

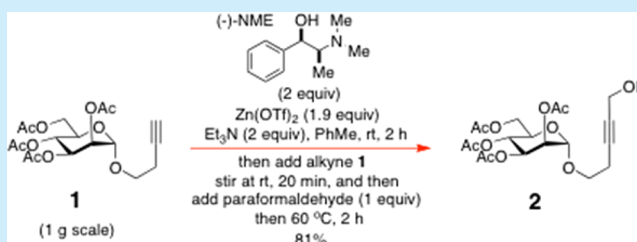
# Carreira Alkynylations with Paraformaldehyde. A Mild and Convenient Protocol for the Hydroxymethylation of Complex Base-Sensitive Terminal Acetylenes via Alkynylzinc Triflates

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## S Supporting Information

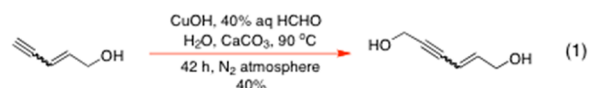
**ABSTRACT:** A new synthetic protocol for the hydroxymethylation of terminal acetylenes is described that involves stoichiometric Carreira alkynylation with solid paraformaldehyde ( $\text{HO}[\text{CH}_2\text{O}]_n\text{H}$ ) in PhMe at 60 °C. Significantly, the method can be successfully applied on acetylenes that possess base-sensitive ester functionality and heterocyclic rings that readily undergo metalation. While *N*-methylephedrine (NME) is generally the best  $\text{Zn}(\text{OTf})_2$ -coordinating ligand for promoting hydroxymethylation, TMEDA can serve as a replacement.



A key requirement of many complex molecule total syntheses is the hydroxymethylation of a terminal acetylene to obtain the corresponding primary propargylic alcohol.<sup>1</sup> Yet, despite this being a reaction of widely acknowledged synthetic importance, no truly general method presently exists for implementing it in good yield, nondestructively, on base-sensitive substrates that possess either ester or amide functionality or readily metalated aromatic heterocyclic ring systems.

The most commonly used protocol for the hydroxymethylation of a terminal acetylene involves deprotonation with an organolithium base at low temperature<sup>1,2</sup> or with ethylmagnesium bromide in an ethereal solvent at reflux<sup>3</sup> or with sodium amide in liquid  $\text{NH}_3$ .<sup>4</sup> The resulting metal acetylide is then reacted with gaseous  $\text{HCHO}$  or solid paraformaldehyde ( $\text{HO}[\text{CH}_2\text{O}]_n\text{H}$ ) ( $n = 4\text{--}100$ ). In some instances, 1,3,5-trioxane is employed as the electrophile but, according to Brandsma,<sup>2c</sup> 1,3,5-trioxane is generally not a competent electrophile for this process, and consequently, it is rarely used. Despite the excellent performance of the aforementioned  $\text{HCHO}$  gas or solid paraformaldehyde alkyne hydroxymethylation methods, none of them can be productively applied on terminal acetylenes that contain base-sensitive functionality of the type mentioned above, which means that there is a major methodological gap in our current synthetic arsenal.

While less basic monosubstituted copper acetylides have been found to react with aqueous  $\text{HCHO}$ , they must be generated with freshly prepared  $\text{CuOH}$ ,<sup>5</sup> and high reaction temperatures are often necessary to achieve even a quite modest conversion into the corresponding primary alcohol (eq 1). In most cases, the



alkyne must also have high water solubility and a low molecular weight for success. In some instances, high pressure is additionally needed for the forward reaction to proceed, as was found by Reppe,<sup>6</sup> in his now classical synthesis of 1,4-dihydroxy-2-butyne for BASF. Here, copper carbide ( $\text{Cu}_2\text{C}_2$ ), acetylene, and aqueous formaldehyde were reacted at 100 °C and 5 atm pressure, in the presence of a catalyst formed from roasted  $\text{CuO}$  and  $\text{Cu}(\text{NO}_3)_2$ . Despite the outstanding success of the Reppe process, the Cu-mediated hydroxymethylation of terminal alkynes often performs poorly when applied on complex, water-insoluble alkynes.

Of the more recent effective synthetic methods that have emerged for complex terminal acetylene hydroxymethylation, Floreancig's adaption<sup>7a</sup> of Negishi's elegant 1,1-disubstituted enol phosphate elimination method<sup>7b</sup> is a particularly noteworthy and powerful contribution. It uses LDA in THF at  $-78$  °C to fashion the desired lithium acetylide, which is thereafter reacted with solid paraformaldehyde at reflux. The latter protocol complements the much earlier dibromoalkene to lithium acetylide conversion of Corey and Fuchs,<sup>8</sup> which also relies on an *in situ* generated lithium acetylide/ $\text{HCHO}$  trapping to achieve its goal.<sup>1a</sup> Yet another much less commonly employed procedure for terminal acetylene hydroxymethylation is the electrolysis of an alkyne with paraformaldehyde and  $\text{Et}_4\text{NOT}$ s in DMF, using a Pt cathode at 3.3 mA  $\text{cm}^{-2}$ .<sup>9</sup> The reaction of monoalkyl acetylenes with 10 mol % of  $\text{Me}_3\text{N}(\text{Bn})\text{OH}$  (TRITON B) and paraformaldehyde in DMSO<sup>10</sup> is another published method for the hydroxymethylation of a terminal acetylene, but frequently this protocol is low yielding when applied on complex terminal acetylene substrates,<sup>10b</sup> and it is, of course, totally incompatible

Received: November 5, 2014

with the presence of labile esters. Although  $\text{CsOH}$ ,<sup>11</sup>  $\text{Sn}(\text{OTf})_2/\text{Et}_3\text{N}$ ,<sup>12</sup>  $\text{ZnCl}_2/\text{Et}_3\text{N}$ ,<sup>13</sup>  $\text{KOtBu}$ ,<sup>14</sup> cat.  $\text{RuCl}_3/\text{cat. In}(\text{OAc})_3/\text{morpholine}$ ,<sup>15</sup> and  $\text{GaI}_3/\text{Et}_3\text{N}$ <sup>16</sup> have all been reported to afford metal acetylides that react readily with aldehydes, it is striking to note that paraformaldehyde or gaseous  $\text{HCHO}$  are always absent from the lists of viable reaction partners that are presented. The same is true for all asymmetric alkynylation processes that have so far been described<sup>17</sup> and while, admittedly, this dearth of reports might simply be due to gaseous  $\text{HCHO}$  or solid paraformaldehyde never having been evaluated in this capacity, equally well, it could be due to these electrophiles simply not performing successfully in these processes.

In this regard, solid paraformaldehyde ( $\text{HO}[\text{CH}_2\text{O}]_n\text{H}$ ) (where  $n = 4\text{--}100$ ) has long been known to cause problems for certain metal acetylide trappings, due to the fact that it is formally a diol polycondensation product of methylene glycol. As such, it has considerable potential to quench alkynyl anions to a very significant degree. Consequentially, dry gaseous  $\text{HCHO}$  is often used in such couplings, and technically, on large scale, such reactions are often difficult to perform safely.

Given all of these problems, there is a pressing need for new, more convenient, reaction technologies that will allow the efficient hydroxymethylation of a wide range of structurally diverse, water-insoluble alkynes with solid paraformaldehyde under mild conditions, most especially alkynes with base-sensitive groups. In this regard, we recently became interested in synthesizing the monosaccharide alkynol derivatives **2**, **4**, and **6** (Table 1) for evaluation as hydrostannation models<sup>18</sup> and synthetic probes for a projected future TMC-171C total synthesis.<sup>19</sup> However, the direct preparation of propargyl alcohols **2** and **4** from the O-acetylated glycosides **1** and **3** did not look feasible using existing established methods because  $n\text{-BuLi}$ ,  $\text{EtMgBr}$ , or  $\text{LDA}$  would all adversely damage the acetate esters present in these two substrates.  $n\text{-BuLi}$  and  $\text{LDA}$  might also cause fragmentation of the dioxolane acetal in **5** due to O-glycoside-directed metalation at C(3) and attendant E1cb elimination, a reaction known to proceed with facility for 2,3-dioxolane benzylidene acetals of  $\alpha\text{-D-mannopyranosides}$ .<sup>20</sup>

After giving the problem some careful thought, we eventually decided to investigate whether a hitherto-undescribed Carreira alkynylation<sup>21</sup> with solid paraformaldehyde might prove useful in this capacity, and herein, we now report that this new hydroxymethylation protocol works eminently well. Not only does it allow for a direct preparation of the O-acetylated glycosides **2** and **4**, it also permits the hydroxymethylation of a wide range of other alkynes with base-sensitive aromatic heterocycle functionality, molecules which ordinarily would undergo competing metalation and hydroxymethylation at other sites if attempted with bases such as  $n\text{-BuLi}$ ,  $\text{EtMgBr}$ , or  $\text{LDA}$ . As a consequence, we have now provided the first truly general solution to the issue of base-sensitive terminal acetylene hydroxymethylation with solid paraformaldehyde.

The first alkyne that we examined in this way was the glycoside **1** (Table 1), and since we had recently successfully used a *catalytic* Carreira asymmetric alkynylation procedure<sup>21</sup> in our total synthesis of (–)-(3R)-inthomycin C,<sup>18b</sup> we initially decided to evaluate these reaction conditions. This entailed us stirring 0.4 equiv of (–)-*N*-methylephedrine (NME), 0.3 equiv of  $\text{Zn}(\text{OTf})_2$ , and 1 equiv of  $\text{Et}_3\text{N}$  in PhMe at rt for 2 h, adding **1**, stirring at rt for 20 min, to enable initial metalation to proceed, and then heating the reactants at 60 °C with 1 equiv of paraformaldehyde for 4 d. Unfortunately, these conditions led to little noticeable reaction to give **2**. A similar outcome was found

Table 1. A New, Mild Hydroxymethylation Procedure for Terminal Alkynes in PhMe

alkyne	( $\text{HO}[\text{CH}_2\text{O}]_n\text{H}$ )	reaction time	product and yield
<b>1</b> (1 g scale)	1 equiv <sup>a</sup>	2 h	<b>2</b> 81%
<b>3</b> (0.57 g scale)	1 equiv <sup>a</sup>	1 h	<b>4</b> 84%
<b>5</b> (1 g scale)	1 equiv <sup>a</sup>	5 h	<b>6</b> 82% (plus 4% recovered alkyne)
<b>7</b> (0.5 g scale)	5 equiv <sup>a</sup>	61 h	<b>8</b> 74%
<b>9</b> (69.5 mg scale)	5 equiv <sup>a</sup>	48 h	<b>10</b> 31% (unoptimized)
<b>11</b> (0.5 g scale)	5 equiv <sup>a</sup>	4 h	<b>12</b> 71%
<b>13</b> (0.31 g scale)	1 equiv <sup>a</sup>	3 h	<b>14</b> 82%
<b>15</b> (102 mg scale)	2.2 equiv <sup>b</sup>	2 h	<b>16</b> 84%
<b>17</b> (0.2 g scale)	2.2 equiv <sup>b</sup>	2 h	<b>18</b> 61%
<b>19</b> (0.2 g scale)	1 equiv <sup>b</sup>	3.5 h	<b>20</b> 64%
<b>21</b> (0.25 g scale)	2.2 equiv <sup>b</sup>	48 h	<b>22</b> 85%

for alkyne **3**, under identical circumstances, except here the reactants were heated at 60 °C with 5 equiv of paraformaldehyde for 20 h. This lack of reaction progress in both *catalytic* cases eventually led us to try Carreira's stoichiometric procedure<sup>21</sup> on **1**. This involved us stirring a THF solution of 1.7 equiv of (–)-NME with 1.6 equiv of  $\text{Zn}(\text{OTf})_2$  and 1.7 equiv of  $\text{Et}_3\text{N}$  for 2 h,<sup>18c</sup> adding 1.5 equiv of alkyne **1**, and continuing stirring for 20

min before adding 1 equiv of paraformaldehyde. Once more, the alkynylation reaction did not proceed satisfactorily at rt. Significantly though, when the reactants were subsequently heated at 60 °C for 14 h, the desired product **2** did start to form, but not in a very clean way. We therefore repeated the reaction on 100 mg scale with respect to **1** (1 equiv), using 1.1 equiv of (–)-NME, 1.1 equiv of  $\text{Zn}(\text{OTf})_2$ , 1.1 equiv of  $\text{Et}_3\text{N}$ , and 1 equiv of paraformaldehyde, except now we conducted the reaction exclusively in PhMe at 60 °C for 6 h. Thereafter, the alkynol **2** was formed cleanly, but only in 29% yield. Wondering whether this lack of reaction progress might simply be due to the difficulties of stirring the biphasic reaction mixture well on small scale, we repeated the reaction with 0.5 g of the alkyne **1** in a greater volume of PhMe. Significantly, the extent of conversion was now much better, and once more, alkynol **2** formed cleanly, but in a greatly improved 65% yield. Following several further rounds of optimization, it was eventually discovered that *vigorous stirring* of 2 equiv of (–)-NME, 1.9 equiv of  $\text{Zn}(\text{OTf})_2$ , and 2 equiv of  $\text{Et}_3\text{N}$  in dry PhMe at rt for 2 h under  $\text{N}_2$  produced a biphasic mixture that went on to react cleanly with 1 equiv of the alkyne **1**. Moreover, when these reactants were stirred at rt for 20 min, and subsequently reacted with 1 equiv of paraformaldehyde at 60 °C over 2 h, **2** was obtained very cleanly in 81% yield on 1 g scale (Table 1). The same reaction was also conducted with (+)-NME to equal effect, showing that both enantiomers of NME work equivalently in these reactions with chiral substrates of this sort.

Next, we applied our (–)-NME conditions to the but-3-ynyl  $\beta$ -D-galactopyranoside **3**<sup>22</sup> and the but-3-ynyl 2,3,4,6-di-O-isopropylidene  $\alpha$ -D-mannopyranoside **5** (Table 1) and again found that the desired propargyl alcohols **4** and **6** were formed cleanly in 84% and 82% yield on 0.57 and 1 g scale, respectively. While these conditions worked extremely well for each of these three substrates, and many others besides, a further increase in the amount of paraformaldehyde (5 equiv) and a longer reaction time did prove necessary to coax the optimal yield from the more hindered terminal alkyne **7**<sup>18a</sup> which possesses multiple bulky protecting groups in close proximity to the acetylene. Of special note, however, was our discovery that the optimized hydroxymethylation conditions could be productively applied with high regioselectivity on each of the readily metalated<sup>23</sup> heterocyclic alkynes **13**, **15**, **17**, **19**, and **21** (Table 1), without the occurrence of undesired competing deprotonation<sup>23</sup> and hydroxymethylation of their heterocyclic rings or the methyl side chain in the case of **21**. This outcome, along with survival of the ester functionality in **2**, **4**, **18**, and **20**, was particularly striking. The lack of O(1)-directed C(3)-metalation and E1cb acetal elimination<sup>20</sup> in the di-O-isopropylidenedated mannopyranoside **5** is another item of note.

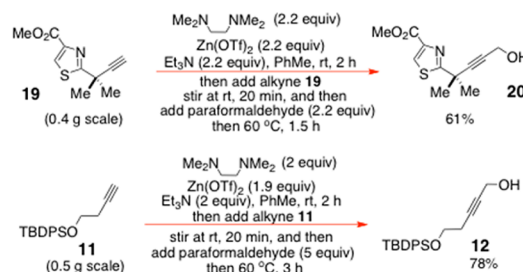
The lowest yield that we have so far encountered is with the acetylene **9**,<sup>18d</sup> a substrate that we could not optimize further due to the dearth of starting material presently available. Nevertheless, the hydroxymethylation did proceed very cleanly, which is contrary to what the 31% yield of **10** might at first suggest.

In this regard, we have found that the best yields generally accrue when these hydroxymethylations are conducted on larger scale (>0.4 g alkyne), where more efficient mixing of the biphasic reaction mixtures can often be achieved. Saying this, we have successfully conducted several experiments on quite small scale and obtained decent yields (see Table 1).

Given the current quite high cost of commercially purchased (–)- and (+)-NME for university research, we draw attention to the fact that both antipodes can be readily synthesized cheaply on large scale by the method of Smith;<sup>24a</sup> the racemate is also easily

accessed.<sup>24b</sup> Even so, we have still attempted to find a much cheaper commercial alternative to NME that works in a near equivalent way. Our screening has revealed that TMEDA can often serve as a reasonably effective and viable replacement for NME in such applications (Scheme 1). Thus, when our

### Scheme 1. TMEDA/ $\text{Zn}(\text{OTf})_2$ / $\text{Et}_3\text{N}$ -Mediated Alkyne Hydroxymethylation

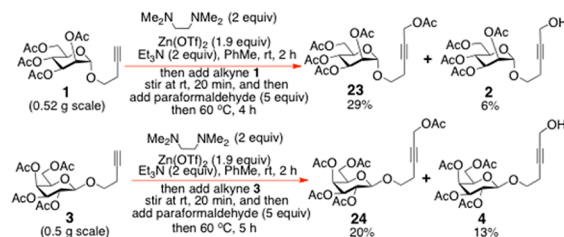


$\text{Zn}(\text{OTf})_2$ /TMEDA/ $\text{Et}_3\text{N}$ /paraformaldehyde conditions were applied to **19** in PhMe at 60 °C for 1.5 h, **20** was formed in 61% yield with its methyl ester intact. The yield of this reaction certainly compared favorably with the 64% yield obtained by the (–)-NME-mediated method and, once again, the heterocyclic ring did not undergo competing metalation and concomitant hydroxymethylation.

Indeed, in the case of alkyne **11**, the TMEDA ligand actually outperformed (–)-NME in the  $\text{Zn}(\text{OTf})_2$ / $\text{Et}_3\text{N}$ -mediated terminal alkyne hydroxymethylation process in PhMe, cleanly affording the known **12**<sup>2d,25</sup> in 78% yield after 3 h at 60 °C.

Even so, one undesired side-reaction that did come to light, when we examined the carbohydrate alkynes **1** and **3** in the  $\text{Zn}(\text{OTf})_2$ /TMEDA/ $\text{Et}_3\text{N}$  process, was competing O-acetyl transfer to the alkynol products **2** and **4**, which occurred alongside hydroxymethylation (Scheme 2). This was not a serious issue in the NME-mediated processes.

### Scheme 2. O-Acetyl Transfer during TMEDA/ $\text{Zn}(\text{OTf})_2$ / $\text{Et}_3\text{N}$ -Mediated Hydroxymethylation of Alkynes **1** and **3**

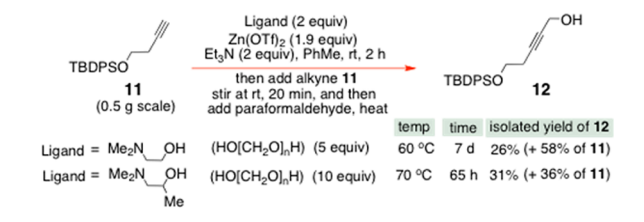


A detailed study of the  $\text{Zn}(\text{OTf})_2$ / $\text{Et}_3\text{N}$ -mediated hydroxymethylation of alkyne **11** with the alternate achiral ligand, (dimethylamino)ethanol ( $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OH}$ ), in place of (–)-NME, under our standard conditions, demonstrated that while this system does indeed provide the desired alkynol **12** very cleanly, it does so only in low yield (26%) (Scheme 3). In fact, the reaction does not reach completion even after it is heated for 7 d at 60 °C. Although 1-(*N,N*-dimethylamino)-2-propanol performs better as a ligand in this system, alkyne hydroxymethylation is still extremely slow, with **12** only being produced in 31% yield after the reaction has been heated at 70 °C for 65 h.

Given that the rate of alkyne hydroxymethylation is greatly diminished when  $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OH}$  or  $\text{Me}_2\text{NCH}_2\text{CH}(\text{Me})\text{OH}$  is employed, we suspect that these sterically less encumbered



**Scheme 3. Use of Me<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>OH and Me<sub>2</sub>NCH<sub>2</sub>CH(Me)OH as Ligands**



ligands are causing extremely stable trimeric alkynylzinc alkoxide complexes<sup>26</sup> to form which, thereafter, are unable to readily dissociate into the monomeric alkynylzinc reagents needed to engage in nucleophilic addition. By way of contrast, when much more sterically crowded NME ligands are employed, these probably form less tightly associated dimeric alkynylzinc alkoxide complexes<sup>26</sup> that have a much greater tendency to dissociate into nucleophilically competent acetylenic anion monomers. These arguments, which are based on Noyori and Kitamura's work on aminoalcohol-accelerated dialkylzinc addition to aldehydes,<sup>26</sup> nicely explain why much faster rates of alkyne hydroxymethylation are observed with the privileged Zn(OTf)<sub>2</sub>/NME/Et<sub>3</sub>N reagent ensemble.

Thus, to conclude, a nonpyrophoric way of hydroxymethylating base-sensitive alkyne substrates has been devised that is compatible with many commonly used alcohol and amine protecting groups.<sup>27</sup> Given the broad scope of this reaction, we expect that it will be employed widely over the coming years.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details and spectra for all new 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.

## ■ ACKNOWLEDGMENTS

We thank QUB for a starter grant (to K.J.H.) and for studentships.

## ■ REFERENCES

- (1) See, for example: (a) Bryostatin 3: Obitsu, T.; Ohmori, K.; Ogawa, Y.; Hosomi, H.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1998**, 39, 7349. (b) (±)-Kallolide B: Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, 60, 796.
- (2) (a) Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* **1970**, 2245. (b) Blanchette, M. A.; Malamas, M. A.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, 54, 2817. (c) Shaap, A.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim.* **1965**, 84, 1200. (d) Hale, K. J.; Bhatia, G. S.; Peak, S. A.; Manaviyar, S. *Tetrahedron Lett.* **1993**, 34, 5343.
- (3) (a) Sondheimer, F. *J. Am. Chem. Soc.* **1952**, 74, 4040. (b) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, 89, 4245. (d) Zwierzak, A.; Tomassy, B. *Synth. Commun.* **1996**, 26, 3593.
- (4) Armitage, J. B.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1951**, 44.

- (5) Heilbron, I. M.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1947**, 1586.
- (6) Baptista, R. J. *Walter Reppe: Pioneer in Acetylene Chemistry*, 2009, <http://www.colorantshistory.org/ReppeChemistry.html> (accessed Dec 9, 2014).
- (7) (a) Peh, G.; Floreancig, P. E. *Org. Lett.* **2012**, 14, 5614. (b) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, 45, 2526.
- (8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
- (9) Torii, S.; Okumoto, H.; Kiyoto, T.; Hikasa, S. *Chem. Lett.* **1988**, 1977.
- (10) (a) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, 68, 3702. (b) Molino, B. F.; Yang, Z. US Patent No. 7,632,807B2, Dec 15, 2009.
- (11) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, 38, 1463.
- (12) Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem.* **1991**, 56, 4091.
- (13) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, 43, 8323.
- (14) Wang, S.-H.; Tu, Y.-Q.; Chen, P.; Hu, X.-D.; Zhang, F.-M.; Wang, A.-X. *J. Org. Chem.* **2006**, 71, 4343.
- (15) Wei, C.; Li, C.-J. *Green Chem.* **2002**, 4, 39.
- (16) Han, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, 36, 7277.
- (17) Review: Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, 351, 963 and references cited therein.
- (18) For the O-directed free radical hydrostannation of propargylic allyl oxygenated alkylacetylenes with Ph<sub>3</sub>SnH/cat. Et<sub>3</sub>B, see: (a) Dimopoulos, P.; Athlan, A.; Manaviyar, S.; George, J.; Walter, M.; Lazarides, L.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2005**, 7, 5369. (b) Synthesis of (3R)-(-)-inthomycin C: Hale, K. J.; Grabski, M.; Manaviyar, S.; Maczka, M. *Org. Lett.* **2014**, 16, 1164. Hale, K. J.; Hatakeyama, S.; Urabe, F.; Ishihara, J.; Manaviyar, S.; Grabski, M.; Maczka, M. *Org. Lett.* **2014**, 16, 3536. (c) Synthesis of C(7)-C(22)-sector of (+)-acutiphycin: Hale, K. J.; Maczka, M.; Kaur, A.; Manaviyar, S.; Ostovar, M.; Grabski, M. *Org. Lett.* **2014**, 16, 1168. (d) Formal total synthesis of (+)-pumiliotoxin B: Manaviyar, S.; Hale, K. J.; LeFranc, A. *Tetrahedron Lett.* **2011**, 52, 2080.
- (19) TMC-171C: Kohno, J.; Asai, Y.; Nishio, M.; Sakurai, M.; Kawano, K.; Hiramatsu, H.; Kameda, N.; Kishi, N.; Okuda, T.; Komatsubara, S. *J. Antibiot.* **1999**, 52, 1114.
- (20) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, 44, 227.
- (21) (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, 122, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123, 9687.
- (22) Bretschneider, H.; Beran, K. *Monatsh. Chem.* **1949**, 80, 262.
- (23) (a) For the rapid (30 s) ring deprotonation and trapping of carboxythiazole methyl esters with LDA/THF at -78 °C, see: Deng, S.; Taunton, J. *Org. Lett.* **2005**, 7, 299. (b) For the *n*-BuLi-mediated C2-deprotonation of *N*-methylimidazole, see: Nilsson Lill, S. O.; Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3054. (c) For an excellent review on metallated heterocycles in synthesis, see: Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, 104, 2667.
- (24) (a) (+)- and (-)-NME can be readily prepared by *N*-methylation of the individual enantiomers of ephedrine with MeI: Smith, S. J. *Chem. Soc.* **1927**, 2056. Ephedrine is presently priced at £63.10 for 100 g. (b) For the industrial production of (±)-NME, see: Sugawara, S.; Yamazaki, T.; Kawanishi, M.; Iwao, J. *Yakugaku Zasshi* **1951**, 71, 530.
- (25) Hale, K. J.; Manaviyar, S.; George, J. *Chem. Commun.* **2010**, 4001.
- (26) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, 30, 49.
- (27) For OMOM ether and *N*-Boc compatibility, see: (a) Krishna, P. R.; Srinivas Reddy, P. *Synlett* **2009**, 209. For OTES compatibility, see: (b) Kleinbeck, F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2009**, 48, 578. For OCH<sub>2</sub>CH<sub>2</sub>TMS compatibility, see: (c) Strand, D.; Rein, T. *Org. Lett.* **2005**, 7, 199. For thiazolidinone NPMB, OSEM, and stereodefined dienyl ester compatibility, see: (d) Williams, B. D.; Smith, A. B., III. *J. Org. Chem.* **2014**, 79, 9284. (e) For OPMB compatibility, see ref 18c.