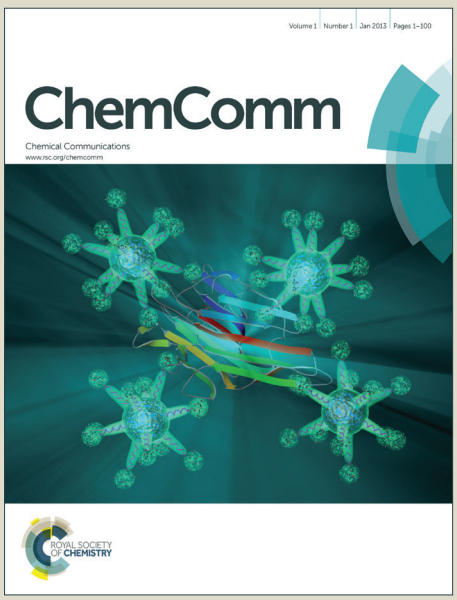
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chemical Communications

RSCPublishing

COMMUNICATION

An Umpolung Approach Toward *N*-Aryl Nitrone Construction: A Phosphine-Mediated Addition of 1,2-Dicarbonyls to Nitroso Electrophiles

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Aditi P. Chavannavar, Allen G. Oliver and Brandon L. Ashfeld*

An umpolung approach toward nitrone construction utilizing a phosphine-mediated addition of 1,2-dicarbonyls to nitroso compounds is reported. The reaction exhibits a high degree of chemoselectivity and provides direct access to isoxazolidines, imines, and trisubstituted alkenes.

Nitrones, which exhibit the reactivity of extended carbonyls characterized by an anionic oxygen and electrophilic carbon separated by a cationic nitrogen, constitute an important class of synthetic building blocks for the construction of complex targets.[1] While nitrones can serve as precursors to 2° and 3° hydroxylamines via nucleophilic additions at carbon, they are mainly exploited as 1,3-dipoles in [3+2] cycloadditions to assemble isoxazolidines and isoxazolines (Figure 1).[2] These heterocyclic motifs are found in a number of biologically active natural products, including the potent anti-tumor alkaloid alsmaphorazine A.[3] Nitrone synthesis is directly achieved by condensation of either a ketone or aldehyde with a hydroxylamine,[4] the N-alkylation of an oxime,[5] or exhaustive C–N oxidation.[6] In each of these methods, the main synthetic disconnect involves the addition of a nucleophilic amine to an electrophilic carbon (Figure 2a). As a result, the construction of ketonitrones using electron poor hydroxylamines is problematic,[7] and issues of chemoselectivity can arise when multiple electrophilic sites are present.[8]

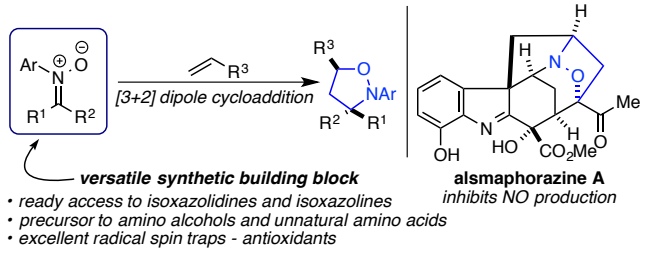


Figure 1. Synthetic utility of nitrones as valuable starting materials in medicinal chemistry and natural product synthesis.

To address these challenges, we sought to develop a method that would directly and *chemoselectively* provide ketonitrones that bear an α-electron withdrawing group, even in the presence of other electrophilic groups. Our strategy relied on an *umpolung* retrosynthetic C–N bond disconnect to avoid the use of nucleophilic amines, an important consideration in biorthogonal reaction development.[9] We speculated that formation of an α-alkoxy anion equivalent **2** through a Ramirez-Kukhtin reaction[10] involving an electron deficient ketone **1** in the presence of an electrophilic nitroso species **3**, would result in C–N bond formation arising from nucleophilic attack at nitrogen (Figure 2b).[11] The generation of **2** from **1** gives rise to a redox condensation event with the desired chemoselectivity to yield nitrone **4**. In contrast to light sensitive diazo compounds **5**, which upon decomposition in the presence of an amine leads to reductive amination adduct **6**, 1,2-dicarbonyls behave as bench stable surrogates that would not require a final oxidation to **4**.[6c,12] Herein, we describe the development of a chemoselective, umpolung approach toward nitrone synthesis that constitutes a departure from conventional dehydration strategies.

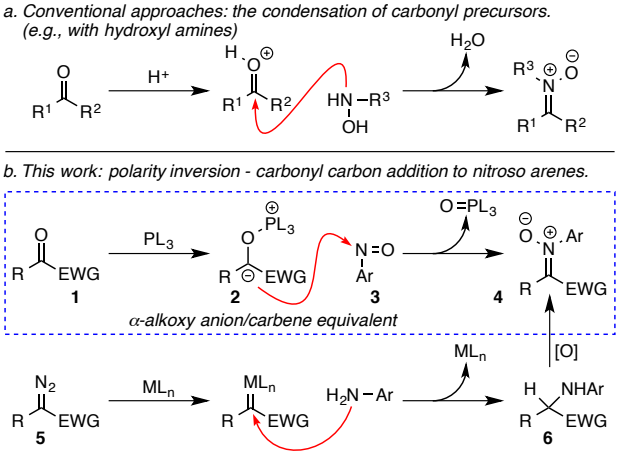
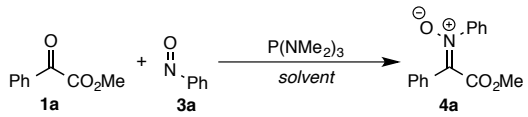


Figure 2. [a]Classic condensation approach: nucleophilic addition of hydroxyl amines to activated carbonyls. [b]Umpolung metal-free addition of ketones to electrophilic nitrosoarenes.

While unclear at the outset, we speculated that the latent carbene-like reactivity of **1** would generate the oxaziridine intermediate through an *N*-alkylation of the nitroso compound *en route* to the desired nitrone. Thus, we focused our attention on evaluating the addition of methyl benzoyl formate (**1a**) to nitrosobenzene (**3a**) in the presence of a P^{III} reagent (Table 1). While PPh_3 and $P(OMe)_3$ proved unreactive, we were pleased to observe that an equimolar amount of **1a**, **3a** and $P(NMe_2)_3$ gave nitrone **4a** albeit in 39% yield (entry 1).[13] Employing a 50% excess of either **1a** or **3a** failed to improve upon this result (entries 2 and 3). However, utilizing a 1.2:1 ratio of **1a**/**3a** with 1.5 equivs of $P(NMe_2)_3$ gave nitrone **4a** in 85% yield (entry 4). Using THF as solvent proved optimal as CH_2Cl_2, PhMe, and MeCN gave diminished yields (entries 5-7) and DMF led to no reaction (entry 8). Thus, we sought to gain a better understanding of this unusual phosphine-mediated umpolung reactivity using a 1.2/1 excess of 1,2-dicarbonyl **1** to nitroso arene **3** in THF for the remainder of our study.

Table 1. Optimization of nitrone formation[a]



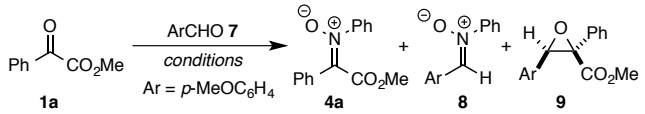
entry	**1a**	**3a**	Solvent	Yield (%)[b]
1[c]	1.0	1.0	THF	39
2[c]	1.5	1.0	THF	30
3[c]	1.0	1.5	THF	33
4	**1.2**	**1.0**	**THF**	**85**
5	1.2	1.0	CH_2Cl_2	50
6	1.2	1.0	PhMe	45
7	1.2	1.0	MeCN	60
8	1.2	1.0	DMF	<5

[a]Conditions: performed on a 0.19 mmol scale with 1.5 equiv of $P(NMe_2)_3$ at –78 ˚C to rt for 6 h. [b]Yields of isolated products. [c]1.0 equivs $P(NMe_2)_3$was employed.

With our optimized conditions in hand, we turned our attention toward examining the chemoselectivity of this method for ketonitrone formation. To that end, addition of α-ketoester **1a** to PhNO in the presence of aldehyde **7** over 10h yielded 59% of ketonitrone **4a** without formation of aldonitrone **8** (Table 2, entry 1).[14] It is important to note that while 79% of aldehyde **7** was recovered, the remainder converted to epoxide **9**. Thus, employing 2 equivs of **1a** and $P(NMe_2)_3$ improved both the yield of **4a** and fully converted **7** to **9** (entry 2).[15] In contrast, condensation of hydroxylamine **10** with **1a** and **7** resulted in quantitative formation of nitrone **8** and recovered **1a** (entry 3). These results highlight the utility of our umpolung approach toward C–N bond formation that allows one to *selectively functionalize a 1,2-dicarbonyl compound in the presence of an aldehyde.*

We next evaluated the structural diversity of the nitroso component compatible with our optimized reaction conditions (Table 3). In general, good yields of the corresponding nitrones were observed with an array of nitrosobenzenes. Both electron rich and electron deficient aryl nitrones **4a-f** were obtained in 74-85% yield. The formation of *N*-4-acetyl phenylnitrone **4f** again highlights the 1,2-dicarbonyl chemoselectivity of this method. Although seemingly impervious to electronic perturbations, increased sterics led to lower yields of the

Table 2. 1,2-Dicarbonyl chemoselectivity[a,b]

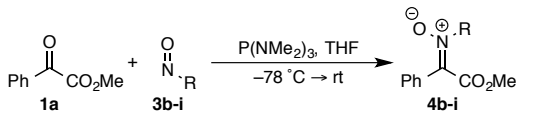


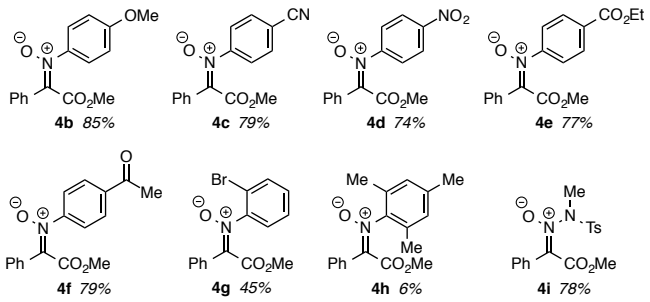
entry	conditions	**4a**	**8**	**9**[d]	**1a**	**7**
1	PhNO**3a**, $P(NMe_2)_3$ THF, –78 ˚C to rt, 10 h	59%	0%	21%	0%	79%
2[c]	PhNO**3a**, $P(NMe_2)_3$ THF, –78 ˚C to rt , 24 h	90%	0%	>98%	0%	0%
3	PhNHOH **10**, THF, rt	0%	82%	0%	95%	0%

[a]Conditions: performed on a 0.47mmol scale with **1a**, **7**, **3a**, and $P(NMe_2)_3$ = 1.2:1:1:1.5. [b]Yields of isolated products. [c]2.4 equivs of **1a** and 3 equivs of $P(NMe_2)_3$ were employed. [d]Ratio of diastereomers determined by ^1H NMR 500 MHz.

corresponding nitrones. For example, *N*-2-bromonitrone **4g** and *N*-mesitylnitrone **4h** were obtained in 45% and 6% yield respectively. Even Diazald® underwent reaction with **1a** to give the *N*-sulfonamide nitrone **4i** in 78% yield. While nitrosoaryl compounds reliably proceeded in good yields, vinyl and aliphatic nitroso compounds led to complex reaction mixtures.

Table 3. Scope of nitroso functional group compatibility[a,b]



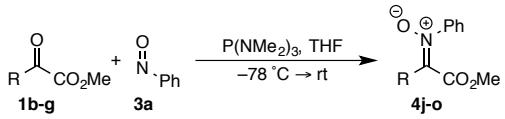


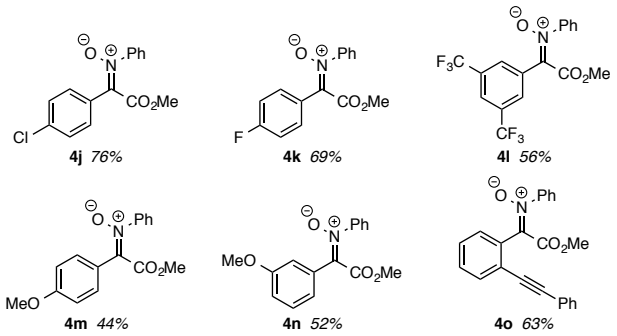
[a]Conditions: **1a** (0.56 mmol), **3** (0.47 mmol), $P(NMe_2)_3$ (0.70 mmol) in THF (0.17M). [b]Yields of isolated products.

In contrast to the nitroso component, the electronics of the α-keto ester **1** had a greater impact on the yield of **4** (Table 4). Electron deficient aryl ketones gave better yields of the corresponding nitrones **4j-l** than electron-rich derivatives **4m** and **4n**. This is consistent with a mechanism involving nucleophilic attack on the α-ketoester by phosphine to generate the reactive phosphalene intermediate.[15a] The reaction proved tolerant of functional handles, such as aryl halides and the aryl alkyne in **4o**.

In addition to α-ketoesters, benzil (**11**) underwent smooth conversion to nitrone **12** with PhNO (**3a**) and $P(NMe_2)_3$ (eq. 1). Likewise, *N*-methyl isatin **13** added to **3a** to give the corresponding nitrone, which upon treatment with allyl bromide (**14a**) gave isoxazolidine **15** in 64% yield as a 1:1 mixture of

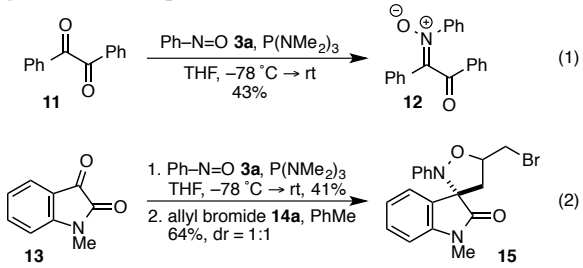
Table 4. Nitroso component functional compatibility[a,b]





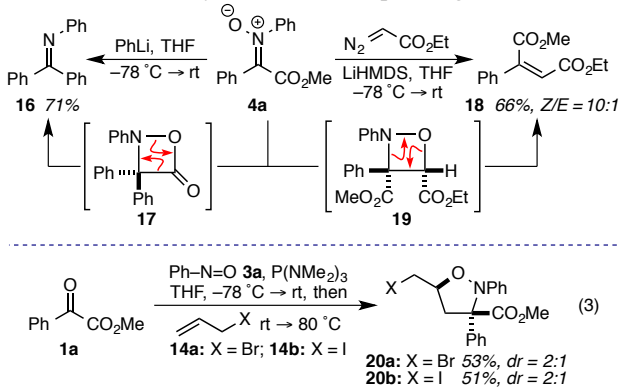
[a]Conditions: **1** (0.56 mmol), **3a** (0.47 mmol), $P(NMe_2)_3$ (0.70 mmol) in THF (0.17 M). [b]Yields of isolated products.

diastereomers (eq. 2). The ease with which adduct **15** was obtained from readily available isatin is significant because spiroisoxazolidineoxindoles feature prominently in a variety of biologically active natural products and pharmaceutical targets.[16] Surprisingly, a survey of the literature revealed few methods for the synthesis of oxindole nitrones.[7a] Often alkylation of the isatinoxime is complicated by side products resulting from *O*-alkylation, an issue that is readily avoided using the method reported herein.[17]



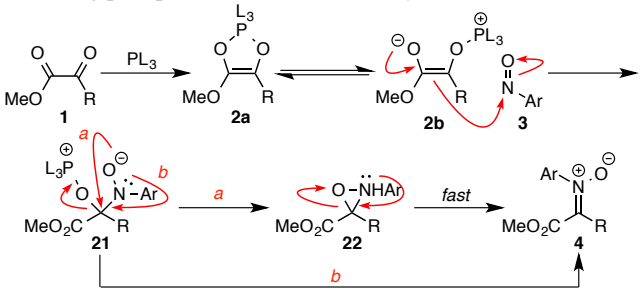
To evaluate the synthetic utility of our method, while exploiting the inherent reactivity of nitrones, we were inspired by a report from Yamamoto and co-workers wherein they used an oxidative decarboxylation approach toward the synthesis of ketones from esters and nitrosobenzene.[18] This led us to speculate that diaryl imines could be obtained directly from the aryl nitrones bearing an α-ester group through an unusual *C–C bond cleavage event*.[19] Gratifyingly, upon treatment of nitrone **4a** with PhLi, benzophenone imine **16** was obtained in 71% yield (Scheme 1). Transesterification of the initial amine oxide adduct to form oxazetidin-4-one **17** leads to expulsion of CO_2 and formation of imine **16**. However, when PhLi was replaced with lithiated ethyldiazoacetate, 2-phenyl-fumarate **18** was formed in 66% yield in a *Z*/*E* = 10:1. In contrast to formation of imine **16**, N_2 displacement by the amine oxy anion leads to oxazetidine **19**, which eliminates nitrosobenzene to give alkene **18**.[20] While formation of strained oxazetidine intermediates **17** and **19** is speculative at this stage, to the best of our knowledge this constitutes the first example of initiating a rapid C–C or C–N bond cleavage of the starting nitrone to yield imines and alkenes respectively.

The mild reaction conditions required for nitrone formation are ideal for the rapid construction of more complex architectures through a cascade reaction sequence. For example, sequential addition of PhNO (**3a**) and $P(NMe_2)_3$ to ketone **1a** followed by either allyl bromide or allyl iodide gave the 3,5-substituted isoxazolidines **20a** and **20b** in 53% and 51% yield respectively as 2:1 mixtures of diastereomers (eq. 3).[21] In addition to being intermediates in natural product synthesis, isoxazolidines are also useful building blocks for the construction of β-amino acids, β-lactams and γ-amino alcohols.[1a,22] This nitrosoarene alkylation/1,3-dipole cycloaddition cascade results in a streamlined approach toward isoxazolidines directly from the corresponding ketone.



Scheme 1. Expanded synthetic versatility of nitrones.

Two plausible isomeric mechanisms for the phosphine-mediated addition of 1,2-dicarbonyls to nitrosoarenes are depicted in Scheme 2. Formation of phosphalene **2a**,[10c,15a] which is equilibrium with the zwitter ionic phosphonium intermediate **2b**, undergoes addition to nitrosoarene **3** to give intermediate **21**.[10f,11d] At this stage, nitrone **4** may be formed in a stepwise fashion via a Mitsunobu-like displacement of phosphine oxide to yield oxaziridine **22** followed by ring opening (Scheme 2, path a), or directly from zwitterion **21** (Scheme 2, path b).[23] While still speculative, this mechanism is consistent with our findings and those of others for reactions involving phosphines and 1,2-dicarbonyls.



Scheme 2. Potential mechanism.

In conclusion, we have developed a complementary approach toward nitrone construction that circumvents a conventional condensation strategy by exploiting the unusual reactivity of 1,2-dicarbonyls with phosphines. The resulting nucleophilic addition of a carbonyl carbon to an electrophilic nitroso constitutes an inverted polarity disconnect that enables the chemoselective functionalization of an α-ketoester in the presence of an aldehyde or ketone. By employing this umpolung strategy the use of basic amines is avoided. The

reaction tolerates an array of nitrosoarenes and 1,2-dicarbonyls, and the nitrone adducts are readily converted into a number of synthetically useful building blocks, including isoxazolines, imines, and fumarates. Additional mechanistic studies and an in-depth evaluation of imine and fumarate formation directly from the corresponding nitrones are currently underway and will be reported in due course.

Financial support for this work was provided by the Stanford University Global Climate and Energy Project and the National Science Foundation (CAREER CHE-1056242).

Notes and references

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, USA. E-mail: bashfeld@nd.edu

† Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/b000000x/

1. (a) R. C. F. Jones and J. N. Martin, in *Synthetic Applications of 1,3-Dipolar Cycloadditions. Chemistry Toward Heterocycles and Natural Products*, eds. A. Padwa and W. H. Pearson, John Wiley & Sons, Hoboken, NJ, 2003; (b) K. B. G. Torssell, in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, ed. H. Feuer, Wiley VCH, Weinheim, Germany, 1988; (c) J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, John Wiley & Sons, New York, 1984, vol. 2.
2. (a) P. Jiao, D. Nakashima and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2008, **47**, 2411; (b) M. A. Voinov, T. G. Shevelev, T. V. Rybalova, Y. V. Gatilov, N. V. Pervukhina, A. B. Burdukov and I. A. Grigor'ev, *Organometallics*, 2007, **26**, 1607; (c) D. Nakashima and H. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 9626; (d) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González and A. Linden, *Angew. Chem., Int. Ed.*, 2005, **44**, 6187; (e) M. P. Sibi, Z. Ma and C. P. Jasperse, *J. Am. Chem. Soc.*, 2004, **126**, 718; (f) W. S. Jen, J. J. M. Wiener and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 9874.
3. K. Koyama, Y. Hirasawa, A. E. Nugroho, T. Hosoya, T. C. Hoe, K.-L. Chan and H. Morita, *Org. Lett.*, 2010, **12**, 4188.
4. J. A. Robl and J. R. Hwu, *J. Org. Chem.*, 1985, **50**, 5913.
5. (a) X. Peng, B. M. K. Tong, H. Hirao and S. Chiba, *Angew. Chem., Int. Ed.*, 2014, **53**, 1959; (b) R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1993, 372; (c) R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929; (d) S. K. Pradharan, K. G. Akamanchi, P. P. Divakaran and P. M. Pradhan, *Heterocycles* 1989, **28**, 813.
6. (a) D.-L. Mo and L. L. Anderson, *Angew. Chem., Int. Ed.*, 2013, **52**, 6722; (b) T. S. Hood, C. B. Huehls and J. Yang, *Tetrahedron Lett.*, 2012, **53**, 4679; (c) C. Gella, E. Ferrer, R. Alibés, F. Busqué, P. de March, M. Figueredo and J. Font, *J. Org. Chem.*, 2009, **74**, 6365; (d) F. P. Ballistreri, U. Chiacchio, A. Rescifina, G. A. Tomaselli and R. M. Toscano, *Tetrahedron*, 1992, **48**, 8677; (e) R. W. Murray and M. Singh, *J. Org. Chem.*, 1990, **55**, 2954; (f) G. Bartoli, E. Marcantoni, M. Petrini and R. Dalpozzo, *J. Org. Chem.*, 1990, **55**, 4456; (g) W. W. Zajac, T. R. Walters and M. G. Darcy, *J. Org. Chem.*, 1988, **53**, 5856.
7. (a) H.-B. Yang and M. Shi, *Org. Biomol. Chem.*, 2012, **10**, 8236; (b) E. Hulsbos, J. Marcus, J. Brussee and A. Vandergen, *Tetrahedron Asymmetry*, 1997, **8**, 1061; (c) I. M. C. Brighente, R. Budal and R. A. Yunes, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1861.
8. (a) J. Moran, J. Y. Pfeiffer, S. I. Gorelsky and A. M. Beauchemin, *Org. Lett.*, 2009, **11**, 1895; (b) J. Y. Pfeiffer and A. M. Beauchemin, *J. Org. Chem.*, 2009, **74**, 8381.
9. J. A. Prescher and C. R. Bertozzi, *Nat. Chem. Biol.*, 2005, **1**, 13.
10. (a) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, 1958, **121**, 466; (b) F. Ramirez, *Pure Appl. Chem.*, 1964, 337; (c) F. Ramirez, *Acc. Chem. Res*, 1968, **1**, 168; (d) W. B. McCormack, *Org. Synth.*, 1973, **5**, 787; (e) F. H. Osman and F. A. El-Samahy, *Chem. Rev.*, 2002, **102**, 629; (f) E. J. Miller, W. Zhao, J. D. Herr and A. T. Radosevich, *Angew. Chem., Int. Ed.*, 2012, **51**, 10605; (g) W. Zhao, D. M. Fink, C. A. Labutta and A. T. Radosevich, *Org. Lett.*, 2013, **15**, 3090.
11. (a) C. P. Frazier, D. Sandoval, L. I. Palmer and J. Read de Alaniz, *Chem. Sci.*, 2013, **4**, 3857; (b) G. Wang, X. Chen, Y. Zhang, W. Yao and C. Ma, *Org. Lett.*, 2013, **15**, 3066; (c) N. Momiyama and H. Yamamoto, *Org. Lett.*, 2002, **4**, 3579; (d) P. Zuman and B. Shah, *Chem. Rev.*, 1994, **94**, 1621.
12. (a) A. Rajasekar Reddy, Z. Guo, F.-M. Siu, C.-N. Lok, F. Liu, K.-C. Yeung, C.-Y. Zhou and C.-M. Che, *Org. Biomol. Chem.*, 2012, **10**, 9165; (b) F. Kröhnke, *Ber. Dtsch. Chem. Ges.*, 1938, **71**, 2583; (c) F. Kröhnke and E. Börner, *Ber. Dtsch. Chem. Ges.*, 1936, **69**, 2006.
13. A major side product from these experiments, which constitutes a majority of the mass balance, is the epoxide resulting from a formal dimerization of the starting α-keto ester as a 1:1 mixture of stereoisomers.
14. (a) R. Y. Suman, P. Kadigachalam, V. R. Doddi and Y. D. Vankar, *Tetrahedron Lett.*, 2009, **50**, 5827; (b) Y. Tomioka, C. Nagahiro, Y. Nomura and H. Maruoka, *J. Heterocycl. Chem.*, 2003, **40**, 121; (c) S. Franco, F. L. Merchán, P. Merino and T. Tejero, *Synth. Commun.*, 1995, **25**, 2275.
15. (a) F. Ramirez, A. S. Gulati and C. P. Smith, *J. Org. Chem.*, 1968, **33**, 13; (b) M. S. Newman and S. Blum, *J. Am. Chem. Soc.*, 1964, **86**, 5598.
16. (a) G. Bhaskar, Y. Arun, C. Balachandran, C. Saikumar and P. T. Perumal, *Eur. J. Med. Chem.*, 2012, **51**, 79; (b) V. V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hübel, D. Rauh and H. Waldmann, *Angew. Chem., Int. Ed.*, 2010, **49**, 5902; (c) D. Sriram, T. R. Bal and P. Yogeeswari, *J. Pharm. Pharm. Sci.*, 2005, **8**, 565; (d) V. N'Goka, T. B. Stenbøl, P. Krogsgaard-Larsen and G. Schlewer, *Eur. J. Med. Chem.*, 2004, **39**, 889.
17. N. Sin, B. L. Venables, X. Liu, S. Huang, Q. Gao, A. Ng, R. Dalterio, R. Rajamani and N. A. Meanwell, *J. Heterocycl. Chem.*, 2009, **46**, 432.
18. J. N. Payette and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 12276.
19. R. H. Crabtree, *Nature*, 2000, **408**, 415.
20. V. A. Roberts and M. E. Garst, *J. Org. Chem.*, 1985, **50**, 893.
21. N. L. Rao, P. J. Dunford, X. Xue, X. Jiang, K. A. Lundeen, F. Coles, J. P. Riley, K. N. Williams, C. A. Grice, J. P. Edwards, L. Karlsson and A. M. Fourie, *J. Pharmacol. Exp. Ther.*, 2007, **321**, 1154.
22. K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.
23. K. W. Ratts and A. N. Yao, *J. Org. Chem.*, 1966, **31**, 1689.

