Breslow Intermediates

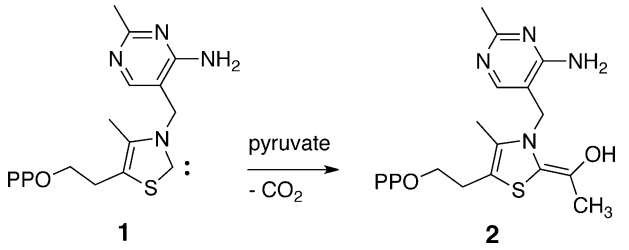
International Edition: DOI: 10.1002/anie.201508368
German Edition: DOI: 10.1002/ange.201508368

Radical [1,3] Rearrangements of Breslow Intermediates

*Sefat Alwarsh, Yi Xu, Steven Y. Qian, and Matthias C. McIntosh**

Abstract: *Breslow intermediates that bear radical-stabilizing N substituents, such as benzyl, cinnamyl, and diarylmethyl, undergo facile homolytic C–N bond scission under mild conditions to give products of formal [1,3] rearrangement rather than benzoin condensation. EPR experiments and computational analysis support a radical-based mechanism. Implications for thiamine-based enzymes are discussed.*

Thiamine diphosphate (TDP) is an essential cofactor for all living things. It is involved in several critical metabolic processes, including the tricarboxylic acid cycle, the pentose phosphate pathway, and amino acid catabolism.[1,2] In 1958, Ronald Breslow postulated that key intermediates in thiamine-catalyzed enzymatic pathways included an N-heterocyclic carbene (NHC; **1**) and an enaminol, for example, **2** (Scheme 1).[3] In pyruvate decarboxylation, for example,

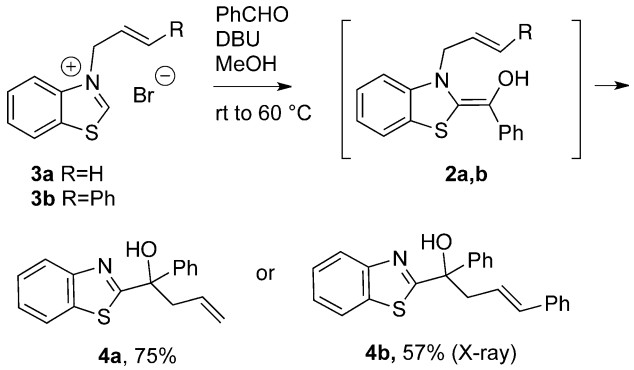


1 2

Scheme 1. Formation of TDP-derived Breslow intermediate **2**. PPO = diphosphate.

addition of the TDP carbene to pyruvate is followed by extrusion of CO_2 to provide unstable enaminol **2**. This and related heterocyclic enaminols have collectively been called Breslow intermediates.[4] Only recently have such compounds been rigorously characterized,[5,6] and new chemistry continues to be revealed.[7]

We recently reported that Breslow intermediates such as **2a** derived from *N*-allyl benzothiazolium bromide and aromatic aldehydes could be captured in a unique Claisen rearrangement to provide 2-butenyl benzothiazoles (Scheme 2; R = H).[8,9] In the course of examining the scope



3a R=H
3b R=Ph

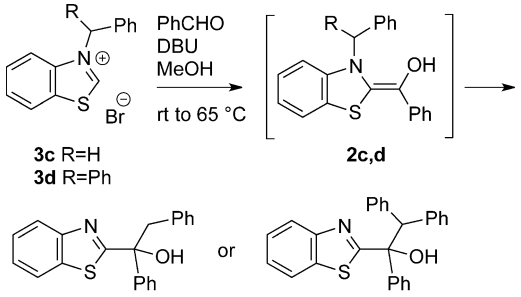
2a,b

4a, 75% **4b**, 57% (X-ray)

Scheme 2. [3,3] and [1,3] Rearrangements of *N*-allyl-substituted Breslow intermediates.[28] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

of the reaction, we were surprised to find that *N*-cinnamyl-substituted salt **3b** provided principally [1,3] rearrangement product **4b** upon reaction with the benzaldehyde, accompanied by only circa 5% of the nominal [3,3] product. The [1,3] rearrangement product clearly implied a stepwise process in competition with the concerted rearrangement.

Reaction of *N*-benzyl and *N*-diphenylmethyl benzothiazolium salts under the same conditions also yielded [1,3] rearrangement products, albeit in diminished yield in the case of benzyl salt **3c** (Scheme 3). The structures were confirmed by X-ray crystallography.[28]



3c R=H
3d R=Ph

2c,d

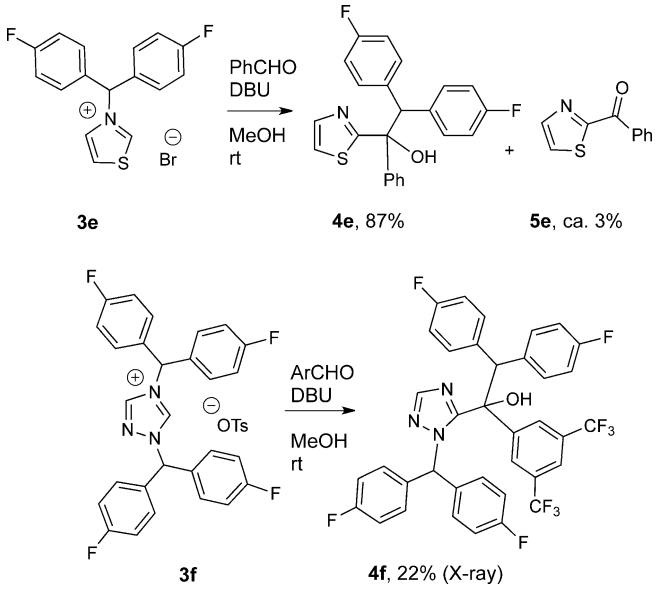
4c, 32% (X-ray) **4d**, 56% (X-ray)

Scheme 3. [1,3] Rearrangements of *N*-benzyl and *N*-diphenylmethyl Breslow intermediates.[28]

Many NHC-catalyzed reactions of aldehydes are presumed to proceed via a Breslow intermediate[10] and so the results reported herein are relevant to NHC catalysis and catalyst design. As benzothiazolium salts are only occasionally employed as NHC catalysts,[11] we exposed thiazolium and triazolium salts to the reaction conditions (Scheme 4). Reaction of thiazolium salt **3e** with benzaldehyde gave a high yield of the [1,3] rearrangement product **4e**, as well as a few percent of ketone **5e**. Treatment of symmetrically substituted

[*] Dr. S. Alwarsh, Prof. M. C. McIntosh
Department of Chemistry and Biochemistry
University of Arkansas
345 N Campus Dr., Fayetteville, AR 72701 (USA)
E-mail: mcintosh@uark.edu
Y. Xu, Prof. S. Y. Qian
Department of Pharmaceutical Sciences
NDSU Dept 2665, 208B Sudro Hall, North Dakota State University
P.O. Box 6050, Fargo, ND 58108-6050 (USA)

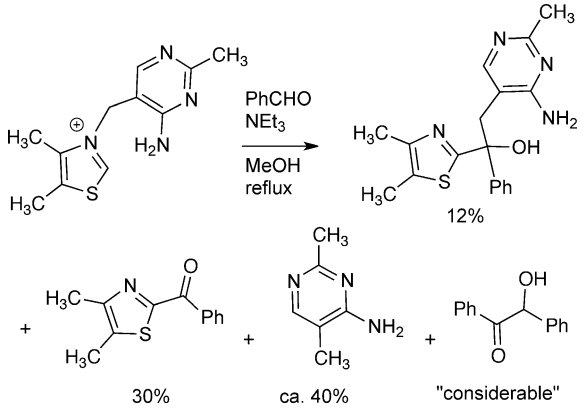
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508368.



Scheme 4. Ambient-temperature [1,3] rearrangements of *N*-di(4-fluorophenyl)methyl Breslow intermediates.[28]

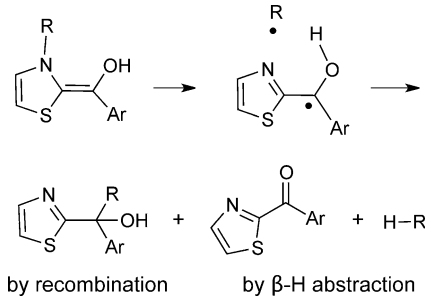
1,2,4-triazole **3f** provided rearrangement product **4f** in low yield as the only isolable product, although interestingly as a single regioisomer resulting from migration of the N4 substituent. No significant amount of benzoin was detected in the crude reaction mixtures based on TLC and ^{1}H NMR analysis. In both cases the rearrangements occurred at ambient temperature.

In 1970, Oka et al. reported a similar [1,3] rearrangement in which thiamine and related compounds underwent reaction with substituted benzaldehydes in methanol at reflux to provide rearranged tertiary alcohol products, albeit in very low yield (Scheme 5; 3-12%, highest yielding example shown).[12] The rearrangement products were accompanied by larger amounts of ketone and pyrimidine products resulting from cleavage of the benzylic C–N bond, as well as a "considerable" amount of benzoin. Thus, thiamine served for a limited period during the reaction as a benzoin catalyst but ultimately decomposed into rearrangement and fragmentation products. Oka et al. proposed a rather elaborate polar mechanism that employed the *ortho* amino group of the pyrimidine substituent to explain the formation of both the ketone and tertiary alcohol, since derivatives lacking the amino group failed to provide the products.[13]



Scheme 5. [1,3] Rearrangement and fragmentation products of thiamine derivatives reported by Oka et al.[12]

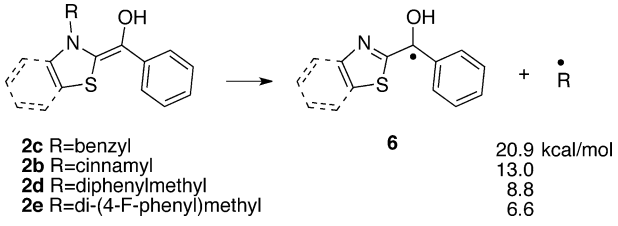
Based on the similarities of the rearrangement and fragmentation products in the reports by Oka et al. and our results reported herein, we propose that all of the products can be explained by the same radical mechanism. C–N bond homolysis of the Breslow intermediate initially forms a geminate radical pair (Scheme 6). The rearrangement product forms by radical recombination, while the ketone and pyrimidine products result from disproportionation, that is, β-hydrogen atom abstraction of the hydroxyl hydrogen by the carbon radical.[14–16]



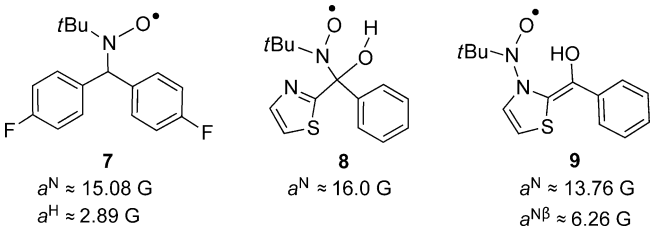
Scheme 6. Proposed radical reaction mechanism.

DFT calculations (B3LYP/6-31G*)[17] of the enthalpy of the homolysis reactions of Breslow intermediates **2b–e** to form the benzyl, cinnamyl, and diarylmethyl radicals and carbinol radicals **6** were +20.9, 13.0, 8.8, and 6.6 kcal mol^{-1}, respectively (Scheme 7).[18] The extraordinarily low enthalpies of reaction are likely due to the highly delocalized nature of carbinol radical **6** and its recovery of aromaticity upon homolysis. The trend in enthalpies for the benzothiazole-based intermediates correlates with the increasing radical-stabilizing ability of the R group as the N substituent.

We sought to obtain direct chemical evidence of radical intermediates, albeit without success. Trapping experiments with 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) gave no isolable addition products.[19] The absence of isolable addition products could be due to more rapid recombination of radicals than escape from the solvent cage.[20,21] Deuterium labeling experiments were problematic because of the relative unreactivity of the intermediate radicals relative to a labeling source.[22] However, EPR experiments gave strong evidence for a radical pathway. The EPR spectrum of the reaction of **3e** with benzaldehyde in the presence of the radical trap 2-methyl-2-nitrosopropane (MNP) was consistent



Scheme 7. Calculated enthalpies of homolysis for intermediates **2b–e** (DFT calculations at the B3LYP/6-31G* level of theory).

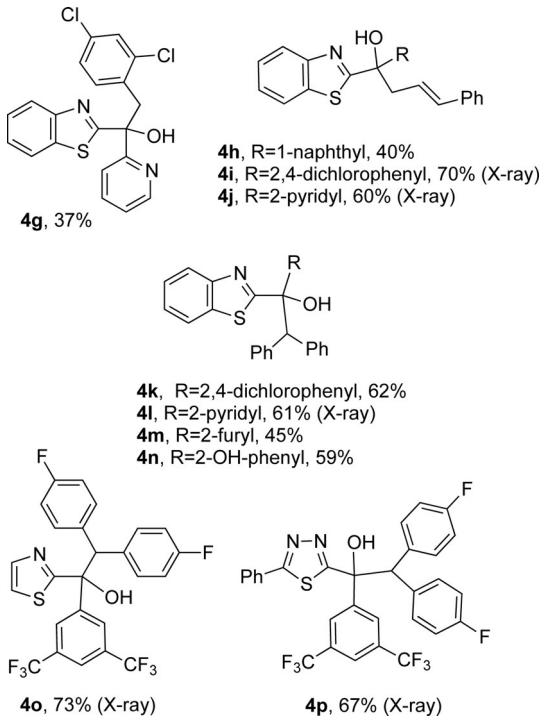


Scheme 8. MNP-trapped radicals consistent with the detected EPR spectrum. a = EPR hyperfine coupling constant, given in gauss (G).

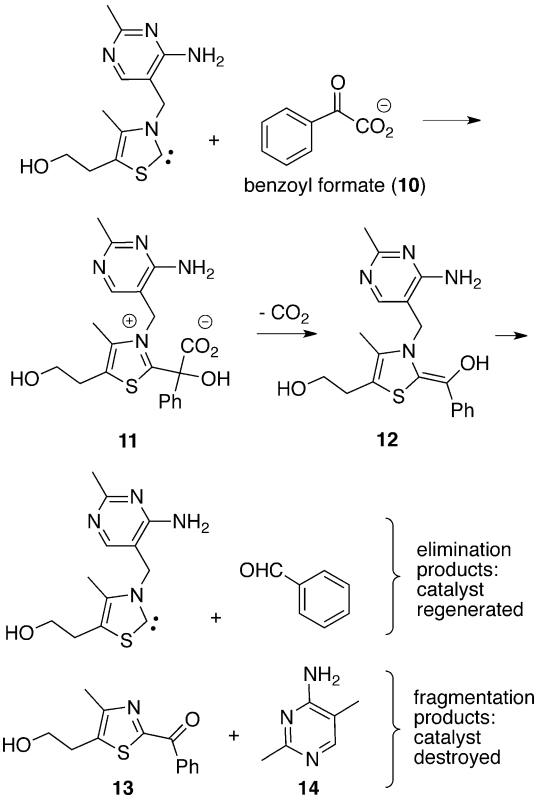
with nitroxyl adducts **7**, **8**,[23] and **9**[24] in an approximately 29:4:1 ratio (Scheme 8).[18]

The [1,3] rearrangement proved to be a generally applicable across a variety of aromatic and heteroaromatic aldehydes. We prepared a variety of benzyl-, cinnamyl-, and diarylmethyl-substituted tertiary alcohols in two steps from the corresponding azole in moderate to good yields (Scheme 9). Both electron-rich and electron-poor aldehydes participated in the reaction. Thiazole, benzothiazole, 1,2,4-triazole, and a 1,3,4-thiadiazole (**4p**) all participated in the rearrangement. From a synthetic perspective, this reaction extends the scope of complex tertiary alcohols that can be prepared via Breslow intermediates beyond those that can participate in a Claisen rearrangement.[8]

We note that the radical homolysis of Breslow intermediates may also have implications in enzymology. Benzoylformate decarboxylase is a thiamine-containing enzyme that catalyzes the conversion of benzoylformate into benzaldehyde and CO_2.[25] In model studies of the enzyme, Kluger and co-workers found that the rate of fragmentation of the derived Breslow intermediate **12** to ketone **13** and pyrimidine



Scheme 9. Azole-containing tertiary alcohols prepared by radical [1,3] rearrangement reactions.[28]



Scheme 10. Competitive reaction pathways for the Breslow intermediate from benzoylformate decarboxylase.

14 is competitive with the rate of formation of benzaldehyde and thiamine (Scheme 10).[26,27] However, exactly how the enzyme avoids the unproductive fragmentation pathway is unknown.

Kluger et al. have studied the so-called Oka fragmentation for some years and have considered several concerted and ionic mechanisms for the reaction.[26,27] It seems likely to us, based on the results described above, that the process occurs by homolysis of the C–N bond of Breslow intermediate **12** followed by disproportionation (see Scheme 6). Kluger and Ikeda reported a deuterium labeling experiment that was argued to be consistent with a polar mechanism,[26h] but the labeling result is equally consistent with a radical disproportionation reaction (compare Scheme 5 and Scheme 6).

In summary, we describe a facile [1,3] radical rearrangement of appropriately substituted Breslow intermediates at temperatures from ambient to circa 65 °C. Although the homolysis reaction places limits on NHC catalyst structure, it provides a novel means of generating a radical pair that can be exploited for organic synthesis. The proposed radical mechanism may also help elucidate how the fragmentation pathway is avoided in Breslow intermediates in thiamine-containing enzymes.

Acknowledgements

This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health (NIH;

Grant Number P30 GM103450) and by the Arkansas Biosciences Institute. We thank Gregory Dudley, Florida State University, for helpful discussions.

Keywords: Breslow intermediates · N-heterocyclic carbenes · radicals · rearrangement · thiamine

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 355–358
Angew. Chem. **2016**, *128*, 363–366

[1] V. I. Bunik, A. Tylicki, N. V. Lukashev, *FEBS J.* **2013**, *280*, 6412–6442.
[2] F. Jordan, M. S. Patel, *Thiamine - Catalytic Mechanisms in Normal and Disease States*, Marcel Dekker, New York, **2004**, p. 588.
[3] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
[4] D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
[5] a) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudoerfl, N. E. Schloerer, J. H. Teles, *Angew. Chem. Int. Ed.* **2012**, *51*, 12370–12374; *Angew. Chem.* **2012**, *124*, 12537–12541; b) A. Berkessel, V. R. Yatham, S. Elfert, J.-M. Neudorfl, *Angew. Chem. Int. Ed.* **2013**, *52*, 11158–11162; *Angew. Chem.* **2013**, *125*, 11364–11369.
[6] D. Meyer, P. Neumann, E. Koers, H. Sjuts, S. Lüdtke, G. M. Sheldrick, R. Ficner, K. Tittmann, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 10867–10872.
[7] J. Rehbein, S.-M. Ruser, J. Phan, *Chem. Sci.* **2015**, *6*, 6013–6018.
[8] S. Alwarsh, K. Ayinuola, S. S. Dormi, M. C. McIntosh, *Org. Lett.* **2013**, *15*, 3–5.
[9] For a recent review of the Claisen rearrangement, see: "Claisen Rearrangements" A. M. Martin-Castro, M. Tortosa, in *Comprehensive Organic Synthesis II, Vol. 5* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 912–977.
[10] For some reviews of NHC-catalyzed reactions of aldehydes, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655; b) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182–1195; c) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511–3522; d) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314–325; *Angew. Chem.* **2012**, *124*, 320–332; e) T. Okano, *Heterocycl. Commun.* **2013**, *19*, 311–326; f) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387.
[11] a) Y. Yano, Y. Tamura, W. Tagaki, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 740–744; b) T. Matsumoto, H. Yamamoto, S. Inoue, *J. Am. Chem. Soc.* **1984**, *106*, 4329–4832; c) T. Matsumoto, M. Ohishi, S. Inoue, *J. Org. Chem.* **1985**, *50*, 603–606; d) T. Matsumoto, T. Enomoto, T. Kurosaki, *J. Chem. Soc. Chem. Commun.* **1992**, 610–611; e) A. Raghunadh, S. S. More, T. K. Chaitanya, Y. S. Kumar, S. B. Meruva, L. V. Rao, U. K. S. Kumar, *Beilstein J. Org. Chem.* **2013**, *9*, 2129–2136.
[12] a) Y. Oka, S. Kishimoto, H. Hirano, *Chem. Pharm. Bull.* **1970**, *18*, 527–533; b) Y. Oka, S. Kishimoto, H. Hirano, *Chem. Pharm. Bull.* **1970**, *18*, 534–541.
[13] In our hands, we were only able to isolate the fragmentation products and benzoin; no [1,3] rearrangement product was detected.
[14] The [1,3] rearrangement of appropriately substituted ketimines to nitriles was demonstrated by Singer et al. and others to be a radical process. Rearrangement of a benzhydryl ketimine occurred at ambient temperature. See: a) K.-W. Lee, N. Horowitz, J. Ware, L. A. Singer, *J. Am. Chem. Soc.* **1977**, *99*, 2622–2627; b) R. C. Neuman Jr., A. P. Sylwester, *J. Org. Chem.* **1983**, *48*, 2285–2287; c) L. F. Clarke, A. F. Hegarty, P. O'Neill, *J. Am. Chem. Soc.* **1992**, *57*, 362–366.
[15] Baldwin et al. reported near ambient temperature [1,3] rearrangements that proceed by C–N bond homolysis of tetraheteroatom-substituted alkenes. See: a) J. E. Baldwin, J. A. Walker, *J. Am. Chem. Soc.* **1974**, *96*, 596–597; b) J. E. Baldwin, S. E. Branz, J. A. Walker, *J. Org. Chem.* **1977**, *42*, 4142–4144.
[16] Tian and Lee recently reported collision-induced ionization (CID) mass spectrometric experiments of *N*-methyl- and *N*-ethyl-*O*-silyl Breslow intermediates in which they proposed that the same N–C homolytic cleavage was occurring: Y. Tian, J. K. Lee, *J. Org. Chem.* **2015**, *80*, 6831–6838.
[17] DFT methods tend to underestimate bond dissociation energy by circa 1–4 kcal mol^{-1} on average. See: Y. Feng, L. Liu, J.-T. Wang, H. Huang, Q.-X. Guo, *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 2005–2013. However, the calculated energies are remarkably low even within that error range. See also: X. Cattoën, H. Gornitzka, F. S. Tham, K. Miqueu, D. Bourissou, G. Bertrand, *Eur. J. Org. Chem.* **2007**, 912–917.
[18] See the Supporting Information.
[19] For a review, see: E. G. Bagryanskaya, S. R. A. Marque, *Chem. Rev.* **2014**, *114*, 5011–5056.
[20] For a discussion of radical cage effects, see "Cage Effects": T. Koenig, H. Fischer, in *Free Radicals, Vol. 1* (Ed.: J. Kochi), Wiley-Interscience, New York, **1973**, pp. 157–189. "Radical Pairs": J. E. Leffler, *An Introduction to Free Radicals*, Wiley, New York, **1993**, p. 287.
[21] Low levels of escape of radical pairs from the solvent cage have been noted in Stevens rearrangements. See: W. D. Ollis, M. Rey, I. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1009–1027.
[22] Toluene and diphenylmethane have significantly weaker C–H bonds than that of methanol ($PhCH_2$–H, 85 kcal mol^{-1}; $HOCH_2$–H, 93 kcal mol^{-1}). See: A. J. Gordon, R. A. Ford, *The Chemist's Companion: a Handbook of Practical Data, Techniques, and References*, Wiley, New York, **1972**. Thus, C–H abstraction from the solvent would be endothermic by 8 kcal mol^{-1} in the case of the benzyl radical, and higher still for cinnamyl and diphenylmethyl radicals. Unsurprisingly, no D-atom transfer was detected upon performing the reactions in CD_3OH.
[23] For radicals similar to **8**, see: I. H. Leaver, G. C. Ramsay, *Tetrahedron* **1969**, *25*, 5669–5675.
[24] For a radical similar to **9**, see: W. Y. Zhao, Z. T. Huang, *Chin. Chem. Lett.* **1991**, *2*, 501–504.
[25] "Benzoylformate Decarboxylase: Intermediates, Transition States, and Diversions" R. Kluger, Q. Hu, I. F. Moore, in *Thiamine: Catalytic Mechanisms in Normal and Disease States*, Marcel Dekker, New York, **2004**, pp. 291–308.
[26] a) R. Kluger, J. F. Lam, C.-S. Kim, *Bioorg. Chem.* **1993**, *21*, 275–283; b) R. Kluger, J. F. Lam, J. P. Pezacki, C.-M. Yang, *J. Am. Chem. Soc.* **1995**, *117*, 11383–11389; c) R. Kluger, I. F. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 6145–6150; d) I. F. Moore, R. Kluger, *Org. Lett.* **2000**, *2*, 2035–2036; e) I. F. Moore, R. Kluger, *J. Am. Chem. Soc.* **2002**, *124*, 1669–1673; f) Q. Hu, R. Kluger, *J. Am. Chem. Soc.* **2002**, *124*, 14858–14859; g) G. Ikeda, R. Kluger, *J. Phys. Org. Chem.* **2004**, *17*, 507–510; h) G. Ikeda, R. Kluger, *Can. J. Chem.* **2005**, *83*, 1277–1280; i) S. O. C. Mundle, G. W. Howe, R. Kluger, *J. Am. Chem. Soc.* **2012**, *134*, 1066–1070.
[27] For a review, see: R. Kluger, K. Tittmann, *Chem. Rev.* **2008**, *108*, 1797–1718.
[28] CCDC1434874 (**4b**), 1434875 (**4c**), 1434876 (**4d**), 1434877 (**4f**), 1434878 (**4i**), 1434879 (**4j**), 1434880 (**4l**), 1434881 (**4o**), and 1434882 (**4p**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre. Please see the Supporting Information for crystallographic data and structures.

Received: September 7, 2015
Published online: November 10, 2015

