Preparation of unsymmetrical ketones from tosylhydrazones and aromatic aldehydes via formyl C–H bond insertion

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Preparation of Unsymmetrical Ketones from Tosylhydrazones and Aromatic Aldehydes *via* Formyl C–H Bond Insertion

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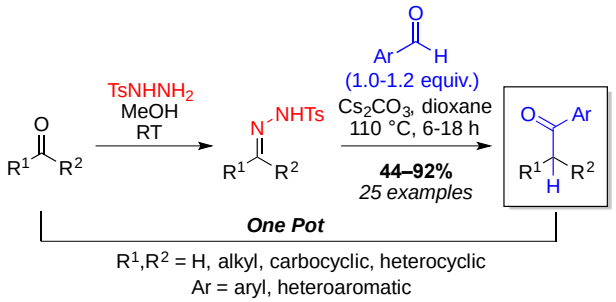
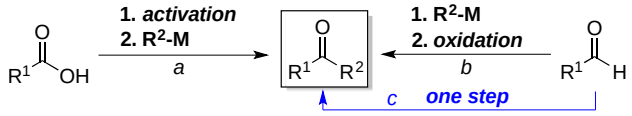
Supporting Information Placeholder



ABSTRACT: Preparation of ketones by insertion of diazo compounds into the formyl C−H bond of an aldehyde is an attractive procedure, but use of structurally diverse diazo compounds is hampered by preparation and safety issues. A convenient procedure for the synthesis of unsymmetrical ketones from bench-stable tosylhydrazones and aryl aldehydes is reported. The procedure can be performed in one pot from the parent carbonyl compound and needs only a base, with no additional promoters being required.

Ketones represent a large and highly diverse class of compounds which are useful in many areas, including materials, fragrances and natural product synthesis. As well as their biological and structural properties, the intrinsic reactivity of ketones makes them valuable synthetic intermediates in the pharmaceutical industry.

Scheme 1. Typical Strategies for the Synthesis of Ketones

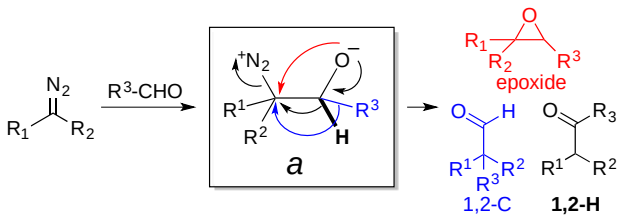


However, the electrophilicity of the carbonyl group can make their preparation challenging. As such, the synthesis of ketones is typically accomplished *via* controlled addition of an organometallic reagent to a higher oxidation state partner such as an ester, acid chloride or Weinreb amide (Scheme 1, a) or by addition to an aldehyde and re-oxidation of the intermediate alcohol (Scheme 1, b).[1-4]

Both of these approaches suffer from poor financial, time, step and redox economies as well as the requirement for potentially unstable and air/moisture sensitive organometallic reagents.[3-5] Therefore, a one-step approach from a substrate in the same oxidation state, such as an aldehyde, represents a highly efficient and desirable process (Scheme 1, c).

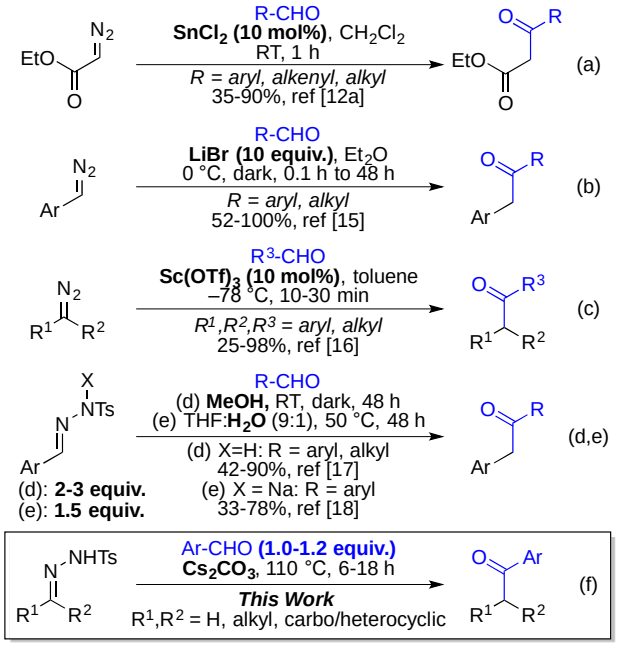
Formation of a ketone from an aldehyde requires formal insertion of a functionalized carbon atom into the aldehyde formyl C–H bond and is commonly achieved using diazo compounds.[6,7]

Scheme 2. Mechanistic Pathways Following Diazo Addition to an Aldehyde



Indeed, addition of a diazo to an aldehyde produces a diazonium alkoxide (Scheme 2, a), from which three main mechanistic pathways may occur: 1. direct displacement of N_2 by the oxyanion to give an epoxide[8] (Scheme 2, red); 2. 1,2-carbon migration to give a substituted aldehyde (Scheme 2, blue); or 3. a 1,2-hydrogen shift to give the desired ketone product (Scheme 2, black). The product distribution from this intermediate is influenced by the nature of the substrate and the reaction conditions employed.[6c,6e,6i-j,7b-c,7g,7o-p,8-11]

Scheme 3. Selected Studies in the Reaction of Diazo Species with Aldehydes to Furnish Ketones



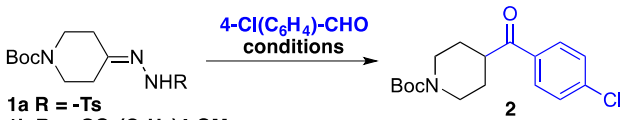
The first practical addition of a diazocarbonyl to an aldehyde followed by a 1,2-hydrogen shift to give a ketone product was described by Roskamp[12] (Scheme 3, a). This process requires a Lewis acid promoter and many examples have subsequently been reported.[6h,6k,7d,7f-o,7q-s,13,14] However, for more general ketone preparation, it is desirable that this mode of reactivity is also applicable to non-acyl diazo species. Examples involving these types of substrates are currently under-represented in the literature. This is undoubtedly due to their problematic preparation and the toxicity and explosive nature of non-stabilised diazo intermediates.[6k,7p]

In one notable example, Anselme described the reaction of aryldiazomethanes with aldehydes promoted by LiBr.[15] Yields were moderate-to-excellent, but limitations of the process included the requirement for 10 equivalents of LiBr, poor performance on sterically crowded substrates, necessity for exclusion of light and long reaction times (Scheme 3, b). A subsequent report by Kingsbury employed catalytic $Sc(OTf)_3$ to couple unstabilised alkyl and aryl diazo compounds with aryl and alkyl aldehydes in low-to-excellent yields in under 30 minutes (Scheme 3, c).[16] However, a major drawback to both of these processes lies in the aforementioned preparation and handling of potentially toxic and explosive diazo species.[6k,7p]

In an attempt to avoid these issues, two simultaneous reports described the use of aryl tosylhydrazones[17] (Scheme 3, d) or aryl tosylhydrazone metal salts[18] (Scheme 3, e) as *in situ* diazo sources for subsequent aldehyde insertion reactions. In the first example, MeOH or EtOH were used since protic solvents were known to promote diazo insertion reactions.[19] However, side reactions of the diazo species with the solvent led to difficult product purification and a large excess of the tosylhydrazone was required to generate satisfactory yields. In the other report, water was used as a protic co-solvent in order to drive the reaction to full conversion and higher yields, but this also led to increased formation of carbon migration and homologated products.[6h,20] In addition to these common problems, these processes only work with *aryl* tosylhydrazones and both require very long reaction times.

In order to address these shortfalls in current methods, we have developed a safe and convenient procedure for the C–H insertion of bench-stable *alkyl* tosylhydrazones into aryl aldehydes (Scheme 3, f). Products of this type are challenging to prepare using traditional multi-step routes, owing to the nature of the reagents required to bring about such transformations.[3,4]

Table 1. Optimisation of Reaction Conditions.[a]

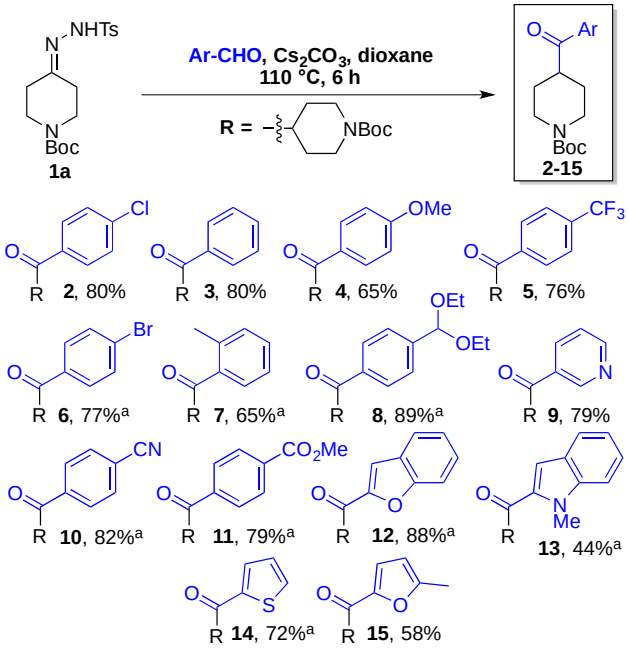


entry	1	base	solvent	equiv. aldeh.	t (h)	yield (%)[b]
1	**1a**	K_2CO_3	1,4-dioxane	1.0	6	0
2	**1a**	Cs_2CO_3	1,4-dioxane	1.0	6	80
3	**1b**	Cs_2CO_3	1,4-dioxane	1.0	18	80
4	**1c**	Cs_2CO_3	1,4-dioxane	1.0	1	0
5	**1a**	Cs_2CO_3	1,4-dioxane	1.1	6	79
6	**1a**	Cs_2CO_3	1,4-dioxane	1.2	6	80
7	**1a**	Cs_2CO_3	toluene	1.0	6	18
8	**1a**	Cs_2CO_3	1,2-DCE	1.0	6	6
9	**1a**	Cs_2CO_3	MeCN	1.0	6	44
10	**1a**	Cs_2CO_3	$PhCF_3$	1.0	6	29
11	**1a**	Cs_2CO_3	1,2-DME	1.0	6	61

[a]Reaction conditions: 0.5 mmol **1**, 0.75 mmol base, 2 mL solvent, sealed tube, 110 °C. [b]Isolated yield.

Our investigations began by performing a screen of conditions using Boc-piperidinone tosylhydrazone **1a** and 4-chlorobenzaldehyde as a model system (Table 1). An initial attempt using K_2CO_3 at 110 °C in dioxane provided complete conversion of tosylhydrazone, but no evidence of product formation (Table 1, entry 1). Pleasingly, however, a change of base to Cs_2CO_3 provided the required product in 80% yield (Table 1, entry 2). This excellent yield is noteworthy, since a Lewis acid promoter is normally required for conversion in this type of process[13,16] and aryl aldehydes have been shown to preferentially deliver 1,2-carbon migration over 1,2-hydrogen migration products.[6i,11] We have previously described the influence of modulating arylsulfonylhydrazone electronics on the rate of diazo release in coupling reactions.[21] Use of an electron-rich PMP sulfonylhydrazone **1b** slows release of the diazo species, although in this instance it provided an identical yield of the product (Table 1, entry 3). As observed in our previous study, the electron deficient 4-nitro analogue **1c** decomposed within 1 hour and no product was isolated (Table 1, entry 4).[21] The yield obtained was shown to be insensitive to the stoichiometry of the aldehyde (Table 1, entries 5-6). Consequently, a 1:1 ratio of tosylhydrazone to aldehyde was retained in further experiments. A short screen of solvents with a similar boiling point to dioxane led to no further increase in yield (Table 1, entries 7-11).

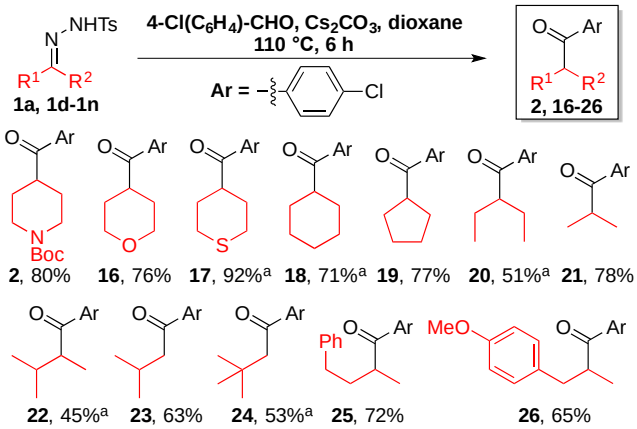
Scheme 4. Isolated Yields from Reaction of 1a with a Range of Aryl Aldehydes



[a]Reaction performed with 1.2 equiv. aldehyde for 18 h.

With optimized conditions in hand (Table 1, entry 2), a range of aryl aldehydes were assessed for their performance in the reaction (Scheme 4).[22] High yields were obtained for electron-neutral (**2-3**), electron-rich (**4**) and electron-poor (**5**) substrates. Brominated ketone **6** and an ester-containing ketone (**11**), which would both be challenging to prepare using organometallic methodology, were prepared cleanly in 77% and 79% yields respectively. An ortho-substituted example was similarly successful in good yield (**7**). Likewise, acetal (**8**) and nitrile (**10**) functionalities were well-tolerated, giving excellent yields of product. Finally, a range of heterocyclic aldehydes also performed well, giving good-to-excellent yields of ketone products (**9**, **12-15**). In some examples, slightly improved yields could be achieved by using 1.2 equivalents of the aldehyde and progressing the reaction for 18 hours.

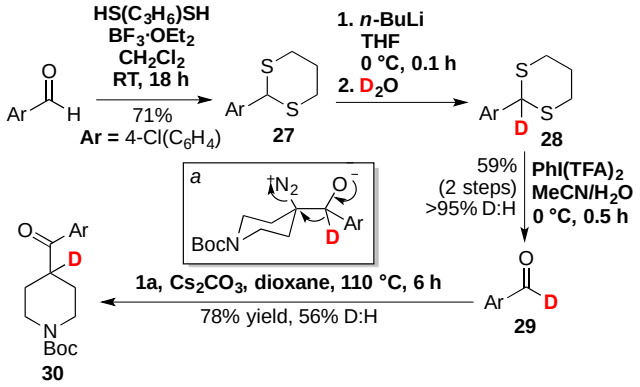
Scheme 5. Isolated Yields from Reaction of a Range of Tosylhydrazones (1a,1d-1n) with 4-Chlorobenzaldehyde



[a]Reaction performed with 1.2 equiv. aldehyde for 18 h.

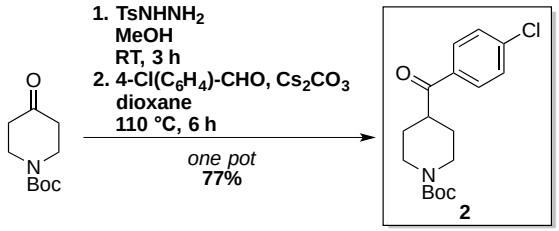
To evaluate the tosylhydrazone component of the reaction, a range of alkyl tosylhydrazones were prepared and subjected to the reaction conditions with 4-chlorobenzaldehyde as a common partner (Scheme 5). High yields were obtained for heterocyclic (**2**, **16-17**) and carbocyclic (**18-19**) products. Isopropyl (**21**), isobutyl (**23**), neopentyl (**24**) and other branched alkyl groups (**20**, **22**) could also be introduced in moderate-to-good yield. Finally, a straight-chain substrate (**25**) and a potentially enolisable example (**26**) performed well under these conditions. Reactions using *benzylic* tosylhydrazones led to complex mixtures of products, presumably due to a switch in reaction mechanism caused by the change in electronic nature of the substrate.

Scheme 6. Preparation of Deuterated 4-Chlorobenzaldehyde 29 and Subsequent Reaction with 1a to give Deuterium-Labelled Product 30.



In order to probe the mechanism of the transformation, deuterated aldehyde **29** was prepared *via* a three-step sequence (Scheme 6). Submission of this aldehyde to the reaction conditions with **1a** gave the ketone product in 78% yield with 56% deuterium incorporation at the position α to the carbonyl group (**30**, Scheme 6). A subsequent reaction run for 18 hours revealed a lower D/H ratio. Therefore, we postulate that the reaction occurs *via* a 1,2-hydrogen shift[16] (Scheme 6, a) and that the product then enolises under the reaction conditions, partially eroding the level of deuterium incorporation.

Scheme 7. One-pot Reaction of 1-Boc-4-piperidinone to form 2.



For practical reasons, we also established that the procedure can be performed as a one-pot reaction. Reaction of a 1:1 stoichiometry of 1-Boc-4-piperidinone and tosylhydrazide in MeOH for 3 hours, removal of the solvent and subjection of the resulting residue to the ketone synthesis conditions with 4-chlorobenzaldehyde gave a 77% yield of the homologated ketone product, **2** (Scheme 7). Since the majority of tosylhydrazones can be prepared without purification in a similar manner, a one-pot procedure is a viable option in most cases.

In summary, we present a safe and convenient procedure for the synthesis of unsymmetrical ketones from bench-stable saturated tosylhydrazones and aryl aldehydes, which avoids the preparation and handling of toxic and explosive diazo compounds. The reaction provides moderate-to-excellent yields of a wide variety of products, uses a 1:1 stoichiometric ratio of the reaction partners, requires no additional promoters or catalysts other than Cs_2CO_3 as a base and can be performed as a one-pot procedure.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, structural assignment and NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons: New York, 2001.

(2) Kürti, L.; Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, 2005.

(3) Li, J.; Zhang, X.; Zhang, Z.; Padakanti, P. K.; Jin, H.; Cui, J.; Li, A.; Zeng, D.; Rath, N. P.; Flores, H.; Perlmutter, J. S.; Parsons, S. M.; Tu, Z. *J. Med. Chem.* **2013**, *56*, 6216-6233.

(4) Uto, Y.; Ogata, T.; Yohei, K.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Deguchi, T.; Watanabe, N.; Konishi, M.; Okuyama, R.; Kurikawa, N.; Takagi, T.; Wakimoto, S.; Ohsumi, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 341-345.

(5) For a review on the preparation and stability of alkyl organometallics, see: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492.
(6) For selected examples of diazo insertion into C–C bonds adjacent to carbonyls, see: (a) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459-465. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619-4622. (c) Nagao, K.; Chiba, M.; Kim, S. -W. *Synthesis* **1983**, 197-199. (d) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725-4726. (e) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434-2435. (f) Morandi, B.; Carreira, E. M. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 9085-9088. (g) Gao, L.; Kang, B. C.; Ryu, D. H. *J. Am. Chem. Soc.* **2013**, *135*, 14556-14559. (h) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283-1290. (i) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055-5058. (j) Dudley, M. E.; Morshed, Md. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. S.; Atuu, M. -R.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599-7608. (k) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350-5361. (l) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2009**, 5153-5155.
(7) For selected examples of diazo insertion into aldehyde formyl C–H bonds, see: (a) Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228-229. (b) López-Herrera, F. J.; Valpuesta-Fernández, M.; García-Claros, S. *Tetrahedron* **1990**, *46*, 7165-7174. (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1994**, 521-523. (d) Sudrik, S. G.; Balaji, B. S.; Singh, A. P.; Mitra, R. B.; Sonawane, H. R. *Synlett* **1996**, 369-370. (e) Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243-8346. (f) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*, 13237-13252. (g) Mahmood, S. J.; Saha, A. K.; Hossain, M. M. *Tetrahedron* **1998**, *54*, 349-358. (h) Phukan, P.; Mohan, J. M.; Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3685-3689. (i) Bandgar, B. P.; Pandit, S. S.; Sadavarte, V. S. *Green Chem.* **2001**, *3*, 247-249. (j) Yadav, J. S.; Subba Reddy, B. V.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005**, *61*, 875-878. (k) Wu, M.; Sun, Q.; Yang, C.; Chen, D.; Ding, J.; Chen, Y.; Lin, L.; Xie, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 869-873. (l) Murata, H.; Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2008**, *49*, 4788-4791. (m) Yadav, J. S.; Subba Reddy, B. V.; Purnima, K. V.; Jhansi, S.; Nagaiah, K.; Lingaiah, N. *Catal. Commun.* **2008**, *9*, 2361-2364. (n) Jeyakumar, K.; Chand, D. K. *Synthesis* **2008**, 1685-1687. (o) Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 11280-11281. (p) Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. *J. Org. Chem.* **2010**, *75*, 8674-8676. (q) Bandyopadhyay, A.; Agrawal, N.; Mali, S. M.; Jadhav, S. V.; Gopi, H. N. *Org. Biomol. Chem.* **2010**, *8*, 4855-4860. (r) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532-8533. (s) Gao, L.; Kang, B. C.; Hwang, G. -S.; Ryu, D. H. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 8322-8325.
(8) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Eur. J. Org. Chem.* **2002**, 1562-1565.
(9) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7090-7091.
(10) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Lee, H. Y.; Reid, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 5973-5974.
(11) Mahmood, S. J.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 3333-3336.
(12) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258-3260. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131-1134.
(13) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297-5299.
(14) Nomura, K.; Iida, T.; Hori, K.; Yoshii, E. *J. Org. Chem.* **1994**, *59*, 488-490.
(15) Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, P. J. *J. Org. Chem.* **1983**, *48*, 4407-4410.
(16) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202-3205.
(17) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458-6461.
(18) Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327-10331.
(19) Bradley, J. N.; Cowell, G. W.; Ledwith, A. *J. Chem. Soc.* **1964**, 4334-4339.
(20) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In *The Chemistry of Diazonium and Diazo Groups*, Patai, S., Ed.; Interscience: New York, 1978.
(21) Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 328-338.

(22) Alkyl aldehydes also react under these conditions, but yields are lower and this is an active area of further development within our laboratory.