Organic LETTERS

Letter

pubs.acs.org/OrgLett

Base-Catalyzed Domino Cyclization of Acetylenes with Ketones to Functionalized Cyclopentenes

Elena Yu. Schmidt,[†] Boris A. Trofimov,*[,†] Ivan A. Bidusenko,[†] Natalia A. Cherimichkina,[†] Igor' A. Ushakov,[†] Nadezhda I. Protzuk,[†] and Yurii V. Gatilov[‡,§]

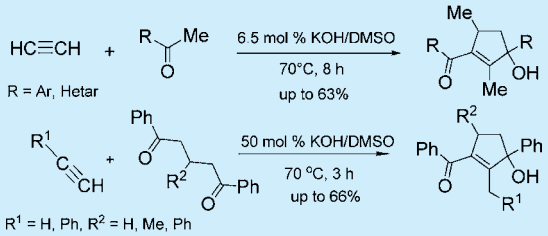
[†]A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033 Irkutsk, Russia

[‡]N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, 9 Lavrentiev Str., 630090 Novosibirsk, Russia

[§]Novosibirsk State University, 2 Pirogov Str., 630090 Novosibirsk, Russia

Supporting Information

ABSTRACT: Acetylene reacts with methylaryl(hetaryl)ketones in the presence of 6.5 mol % KOH in DMSO to give diastereoselectively in single operationally functionalized cyclopentenes. This domino cyclization involving two molecules of acetylene and two molecules of ketone proceeds with the formation of four C−C bonds. The complementary assembly of the cyclopentenes with similar functionalities from acetylenes and 1,5-diketones has been developed.



The discovery of new reactions which led to the formation of the C−C bonds, particularly several ones constituting pharmaceutically and synthetically important structures via a single-pot methodology, is a well-recognized challenge of organic chemistry.[1] Alkynes due to their exceptionally high and multifaceted reactivity are especially rewarding materials[2] for such reactions as cyclotrimerization,[2a,3] cyclotetramerization,[2a] pyridine,[2a,3c,4] and pyrrole[5] synthesis. Currently, this goal is successfully achieved with the help of transition-metal-based catalysts.[2−5] Along this avenue, less common are cascade assemblies of cyclic structures with participation of alkynes and appropriate nucleophile in the presence of bases (most often such as alkaline metal hydroxide or alkoxide/DMSO systems).[6] Among such domino type reactions are one-pot syntheses of pyrroles,[6,7] 7-methylene-6,8-dioxabicyclo[3.2.1]octanes (**A**),[8] Δ^2-isoxazolines (**B**),[9] δ-carboline,[10] 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes (**C**),[11] azulenones (**D**),[12] and functionalized thiophenes **E**[13] (representative examples are given in Figure 1).

Here we report on a serendipitous finding that, in the presence of minor amounts of KOH in DMSO, two molecules of acetylene **1a** and two molecules of ketones **2** upon moderate heating are diastereoselectively assembled to functionalized cyclopentenes **3** in a yield of up to 63% (Table 1). After careful investigation of the reaction features, we have selected 6.5 mol % KOH (relative to ketone **2**), 70 °C, and 8 h to be near to optimal conditions for the synthesis of cyclopentenes **3**.

The reaction is commonly carried out with excess acetylene under pressure in a closed reactor. The initial acetylene pressure at ambient temperature is 12−14 atm, reaching its maximum (~16−18 atm) at the reaction temperature and then dropping as the reaction progresses.

It is important that cyclopentenes **3** are formed exclusively as single diastereomers; i.e., the reaction is strictly stereoselective.

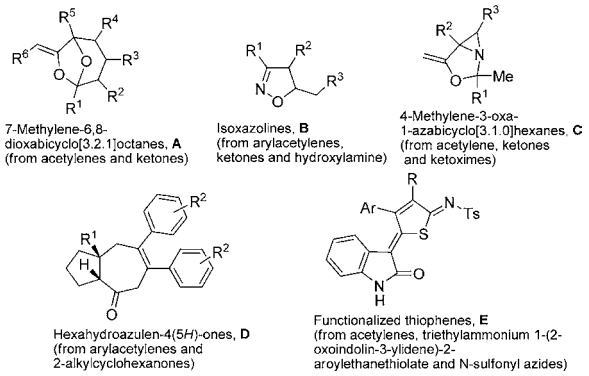


Figure 1. Representative products of the base-promoted domino reactions of acetylenes with ketones and other reactants.

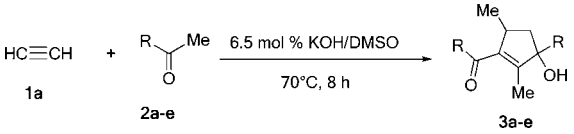
The structure of cyclopentenes unambiguously follows from single-crystal X-ray analysis of one of their representatives, **3a** (Figure 2).

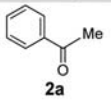
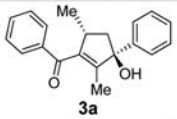
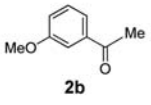
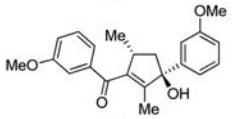
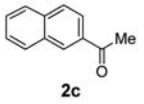
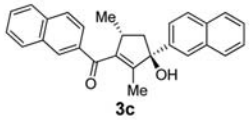
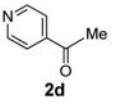
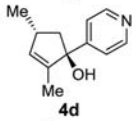
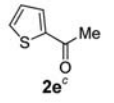
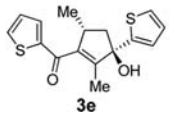
A five-membered cycle of molecule **3a** is in envelope conformation and the C(4) atom is deviated by 0.320(2) Å from the plane of other atoms. The benzoyl fragment is nonplanar, the torsion angle O(1)C(6)C(7)C(12) being 30.5(2)°. The carbonyl moiety is out of plane of the double bond [the torsion angle C(2)C(1)C(6)O(1) equals 52.6(2)°]. In the crystal, the molecules are bonded in chains by H-bonding O(2)−H···O(1) [the distance H···O is 1.96(2) Å; the angle O−H···O is 173(2)°].

Received: June 29, 2014
Published: July 23, 2014

dx.doi.org/10.1021/ol501881e | *Org. Lett.* 2014, 16, 4040−4043

Table 1. Substrate Scope and the Products Yield for the Reaction of Acetylene 1a with Ketones 2a−e in the Presence of the KOH/DMSO System[a]



ketone, 2	product, 3	yield[b] (%)
 2a	 3a	62
 2b	 3b	51
 2c	 3c	63
 2d	 4d	55
 2e[c]	 3e	55

[a]Reaction conditions: initial pressure of acetylene **1a** at ambient temperature was 12−14 atm (stirred reactor), ketone **2** (17.0 mmol), KOH·0.5H_2O (0.07 g, 1.1 mmol), DMSO (50 mL). [b]Isolated yield after column chromatography (basic Al_2O_3, hexane−$CHCl_3$). [c]The reaction was carried out using 50 mol % of KOH at 80 °C.

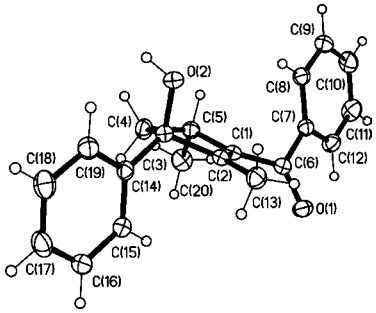


Figure 2. X-ray structure of cyclopentene **3a** (crystal grown from Et_2O; CCDC 986429).

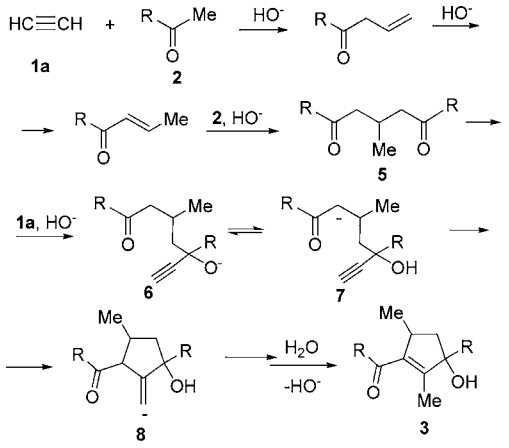
The ^1H and ^{13}C NMR spectra and 2D NOESY spectra are in agreement with the structure of **3a** (Figure 3).

Table 1 shows that the assembly of cyclopentenes **3** from acetylene and ketones tolerates both acetylarenes **2a−c** and acetylhetarenes **2d,e**. For all the ketones studied, the isolated yields of **3** range from 51% to 63%. Under these conditions, the conversion of the starting ketones **2** is close to 100%. In the reaction mixtures, there are always some amounts of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **A** (Figure 1), easily separated from the major products by column chromatography.

In the case of 4-acetylpyridine **2d**, the reaction proceeds with the complete loss of the pyridyl carbonyl function to deliver cyclopentene **4d**.

The key intermediate of the cascade formation of cyclopentenes **3** is believed to be 1,5-diketone **5**,[8b] which further undergoes the Favorsky ethynylation and subsequent ring closure of the acetylenic ketoalcoholate **6** (Scheme 1). The intermediate **5** may result from the nucleophilic addition of two molecules of a ketone to acetylene (first, C-vinylation of the ketone, then prototropic rearrangement of the adduct, and the Michael addition of the second molecule of deprotonated ketone to α,β-unsaturated ketone). The cyclization of intermediate **6** to cyclopentane **8** likely occurs via the nucleophilic addition of carbon-centered anion **7** to the triple bond (Scheme 1). A likely model of the diastereoselectivity of the reaction is the template effect of the potassium cation which retains enolizable carbonyl function and a hydroxyl group on one side of the closing ring, though this will be a subject of our special investigation.

Scheme 1. A Plausible Pathway for the Cascade Formation of Cylcyclopentenes 3



Thus, this assembling involves the formation of four C−C bonds in one synthetic operation.

According to Scheme 1, cyclopentenes **3** might also be assembled from acetylenes and 1,5-diketones **5** are readily available via the condensation of aldehydes with two molecules of ketones.[14] Indeed, it came true. The reaction of acetylenes **1a,b** with 1,5-diketones **5a−c** has been conducted under the best conditions selected from numerous experiments, in which the major reaction parameters (the catalyst and reactant concentration, reaction temperature, and time) are varied (Table 2). These conditions allow the complete conversion of 1,5-diketones **5**.

From Table 2, it follows that the reaction is suitable for both substituted acetylenes (such as phenylacetylene **1b**) and diverse 1,5-diketones **5**. Expectedly, yields of the products as well as sometimes their structure depend remarkably on the substituents in 1,5-diketone molecules.

As in the straightforward reaction of acetylene **1a** with ketones **2** (Table 1), in certain cases, deacylation of cyclopentenes **3** takes place (formation of cyclopentenes **4**). The deacylation can be

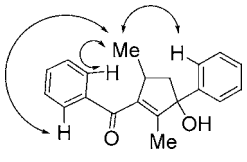
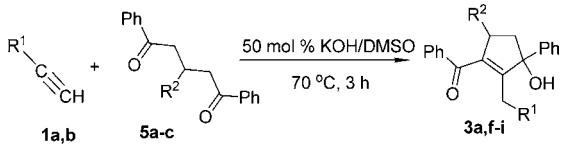


Figure 3. Characteristic NOESY correlations for cyclopentene **3a**.

dx.doi.org/10.1021/ol501881e | Org. Lett. 2014, 16, 4040−4043

Table 2. Product Yields for the Reaction of Acetylenes 1a,b with 1,5-Diketones 5a–c in the Presence of the KOH/DMSO System



acetylene, **1**	1,5-diketone, **5**	product, **3**	yield[a] (%)
HC≡CH **1a**[b,c]	**5a**	**3a**	65
HC≡CH **1a**[b]	**5b**	**3f**[d]	36
1b[e]	**5a**	**3g**	13
		4g	40
1b[e]	**5b**	**3h**	20
		9h	50
1b[e]	**5c**	**3i**	66
		4i	25

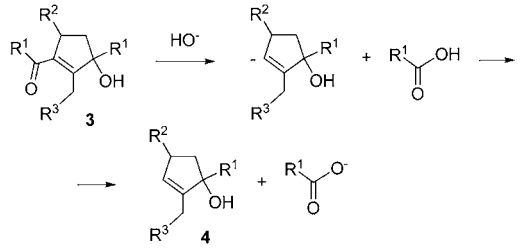
[a]Isolated yield after column chromatography (basic Al_2O_3, hexane, CH_3Cl). [b]The reactions were carried out with acetylene **1a** [initial pressure at ambient temperature was 12–14 atm (stirred reactor)], 1,5-diketone **5** (6 mmol), KOH·0.5H_2O (0.2 g, 3 mmol), DMSO (50 mL). [c]The reaction time was 0.5 h. [d]Diastereomers ratio = 4:1. [e]Acetylene **1b** (7.7 mmol).

understood as a nucleophilic attack by hydroxide ion at the acyl carbon resulting in displacement of the cyclopentenol anion (Scheme 2). This scheme is supported by isolation of 4-pyridinecarboxylic acids in 32% yield from the acidified reaction mixture.

In the reaction of phenylacetylene **1b** with 1,5-diketone **5b**, the formed cyclopentene **3h** undergoes both deacylation and dehydration to the corresponding cyclopentadiene **9h** (Table 2, Scheme 3). The driving force of dehydration of the intermediate cyclopentenol **4h** is likely the formation of the cyclopentadiene conjugated with two benzene rings.

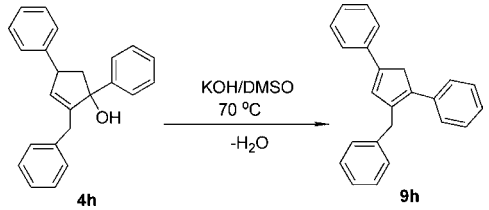
It is obvious that, upon optimization, both deacylation and dehydration can be implemented as one-pot procedures, directly from acetylenes and ketones. Thus, this reaction opens an easy one-step access from cheap available materials not only to

Scheme 2. Deacylation of Cyclopentenes 3 under the Action of Hydroxide Anion



R^1 = 4-Pyridyl, R^2 = Me, R^3 = H (**3d**, **4d**); R^1 = Ph, R^2 = Me, R^3 = Ph (**3g**, **4g**); R^1 = Ph, R^2 = H, R^3 = Ph (**3i**, **4i**)

Scheme 3. Dehydration of Cyclopentene 4h to the Cyclopentadiene 9h



acylpentenols but also to acyl-free cyclopentenes and -pentadienes.

The functionalized cyclopentenes are widely used pharmaceutical building blocks, e.g. to synthesize englerin A (a potent inhibitor of renal cancer),[15] neomangicol (cytotoxic agent against human colon carcinoma),[16] and trichodermone A (antibacterial medicine).[17] Cyclopentenes are common precursors of antiviral nucleosides,[18] iridoids (natural sedative, antimalarial, analgesic, and cytotoxic agents),[19] and carbocyclic nucleosides (active against cowpox and severe acute respiratory syndrome virus).[20] The molecules of carbovir, a potent inhibitor of HIV-1 replication, and abacavir, a drug to combat AIDS, contain a functionalized hydroxycyclopentene structural unit.[21] The cyclopentenol moiety is a part of the nucleoside antibiotic aristeromycin.[22]

The introduction of substituents, particularly functional ones, into the cyclopentene ring remains a synthetic challenge. An approach to 2,3-disubstituted hydroxycyclopentenes through two consecutive additions of electrophiles to a cyclopentene bisanionic synthon is recently reported.[23] Aroylcyclopentenes are formed via cyclizations of silyloxyenynes in the presence of $AuCl_3$ with phosphine ligands.[24] Substituted cyclopentenols are also synthesized by the enal–alkyne reductive cycloaddition in the presence of a Ni complex.[25] Nine steps are required to synthesize benzyloxycyclopentenol starting from 2,3-*O*-isopropylideneglyceraldehyde.[26] Functionalized hydroxycyclopentenes are prepared from unsaturated 1,6-dicarbonyl compounds in the presence of secondary amines.[27] Likewise, base-catalyzed cyclization of unsaturated thiol esters containing an aldehyde function furnishes functionalized cyclopentenols.[28] In an earlier work, it has been shown that the reduction of epoxide prepared by the oxidation of cyclopentadiene yields hydroxycyclopentene.[29] Hydroxycyclopentenes, 15 years earlier, were obtained from γ-allenic aldehydes by intramolecular heteroene synthesis.[30]

Despite the above advances in the synthesis of functionalized cyclopentenes, their one-pot assembly from such available and cheap starting materials as acetylenes and ketones under

dx.doi.org/10.1021/ol501881e | *Org. Lett.* 2014, 16, 4040–4043

transition-metal-free conditions opens additional possibilities for their synthetic and pharmaceutical applications.

Apparently, larger scale synthesis of cyclopentenes via this reaction requires special optimization. Optimistically, our first attempt to scale up the reaction using 10 g of ketone **2a** gave a 42% yield of cyclopentene **3a** thus implying applicability of the reaction for large scale synthesis.

In conclusion, a facile one-pot diastereoselective assembly of functionalized cyclopentenes from two molecules of acetylene and two molecules of ketone in the presence of a KOH/DMSO system has been discovered. The assembly involves four C−C bond forming reactions in one synthetic operation. 1,5-Diketones have been shown to be the key intermediates of the reaction, and their condensation with acetylenes under similar conditions to give the same cyclopentenes has been implemented. These approaches allow cyclopentenes to be synthesized in a yield up to 66%. In view of the high pharmaceutical importance of the functionalized cyclopentenes, this simple and conceptually new synthetic strategy may become another route to cyclopentenes and a fresh contribution to both acetylene and ketone chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The experimental procedure, compound characterization, ^{1}H and ^{13}C NMR spectra of all compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: boris_trofimov@irioch.irk.ru.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant of Russian Scientific Foundation (Project No. 14-13-00588).

■ REFERENCES

(1) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(2) (a) Trotuş, I.-T.; Zimmermann, T.; Schüth, F. *Chem. Rev.* **2014**, *114*, 1761. (b) Schobert, H. *Chem. Rev.* **2014**, *114*, 1743.

(3) (a) Sherrill, A. B.; Lusvardi, V. S.; Barteau, M. A. *Langmuir* **1999**, *15*, 7615. (b) Karpiniec, S. S.; McGuinness, D. S.; Britovsek, G. J. P.; Patel, J. *Organometallics* **2012**, *31*, 3439. (c) Maretina, I. A.; Ionin, B. I. *Alkynes in Cycloadditions*; Tebby, J. C., Ed.; Wiley: Weinheim, 2014.

(4) (a) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (c) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (d) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. J. *Organomet. Chem.* **2006**, *691*, 4434.

(5) (a) Camp, J. *Chemistry Today Catalysis Applications* **2012**, *30*, 6. (b) Ngwerume, S.; Lewis, W.; Camp, J. E. *J. Org. Chem.* **2013**, *78*, 920.

(6) Trofimov, B. A. *Curr. Org. Chem.* **2002**, *6*, 1121.

(7) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Yu.; Sobenina, L. N. *Adv. Heteroatom. Chem.* **2010**, *99*, 209.

(8) (a) Trofimov, B. A.; Schmidt, E. Yu.; Ushakov, I. A.; Mikhaleva, A. I.; Zorina, N. V.; Protsuk, N. I.; Senotrusova, E. Yu.; Skital'tseva, E. V.; Kazheva, O. N.; Aleksandrov, G. G.; Dyachenko, O. A. *Eur. J. Org. Chem.* **2009**, 5142. (b) Schmidt, E. Yu.; Bidusenko, I. A.; Protsuk, N. I.; Ushakov, I. A.; Trofimov, B. A. *Eur. J. Org. Chem.* **2013**, 2453.

(9) Schmidt, E. Yu.; Tatarinova, I. V.; Ivanova, E. V.; Zorina, N. V.; Ushakov, I. A.; Trofimov, B. A. *Org. Lett.* **2013**, *15*, 104.

(10) Trofimov, B. A.; Schmidt, E. Yu.; Mikhaleva, A. I.; Zorina, N. V.; Ushakov, I. A.; Afonin, A. V.; Vasiltsov, A. M. *Mendeleev Commun.* **2007**, *17*, 40.

(11) Trofimov, B. A.; Schmidt, E. Yu.; Mikhaleva, A. I.; Ushakov, I. A.; Protsuk, N. I.; Senotrusova, E. Yu.; Kazheva, O. N.; Aleksandrov, G. G.; Dyachenko, O. A. *Tetrahedron Lett.* **2009**, *50*, 3314.

(12) Trofimov, B. A.; Schmidt, E. Yu.; Skital'tseva, E. V.; Zorina, N. V.; Protsuk, N. I.; Ushakov, I. A.; Mikhaleva, A. I.; Dyachenko, O. A.; Kazheva, O. N.; Aleksandrov, G. G. *Tetrahedron Lett.* **2011**, *52*, 4285.

(13) Jiang, B.; Tu, X.-J.; Wang, X.; Tu, S.-J.; Li, G. *Org. Lett.* **2014**, DOI: doi.org/10.1021/ol501404x.

(14) (a) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253. (b) Shankar, R.; Jha, A. K.; Singh, U. S.; Hajela, K. *Tetrahedron Lett.* **2006**, *47*, 3077. (c) Yanagisawa, A.; Takahashi, H.; Arai, T. *Tetrahedron* **2007**, *63*, 8581.

(15) Li, Zh.; Nakashige, M.; Chain, W. J. *J. Am. Chem. Soc.* **2011**, *133*, 6553.

(16) Wood, J. L.; Pujanauski, B. G.; Sarpong, R. *Org. Lett.* **2009**, *11*, 3128.

(17) Krishna, P. R.; Kadiyala, R. R. *Tetrahedron Lett.* **2010**, *51*, 4981.

(18) Ludek, O. R.; Marquez, V. E. *Tetrahedron* **2009**, *65*, 8461.

(19) Lee, S.; Paek, S.-M.; Yun, H.; Kim, N.-J.; Suh, Y.-G. *Org. Lett.* **2011**, *13*, 3344.

(20) Cho, J. H.; Bernard, D. L.; Sidwel, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140.

(21) (a) Parker, W. B.; White, E. L.; Shaddix, S. C.; Ross, L. J.; Buckheit, R. W.; Germany, J. M.; Secrist, J. A.; Vincell, R.; Shannon, W. M. *J. Biol. Chem.* **1991**, *266*, 1754. (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (c) Roulland, E.; Monneret, C.; Florent, J.-C. *Tetrahedron Lett.* **2003**, *44*, 4125. (d) Nayek, A.; Banerjee, S.; Sinha, S.; Ghosh, S. *Tetrahedron Lett.* **2004**, *45*, 6457.

(22) Parry, R. J.; Haridas, K. *Tetrahedron Lett.* **1990**, *31*, 7549.

(23) Luparia, M.; Vadalà, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2006**, *8*, 2147.

(24) Brazeay, J. F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742.

(25) Jenkins, A. D.; Herath, A.; Song, M.; Montgomery, J. *J. Am. Chem. Soc.* **2011**, *133*, 14460.

(26) Yang, Y.-X.; Li, Z.; Feng, H.-J.; Chena, G.-R.; Li, Y.-C. *Tetrahedron Lett.* **2010**, *51*, 3848.

(27) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771.

(28) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687.

(29) Healy, E. F.; Lewis, J. D.; Minniear, A. B. *Tetrahedron Lett.* **1994**, *35*, 6647.

(30) Bertrand, M.; Roumestant, M.-L.; Silvestre-Panthet, P. *J. Chem. Soc., Chem. Commun.* **1979**, 529.