Stereoselective and Catalytic Synthesis of *anti* β-Alkoxy-α-Azido Carboxylic Derivatives

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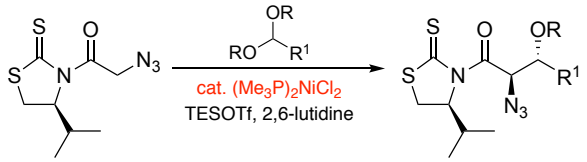
Supporting Information Placeholder



ABSTRACT: Direct addition of a chiral *N*-azidoacetyl thiazolidinethione to a variety of dialkyl acetals catalyzed by a commercially available and structurally simple nickel(II) complex gives access in good yields and a highly stereocontrolled manner to *anti* β-alkoxy-α-azido carboxylic derivatives which, in turn, can be easily converted into a wide array of enantiomerically pure compounds.

Anti β-hydroxytyrosine derivatives are key structural motifs in a variety of biologically active compounds, ranging from structurally simple 3-acyltetramic acids[1] to much more complex vancomycin antibiotics[2] or cyclodepsipeptides such as stellatolides (Figure 1).[3]

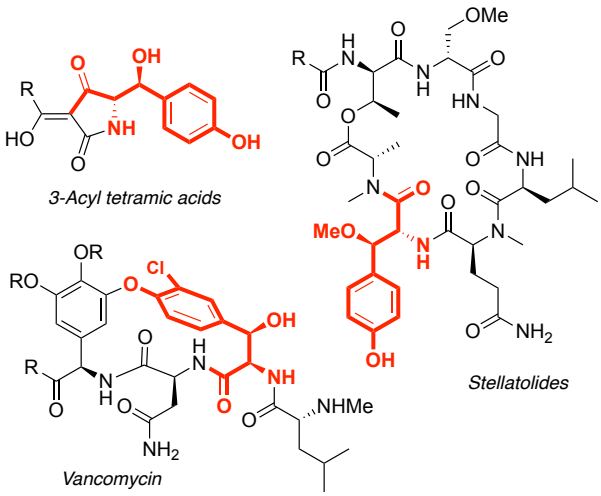
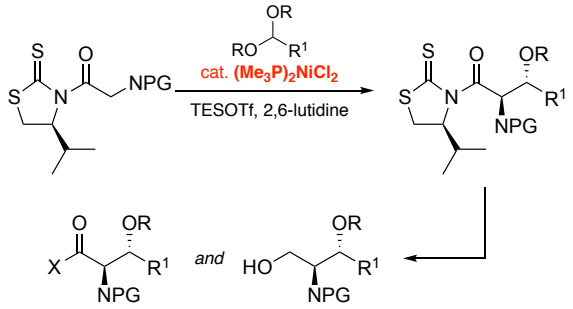


Figure 1. *anti* β-Hydroxytyrosine fragments in natural products

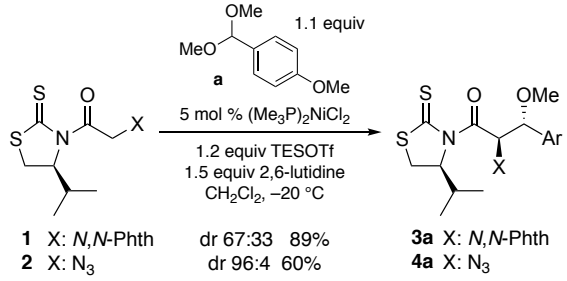
It should therefore come as no surprise that their synthesis has attracted much attention, but, despite considerable effort, that goal has remained elusive. Lipton reported a single example of a highly enantioselective and diastereoselective synthesis of *anti* β-methoxytyrosine through asymmetric aziridination of the TBS-protected methyl *p*-coumarate followed by ring opening in methanol.[4] In turn, Hamada found that α-amino-β-aryl-β-keto esters can be hydrogenated through dynamic kinetic resolution in the presence of a chiral iridium catalyst to give the corresponding *anti* α-amino-β-hydroxy acids as a single diastereomer with excellent enantiocontrol;[5,6] however, the high pressure and long reaction time required (100 atm for four days) have thwarted further applications. Alternative aldol-based approaches might seem much more promising, but their scope is still very limited.[7] Maruoka reported the enantioselective synthesis of *anti* α-amino-β-hydroxy acids through aldol reactions from a glycinate Schiff base catalyzed by a chiral quaternary ammonium salt, but aromatic aldehydes turned out to be unsuitable substrates.[8] More recently, Kumagai and Shibasaki have described a highly diastereoselective and enantioselective catalytic aldol reaction of α-azido 7-azaindolinylacetamide; but this is restricted to *ortho*-substituted aromatic aldehydes.[9] In the face of this lack of experimentally simple and broad ranging synthetic methods, we envisaged that the direct addition of chiral *N*-glycyl thiazolidinethiones to dialkyl acetals catalyzed by nickel(II) complexes might afford *anti* β-alkoxy-α-amino carboxylic derivatives.[10,11] Herein, we report that $(Me_3P)_2NiCl_2$ triggers the stereocontrolled addition of a chiral *N*-2-azidoacetyl thiazolidinethione (NPG: N_3 in Scheme 1) to aromatic and propargylic dialkyl acetals to give *anti* β-alkoxy-α-azido adducts[12] which, in turn, can be easily converted into a plethora of enantiomerically pure intermediates.

Scheme 1. Direct and catalyzed addition of *N*-(2-azaacetyl) thiazolidinethiones to dialkyl acetals



Exploratory experiments indicated that most of the amino protecting groups (NPG: Boc, Fmoc, Z, and Bz in Scheme 1) were unsuitable for our purposes. Only nickel(II) catalyzed addition of phthaloyl and azido derivatives, **1** and **2** respectively in Scheme 2,[13] to the dimethyl acetal of *p*-anisaldehyde (**a**), which gave the desired adducts in good yields. Unfortunately, and despite our efforts, we did not succeed in exerting proper stereocontrol over the configuration of the β-stereocenter from **1**, and adduct **3a** was isolated as a 67:33 diastereomeric mixture in an overall yield of 89% (Scheme 2). In contrast, *N*-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione **2** gave adduct **4a** as a 96:4 mixture of diastereomers with a 60% yield (Scheme 2).

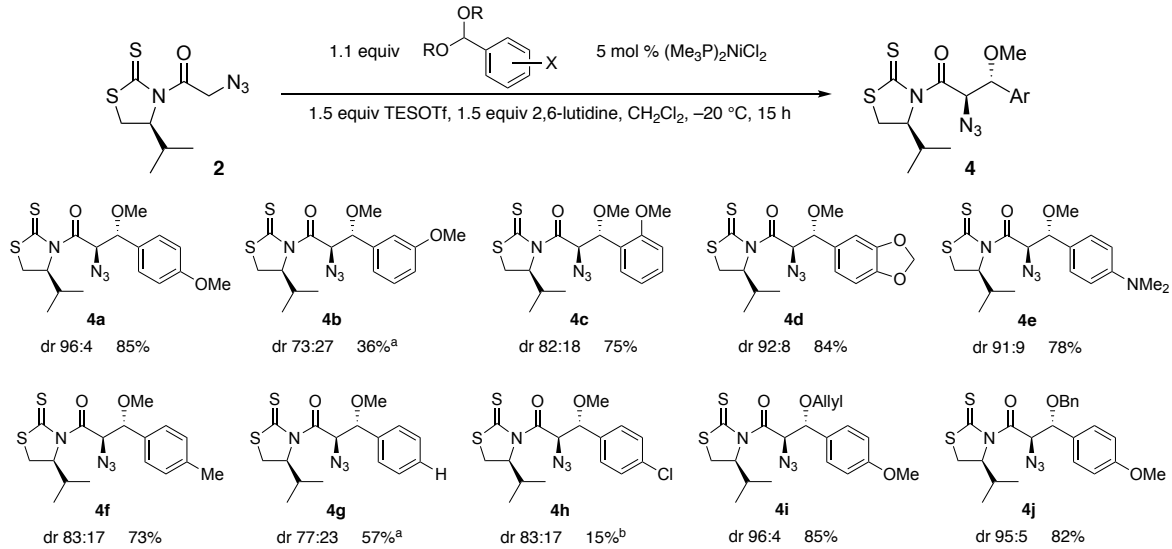
Scheme 2. Preliminary results



Following comprehensive optimization, we finally found that the direct reaction of **2** with the acetal **a** (1.1 equivalents) using 5 mol % of commercially available $(Me_3P)_2NiCl_2$, 1.5 equivalents of TESOTf and 2,6-lutidine for 15 h at –20 °C led to a 96:4 diastereomeric mixture from which the pure *anti* adduct **4a** was isolated with an 85% yield (Scheme 3). Once the synthesis of such a β-methoxytyrosine precursor had been completed, we next applied the abovementioned conditions to a variety of dimethyl acetals from aromatic aldehydes. As shown in Scheme 3, the methoxy–substituted acetals **a–c** revealed the dramatic influence of the electronic character of the aryl group on the outcome of these additions. Indeed, the diastereomeric ratio dropped from 96:4 to 73:27 and improved again to 82:18 when we passed from 4-OMe to 3-OMe and 2-OMe acetals respectively (compare **4a–c** in Scheme 3). In accordance with such a trend, piperonal and 4-NMe_2 dimethyl acetals, **d** and **e** respectively, also furnished the *anti* adducts **4d** and **4e** in high diastereomeric ratios and yields (Scheme 3). The less activated tolyl and phenyl acetals, **f** and **g** respectively, afforded the *anti* adducts with a progressively poorer stereocontrol; whereas the deactivated 4-chloro dimethyl acetal (**h**) required 20 mol % of $(Me_3P)_2NiCl_2$ to obtain **4h** with a meager 15% yield (Scheme 3). Finally, the alkyl group R did not have any effect on these reactions. Indeed, the allyl and benzyl acetals, **i** and **j** respectively, gave the corresponding *anti* adducts **4i** and **4j** with diastereoselectivities and yields close to those for the dimethyl acetal **a** (Scheme 3).[14]

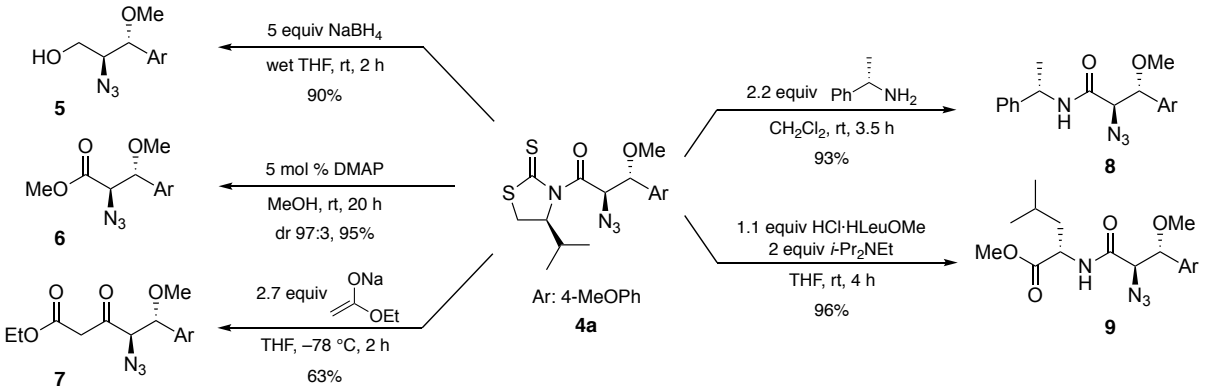
Thiazolidinethiones are renowned among the chiral auxiliaries for their ease of removal;[15] so **4a** was smoothly converted into the enantiomerically pure alcohol **5**, ester **6**, and keto ester **7** under mild conditions (Scheme 4). Furthermore, treatment of **4a** with (*S*) α-methylbenzylamine afforded amide **8**, whose X-ray analysis permitted us to establish the *anti* configuration of **4**.[16] In turn, a parallel reaction with 1 equivalent of methyl leucinate hydrochloride gave the dipeptide **9** with a 96% yield in a straightforward manner (Scheme 4).

Scheme 3. Diastereoselective and nickel(II) catalyzed addition of (*S*) *N*-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (2) to dialkyl acetals of aromatic aldehydes



[a] 10 mol % $(Me_3P)_2NiCl_2$. [b] 20 mol % $(Me_3P)_2NiCl_2$.

Scheme 4. Removal of the chiral auxiliary

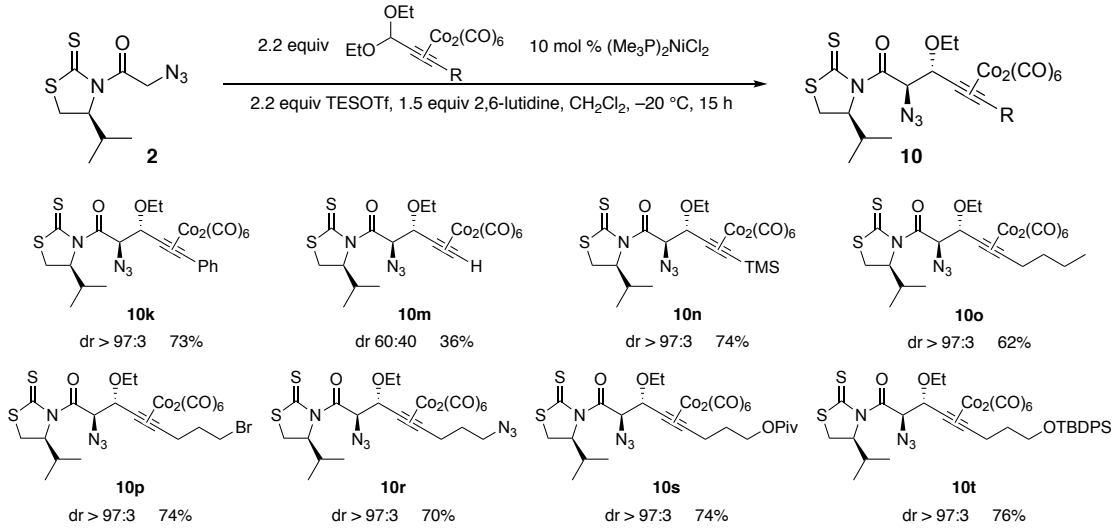


Aiming to expand the scope of this transformation, we then focused our attention on other acetals. Since Schreiber reported that cobalt-derived propargylic acetals easily undergo S_N1-like reactions,[17,18] we envisaged that their use might provide access to a much larger range of compounds. Thus, we were pleased to observe that model cobalt phenylpropargylaldehyde diethyl acetal (**k**) participated in a highly stereoselective reaction with **2**. Indeed, its direct addition to **2** using 10 mol % of $(Me_3P)_2NiCl_2$, 2.2 equivalents of TESOTf, and 1.5 equivalents of 2,6-lutidine provided diastereomerically pure **10k** with 73% yield (Scheme 5). These conditions were further applied to a number of acetals **k–t**[19] possessing a wide array of functional groups to obtain **10k–t** as single diastereomers in high yields, with the exception of **10m**, from the simple propargylaldehyde diethyl acetal (Scheme 5). All together, these results show that the addition of **2** catalyzed by a nickel(II) complex to properly activated acetals provides a totally stereocontrolled access to highly functionalized *anti* β-alkoxy-α-azido carboxylic derivatives.

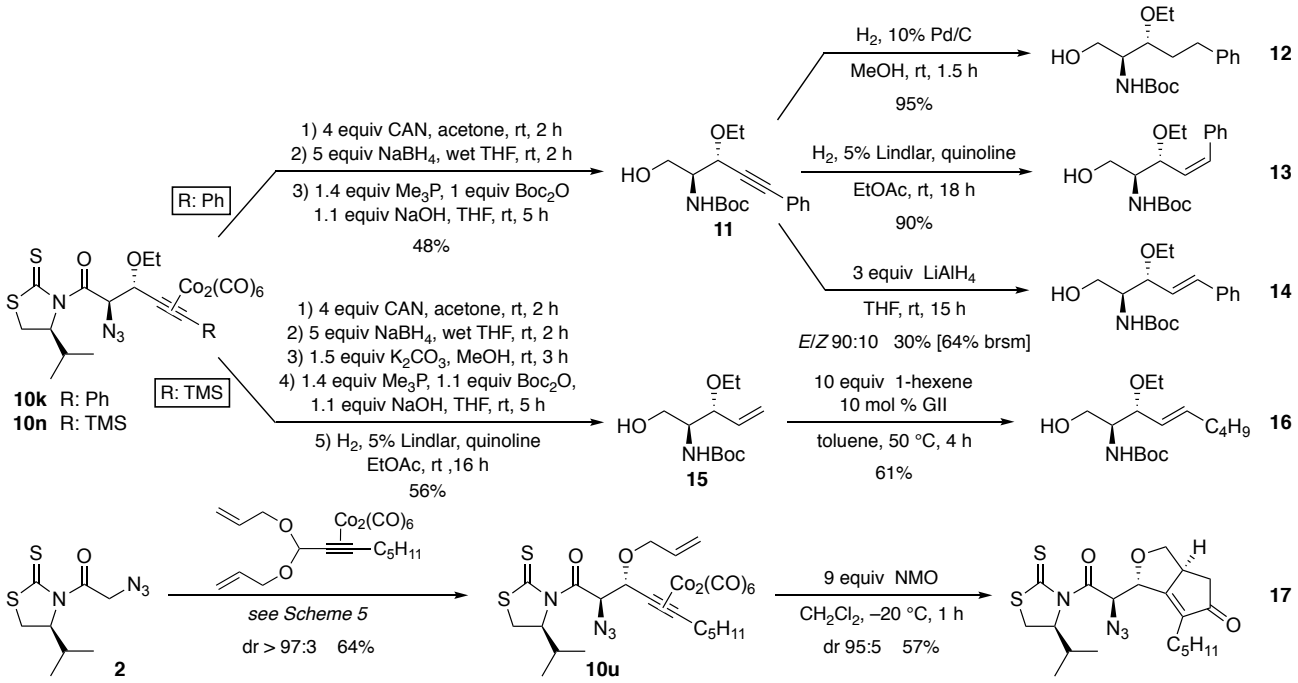
Importantly, the resulting adducts **10** can be transformed into a variety of advanced intermediates. As shown in Scheme 6, appropriate manipulation of adduct **10k** produced the Boc-protected amino alcohol **11** in a 48% overall yield. This can then be hydrogenated to the alkyl **12** or *Z*-alkenyl derivative **13** in excellent yields. Unfortunately, the obtention of the *E*-counterpart **14** was much more troublesome. Attempts to reduce the triple bond with Na/NH_3 or by means of ruthenium catalysts[20] were unsuccessful; it was finally achieved by treatment with $LiAlH_4$ but in a poor yield (*E*/*Z* 90:10, 30%, 64% brsm). Alternatively, **10n** was smoothly converted into the terminal alkene **15**, which underwent a cross-metathesis reaction with 1-hexene to produce the *E*-alkene **16**.[21] Finally, we also took advantage of the *anti* adduct **10u** containing an allyloxy group close to the cobalt-activated triple bond to carry out Pauson-Khand cyclization[22] that furnished the densely functionalized cyclopentenone **17** in a 57% yield under very mild conditions (Scheme 6). All together, these results prove that adducts **10** are suitable materials to access to a wide array of enantiomerically pure *anti* 3-alkoxy-2-amino hydroxy derivatives.

In summary, direct Lewis acid-mediated reaction of *N*-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione **2** with aromatic and propargylic acetals catalyzed by 5–10 mol % of a structurally simple nickel(II) complex provides the corresponding *anti* α-alkoxy-β-azido derivatives in good yield with high stereocontrol. In turn, the resultant adducts can be converted into a variety of enantiomerically pure intermediates in a straightforward manner.

Scheme 5. Diastereoselective and nickel(II) catalyzed addition of (*S*) *N*-2-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione (2) to diethyl acetals of propargylic aldehydes



Scheme 6. Conversion of adducts 10 into enantiomerically pure compounds



ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, physical, and spectroscopic data for **2**, adducts **4a–j**, **10k–u**, derivatives **5–9**, **11–17**, as well as X-ray of **8** (PDF).
Copies of ^{1}H and ^{13}C spectra for new compounds (PDF)
The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Mo, X.; Li, Q.; Ju, J. *RSC Adv.* **2014**, *4*, 50566. (b) Bruckner, S.; Haase, R. G.; Schobert, R. *Chem. Eur. J.* **2017**, *23*, 5692.
(2) Okano, A.; Isley, N. A.; Boger, D. L. *Chem. Rev.* **2017**, *117*, 11952.
(3) Martín, M. J.; Rodríguez-Acebes, R.; García-Ramos, Y.; Martínez, V.; Murcia, C.; Digón, I.; Marco, I.; Pelay-Gimeno, M.; Fernández, R.; Reyes, F.; Francesch, A. M.; Munt, S.; Tulla-Puche, J.; Albericio, F.; Cuevas, C. *J. Am. Chem. Soc.* **2014**, *136*, 6754.
(4) Cranfill, D. C.; Lipton, M. A. *Org. Lett.* **2007**, *9*, 3511.
(5) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784.
(6) For a related procedure using transfer hydrogenation under milder conditions see: Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274.
(7) For an early report on the difficulty to get access to *anti* α-amino aldol adducts see: Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39.
(8) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685.
(9) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6236.
(10) For previous Ti-based stoichiometric additions see: (a) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615. (b) Baiget, J.; Caba, M.; Gálvez, E.; Romea, P.; Urpí, F.; Font-Bardia, M. *J. Org. Chem.* **2012**, *77*, 8809.
(11) For previous Ni-based catalytic additions see: (a) Romo, J. M.; Gálvez, E.; Nubiola, I.; Romea, P.; Urpí, F.; Kindred, M. *Adv. Synth. Catal.* **2013**, *355*, 2781. (b) Fernández-Valparís, J.; Romo, J. M.; Romea, P.; Urpí, F.; Kowalski, H.; Font-Bardia, M. *Org. Lett.* **2015**, *17*, 3540. (c) Kennington, S. C. D.; Romo, J. M.; Romea, P.; Urpí, F. *Org. Lett.* **2016**, *18*, 3018.
(12) The addition probably proceeds through the antiperiplanar approach of a putative oxocarbenium intermediate to a chelated nickel(II) enolate, as described in Reference 10a and 11b.
(13) For an overview on the synthesis and reactivity of *N*-acyl thiazolidinethiones see: Romea, P.; Urpí, F. *Org. Synth.* **2013**, *90*, 182.
(14) For other Lewis acid-mediated additions to dibenzyl acetals see: Gálvez, E.; Parelló, R.; Romea, P.; Urpí, F. *Synlett* **2008**, 2951.
(15) For original reports see: (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (b) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243.
(16) Crystallographic data for amide **8** has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1574237. A copy of the data can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).

(17) (a) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. (b) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(18) For an analysis on the electrophilicity of cobalt carbonyl stabilized propargylium ions see: Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900.

(19) Acetals **k–t** have been synthesized in accordance with standard procedures and purified by column chromatography, see: (a) Varghese, V.; Saha, M.; Nicholas, K. M. *Org. Synth.* **1989**, *67*, 141. (b) Reference 17 and 18.

(20) (a) Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922. (b) Trost, B. M.; Hung, C.-I. *J. Am. Chem. Soc.* **2015**, *137*, 15940.

(21) *Olefin Metathesis. Theory and Practice*; Grela, K., Ed.; John Wiley & Sons: Hoboken, 2014.

(22) (a) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (b) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2016**, *116*, 5744.