011**, 883 – 886; b) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879 – 9884; c) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407 – 1409; d) K. J. Fraunhoffer, N. Prabagaran, L. E. Sirois, M. C. White, *J. Am. Chem. Soc.* **2006**, *128*, 9032 – 9033.

[5] a) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191 – 206; b) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654 – 2672.

[6] For selected references, see: a) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Ketalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706 – 10716; b) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692 – 10705; c) J. J. Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem.* **2009**, *121*, 7024 – 7027; *Angew. Chem. Int. Ed.* **2009**, *48*, 6892 – 6895; d) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570 – 14571.

[7] a) K. Yoganathan, C. Rossant, Y. Huang, M. S. Butler, A. D. Buss, *J. Nat. Prod.* **2003**, *66*, 1116 – 1117; b) A. Arnone, G. Assante, G. Nasini, S. Strada, A. Vercesi, *J. Nat. Prod.* **2002**, *65*, 48 – 50.

[8] A. K. Yudin, *Catalyzed Carbon–Heteroatom Bond Formation*, Wiley-VCH, Weinheim, **2011**, pp. 35 – 68.

[9] a) B. Dangel, J. Johnson, D. Sames, *J. Am. Chem. Soc.* **2001**, *123*, 8149 – 8150; b) L. Min, S. Chang, *Tetrahedron Lett.* **2006**, *47*, 1375 – 1379.

[10] Platinum is more expensive than palladium (10.000$/mol versus 1500$/mol, respectively).

[11] A. Correa, R. Martin, *J. Am. Chem. Soc.* **2009**, *131*, 15974 – 15975.

[12] While this manuscript was in preparation, an elegant Pd-promoted reductive elimination toward C(sp^3)–O bonds was reported: S. L. Marquard, J. F. Hartwig, *Angew. Chem.* **2011**, *123*, 7257 – 7261; *Angew. Chem. Int. Ed.* **2011**, *50*, 7119 – 7123.

[13] For a review on reductive elmininations of high-valent species to C–O bonds, see: A. N. Vedernikov, *Top. Organomet. Chem.* **2010**, *31*, 101.

[14] For a recent report of C(sp^2)–O bond formation initiated by phenol-directed C(sp^2)–H activation, see: B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 9250 – 9253.

[15] J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936.

[16] For a related Pd^{IV}-catalyzed oxygenation of unactivated C(sp^3)–H bonds, see: a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300 – 2301; b) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542 – 9543.

[17] For a recent synthesis of benzolactones by C(sp^2)–H activation with alkyl halides or alkenes, see: a) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 6213 – 6216; *Angew. Chem. Int. Ed.* **2009**, *48*, 6097 – 6100; b) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153 – 4155.

[18] See the Supporting Information for details.

[19] a) A. Flores-Gaspar, R. Martin, *Adv. Synth. Catal.* **2011**, *353*, 1223 – 1228; b) P. Álvarez-Bercedo, A. Flores-Gaspar, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 466 – 467; c) P. Álvarez-Bercedo, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 17352 – 17353.

[20] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345.

[21] a) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222 – 7228; b) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967 – 971; c) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137 – 14151; d) Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916 – 5921, and references therein.

[22] B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 4960 – 4964; *Angew. Chem. Int. Ed.* **2008**, *47*, 4882 – 4886.

[23] a) L. J. Goossen, C. Linder, N. Rodríguez, P. P. Lange, A. Fromm, *Chem. Commun.* **2009**, 7173 – 7175; b) J. Cornella, C. Sanchez, D. Banawa, I. Larrosa, *Chem. Commun.* **2009**, 7176 – 7178.

[24] Future investigations are aimed at improving catalyst performance as unreacted starting material was recovered from reactions with 50–70% yield.

[25] For an elegant macrolactonization method initiated by C–H oxidation by π-allyl intermediates, see Ref. [4d].

[26] A substituent at the 5-position was required for selectively activating the benzylic C–H bond. Indeed, the reaction of the corresponding *ortho*-methylbenzoic acid did not afford any benzolactone at all.

[27] No conversion to products was observed.

[28] For related processes, see: a) R. Kuwano, H. Kusano, *Org. Lett.* **2008**, *10*, 1979; b) H. Grennberg, J. E. Bäckvall, *Chem. Eur. J.* **1998**, *4*, 1083.

[29] R. Giri, J. Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14082 – 14083.

[30] For selected reviews, see: a) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824 – 889; b) L. M. Xu, B. J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712 – 733; c) K. Muñiz, *Angew. Chem.* **2009**, *121*, 9576 – 9588; *Angew. Chem. Int. Ed.* **2009**, *48*, 9412 – 9423.

[31] M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857 – 4963.

[32] These results do not allow us to rule out a C(sp^3)–H activation via benzylic radicals.

