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Interrupting Nazarov Reaction with Different Trapping Modality: Utilizing Potassium Alkynyltrifluoroborate as a σ-Nucleophile

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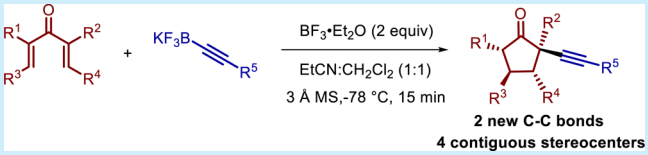
Supporting Information

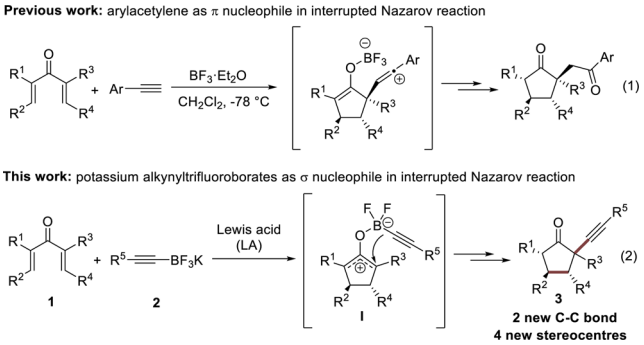
ABSTRACT: The putative oxyallyl cation intermediate generated following Nazarov cyclization of dienone has been successfully intercepted with potassium alkynyltrifluoroborates which act as σ-nucleophiles in the presence of $BF_3{\cdot}Et_2O$. This new trapping modality allowed unprecedented introduction of an alkynyl moiety to the cyclopentanone framework by means of an interrupted Nazarov reaction. The α-alkynyl cyclopentanone product can be further transformed into an array of densely functionalized cyclic compounds.



Nazarov cyclization has long been recognized as a powerful tool for the construction of cyclopentanoid compounds.[1] Recent interests to expand the synthetic utility of Nazarov cyclization revolve around developing catalytic asymmetric variants,[2] discovering surrogate pentadienyl cation precursors,[3] and exploring cascade processes initiated by electrocyclic ring closure via interception of a cyclic oxyallyl cation.[4] With regard to the latter, a diverse range of nucleophiles including hydride-,[5] carbon-,[6] and heteroatom-based[7] nucleophiles have been employed to render an elaborated cyclopentanoid framework. While there are ample precedents of carbon-based nucleophiles participating in interrupted Nazarov reactions, almost all reported reactions involve the use of π nucleophiles such as alkenes, dienes, enol derivatives, electron-rich arenes, and heteroaromatics. Recently, West's group reported a novel mode of oxyallyl cation trapping in which aryl acetylenes functioned as a competent π nucleophile furnishing α-phenacyl cyclopentanones via carboalkoxylation of an alkyne (Scheme 1, eq 1).[6f] In contrast, the use of a σ carbon-based nucleophile in interrupting Nazarov cyclization has not been extensively reported.[6g]

Organoboron compounds have gained considerable attention as privileged reagents for C−C bond formation in organic synthesis following the discovery of the Suzuki−Miyaura coupling reaction.[8] While trivalent boronic acids and esters constitute the most common organoboron reagents utilized in organic synthesis, the tetravalent potassium organotrifluoroborate salts which exhibit exceptional stability toward air and moisture have increasingly found widespread application in transition-metal-catalyzed reactions.[9] Apart from their pervasive use in cross-coupling reactions with a plethora of coupling partners,[10] potassium organotrifluoroborates have also been demonstrated to undergo nucleophilic addition to an iminium ion in a Petasis borono-Mannich reaction.[11] In addition, the nucleophilic properties of organotrifluoroborates have also been exploited in reactions with oxocarbenium[12] and acylium[13] ion intermediates in the presence of a Lewis acid.

Scheme 1. Trapping of Nazarov Intermediate with Acetylene and Potassium Alkynyltrifluoroborate



In view of the competence of organotrifluoroborates to participate in nucleophilic addition to a stabilized carbocation, we envisioned that treatment of dienone **1** and potassium alkynyltrifluoroborates **2** with a suitable Lewis acid would result in initial Nazarov cyclization which in turn initiates a cascade C−C bond-forming event via fortuitous trapping of oxyallyl cation intermediate **I** to ultimately furnish α-alkynyl cyclopentanone **3** (Scheme 1, eq 2). It is noteworthy that if successful the overall process occurs with formation of two new C−C bonds along with four contiguous stereocenters. Additionally, alkynyl functionality incorporated into a cyclopentanone framework could serve as a versatile handle for further functional group transformations.

At the outset of this study, we focused on treatment of symmetrically substituted 1,4-dien-3-one **1a** and potassium phenylethynyltrifluoroborate **2a** with a Lewis acid to effect the proposed intermolecular interrupted Nazarov reaction. A preliminary experiment in which dienone **1a** was treated with 2 equiv of $BF_3{\cdot}Et_2O$ in the presence of 2 equiv of alkynyl-

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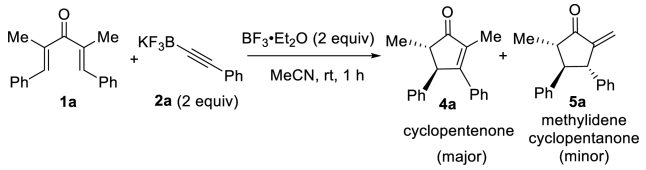
Org. Lett. XXXX, XXX, XXX−XXX

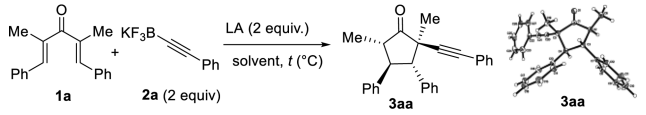
trifluoroborate **2a** in acetonitrile at room temperature did not furnish the desired α-alkynyl cyclopentanone product. Instead, complete consumption of dienone **1a** after stirring for 1 h was accompanied by formation of a regioisomeric mixture of cyclopentenone **4a** and methylidene cyclopentanone **5a** (Scheme 2).

Scheme 2. Initial Attempt to Interrupt Nazarov Intermediate



The outcome of our preliminary study suggested that at ambient temperature the competing termination pathways via proton elimination prevail over the anticipated interception of an oxyallyl cation by nucleophilic attack of the alkynyl moiety. Based on this initial observation, we postulated that varying the reaction temperature could potentially exert significant influence on the fate of the oxyallyl cation, as heat tends to favor elimination over an addition reaction. Initially, lowering the reaction temperature to −40 °C for reaction in acetonitrile proved to be futile, affording only noninterrupted products **4a** and **5a** (Table 1, entry 2). Later when the reaction was carried out at −78 °C in dichloromethane as solvent in the presence of 2 equiv of BF_3·Et_2O, we observed a trace amount of alkynyl cyclopentanone **3aa** resulting from interruption of the Nazarov reaction along with substantial byproduct cyclopentenone **4a** (Table 1, entry 3). To our surprise, when a combination of propionitrile and dichloromethane in a 1:1 ratio was employed as the reaction solvent, the reaction yield improved noticeably to 63% (Table 1, entry 5). When the reaction was performed under rigorously dry conditions with anhydrous BF_3·Et_2O in a 1:1 mixture of anhydrous propionitrile/anhydrous dichloromethane in the presence of 3 Å molecular sieves, the yield can be significantly increased to 92% (Table 1, entry 6). The relative stereochemical assignment of the newly formed stereogenic centers in cyclopentanone **3aa** was unambiguously determined by single crystal X-ray diffraction analysis.[14]

Table 1. Screening of Reaction Parameters[a]

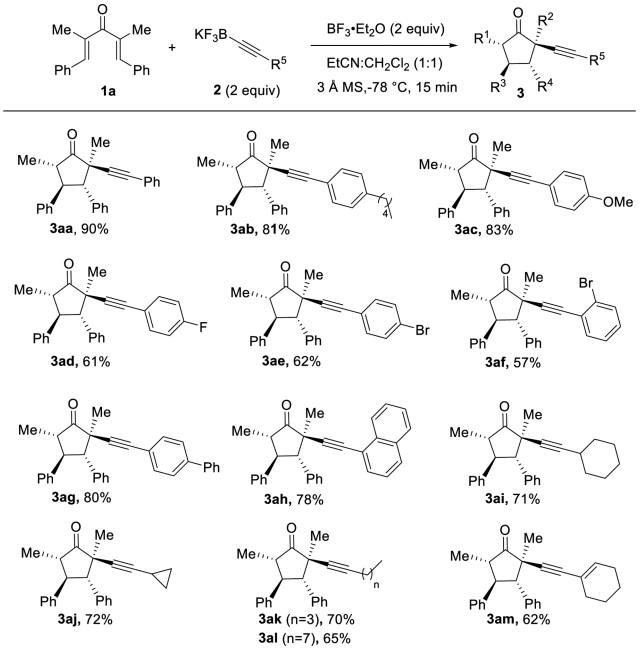


entry	LA	solvent	t (°C)	yield (%)[b]
1	BF_3·Et_2O	CH_3CN	rt	–[c]
2	BF_3·Et_2O	CH_3CN	−40	–[c]
3	BF_3·Et_2O	CH_2Cl_2	−78	traces[d]
4	BF_3·Et_2O	EtCN	−78	41
5	BF_3·Et_2O	EtCN/CH_2Cl_2 (1:1)	−78	63
6[e]	BF_3·Et_2O	EtCN/CH_2Cl_2 (1:1)	−78	92 (90)[f]
7[g]	BF_3·Et_2O	EtCN/CH_2Cl_2 (1:1)	−78	52
8[h]	BF_3·Et_2O	EtCN/CH_2Cl_2 (1:1)	−78	26
9	$AlCl_3$	EtCN/CH_2Cl_2 (1:1)	−78	47
10	$SiCl_4$	EtCN/CH_2Cl_2 (1:1)	−78	44
11	$SnCl_4$	EtCN/CH_2Cl_2 (1:1)	−78	32
12	$TiCl_4$	EtCN/CH_2Cl_2 (1:1)	−78	22

[a]Reactions were carried out using dienone **1a** (0.1 mmol, 1 equiv) in solvent (0.1 M in **1a**) for 15 min. [b]NMR yields with CH_2Br_2 as internal standard. [c]**4a** and **5a** were obtained. [d]**4a** was obtained as major product. [e]Anhydrous propionitrile/dichloromethane with anhydrous BF_3·Et_2O in the presence of 3 Å MS (200 wt %) was used. [f]Yield in parentheses is isolated yield. [g]Performed at 0.05 M in **1a**. [h]Performed using 1.1 equiv of **2a** and BF_3·Et_2O.

Having established the optimized conditions, the scope of potassium alkynyltrifluoroborate applicable to the present interrupted Nazarov reaction was scrutinized by performing the reaction with a diverse range of substituted potassium alkynyltrifluoroborate derivatives (Scheme 3). In general, a multitude of phenylethynyltrifluoroborates containing electron-donating or weakly electron-withdrawing substituents on the phenyl ring efficiently intercepted a Nazarov intermediate resulting from cyclization of dienone **1a** to furnish corresponding α-alkynyl cyclopentanones **3ab**−**3ag** in yields ranging from 57% to 83% as single diastereomers. It is notable that electron-withdrawing phenylalkynyltrifluoroborates afforded lower yields of interrupted products **3ad**−**3af** owing to the diminished migratory aptitude of the alkynyl moiety. A more sterically hindered naphthylethynyltrifluoroborate also reacted smoothly to afford cyclopentanone **3ah** in 78% yield. In addition, alkynyltrifluoroborates bearing a cyclopropyl or cyclohexyl substituent also proved to be viable nucleophiles in intercepting the oxyallyl cation providing cyclopentanones **3ai** and **3aj** in 71% and 72% yield, respectively. Similarly, alkynyltrifluoroborates substituted with an acyclic hydrocarbon chain also furnished the desired cyclopentanones **3ak** and **3al** in good yields. In all cases, it is notable that the reactions ensued with complete diastereoselectivities in which the α-alkynyl cyclopentanones were isolated as single diastereomers.

Scheme 3. Scope of Alkynyltrifluoroborates



With the scope of potassium alkynyltrifluoroborates defined, we shifted our attention to demonstrate the general utility of this reaction by employing dienone **1b**−**1f**. For unsymmetrically substituted dienones, th eregioselectivity aspect of the trapping event can potentially raise an issue to be addressed (Table 2, entries 3−5). In the case of dienone **1d**, the reaction proceeded

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Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Scope of Divinyl Ketones[a]

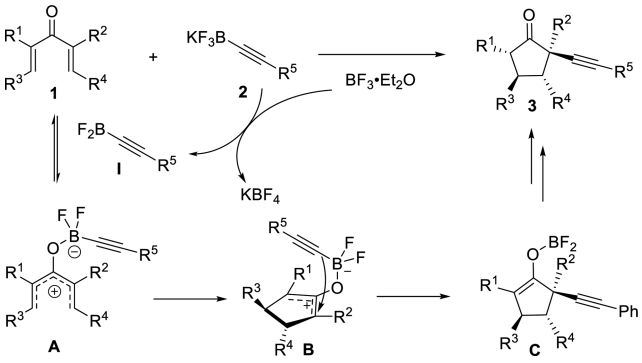
entry	1	R^1	R^2	R^3	R^4	yield (%)[b]
1	**1b**	Me	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	88 (**3ba**)
2	**1c**	Me	Me	4-ClC_6H_4	4-ClC_6H_4	75 (**3ca**)
3	**1d**	*n*-Pr	Me	Ph	Ph	51 (**3da**)[c]
4	**1e**	Me	Me	*t*-Bu	Ph	72 (**3ea**)
5	**1f**	Me	H	Ph	Ph	–[d]

[a]Reactions were carried out using dienone **1** (0.1 mmol, 1 equiv) in solvent (0.1 M in **1a**). [b]Isolated yields. [c]**3ca** was isolated as an inseparable mixture of regioisomers/diastereomers in a 9:1 ratio. [d]No reaction at −78 °C; at −40 °C only noninterrupted cyclopentenone product was obtained.

in a regioselective manner in which trapping occurs preferentially at the α-carbon substituted with a methyl group to afford **3da** in 51% yield along with a minor amount of inseparable regioisomers/diastereomers in a 9:1 ratio. For dienone **1e**, the sterically demanding *tert*-butyl group at the β-position dictates that the addition of an alkyne moiety to the oxyallyl cation takes place exclusively at the α-carbon distal to the *tert*-butyl group to avoid eclipsing torsional strain in the alternate transition state leading to the other regioisomer. Unsymmetrical dienone **1f**, however, was found to be unreactive at −78 °C even after a prolonged reaction time. When the reaction was performed at −40 °C, the Nazarov cyclization ensued to give the non-interrupted product without formation of any desired interrupted product. The apparent lower reactivity of dienone **1f** which lacks a methyl group at one of the α-positions can be ascribed to an increase in proportion of molecules adopting the unreactive *s*-trans/*s*-cis conformer.

A plausible reaction mechanism for the formation of α-alkynyl cyclopentanone **3** can be proposed as illustrated in Scheme 4. In

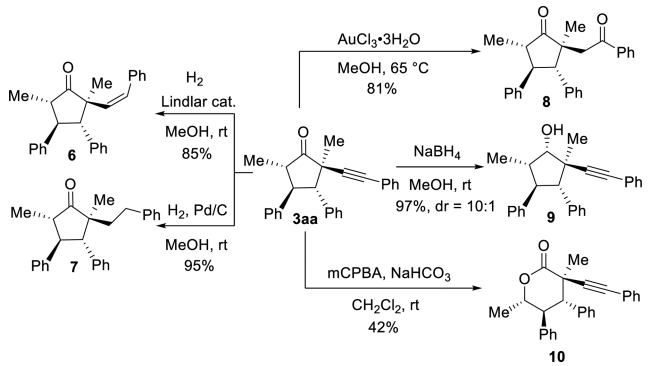
Scheme 4. Proposed Mechanism for Trapping



the initial step, upon mixing of potassium alkynyltrifluoroborate **2** with $BF_3{\cdot}Et_2O$, the corresponding Lewis acidic organodifluoroborane **I** is generated *in situ*. The organodifluoroborane would then act as the effective Lewis acid through complexation with the carbonyl group of dienone **1**, thereby forming zwitterionic pentadienyl cation intermediate **A**. A facile 4π conrotatory electrocyclic ring closure results in the formation of the oxyallyl cation intermediate **B** in which the R^3 and R^4 substituents are disposed trans to each other. Migration of the alkynyl group from the boron center to the oxyallyl cation occurs with remarkable diastereofacial selectivity from the face opposite to the bulky adjacent substituent to minimize developing torsional strain in the transition state leading to boron enolate **C**. Ultimately, diastereoselective protonation of enolate **C** selectively provides a diastereomer in which all the sterically demanding substituents on the cylopentanone scaffold are in the *trans* configuration.

To exemplify the synthetic utility of an α-alkynyl cyclopentanone, we have carried out a number of functional group manipulations to afford a series of densely functionalized structures (Scheme 5). First, the alkyne moiety can be partially

Scheme 5. Synthetic Transformation of 3aa



reduced to afford alkenyl substituted cyclopentanone **6** in the presence of a Lindlar catalyst or completely reduced to cyclopentanone **7** with Pd/C in methanol. In addition, compound **8** containing a 1,4-dicarbonyl group can be readily prepared in 81% yield through $AuCl_3$-catalyzed hydration of **3aa**. Sodium borohydride reduction of cyclopentanone **3aa** led to formation of cyclopentanol **9** in 97% yield with a diastereomeric ratio of 10:1. Furthermore, Baeyer–Villiger oxidation of **3aa** resulted in ring expansion to furnish highly functionalized δ-lactone **10**.

In conclusion, we have demonstrated the reactivity of potassium alkynyltrifluoroborates as a σ-nucleophile in trapping the oxyallyl cation generated through Nazarov cyclization of dienones to furnish α-alkynyl cyclopentanones with high diastereoselectivity. The present method represents the first example in which an sp-hybridized alkyne group has been successfully introduced to a cyclopentanone scaffold via interrupted Nazarov reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01606.

Experimental procedures and characterization data for new compounds (PDF)

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†R.W. and S.W. contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews on Nazarov reaction, see: (a) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531. (b) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851. (c) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621. (d) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam; Vol. *5*, p 827. (e) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979. (f) Di Grandi, M. J. *Org. Biomol. Chem.* **2014**, *12*, 5331. (g) Wenz, D. R.; Read de Alaniz, J. *Eur. J. Org. Chem.* **2015**, *2015*, 23.

(2) (a) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (b) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075. (c) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (d) Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78. (e) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266. (f) Cao, P.; Deng, C.; Zhou, Y.-Y.; Sun, X.-L.; Zheng, J.-C.; Xie, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4463. (g) Hutson, G. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 4988. (h) Raja, S.; Nakajima, M.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2762.

(3) (a) Wu, Y.-K.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410. (b) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2011**, *13*, 414. (c) Shimada, N.; Stewart, C.; Bow, W. F.; Jolit, A.; Wong, K.; Zhou, Z.; Tius, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5727. (d) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504. (e) Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454. (f) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348. (g) William, R.; Wang, S.; Ding, F.; Arviana, E. N.; Liu, X.-W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10742.

(4) For a review on interrupted Nazarov reactions, see: Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676.

(5) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221.

(6) (a) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970. (b) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091. (c) Wu, Y.-K.; Dunbar, C. R.; McDonald, R.; Ferguson, M. J.; West, F. G. *J. Am. Chem. Soc.* **2014**, *136*, 14903. (d) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685. (e) Wu, Y.-K.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584. (f) Wu, Y.-K.; West, F. G. *Org. Lett.* **2014**, *16*, 2534. (g) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8616. (h) Wang, Y.; Schill, D. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747. (i) Rieder, C. J.; Fradette, R. J.; West, F. G. *Heterocycles* **2010**, *80*, 1413. (j) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073.

(7) (a) Marx, V. M.; Burnell, D. J. *Org. Lett.* **2009**, *11*, 1229. (b) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629. (c) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213. (d) William, R.; Leng, W. L.; Wang, S.; Liu, X.-W. *Chem. Sci.* **2016**, *7*, 1100.

(8) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(9) (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (c) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288.

(10) (a) Darses, S.; Brayer, J.-L.; Demoute, J.-P.; Genet, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393. (b) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457. (c) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107. (d) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424. (e) Stefani, H. A.; Cella, R.; Dörr, F. A.; Pereira, C. M. P.; Zeni, G.; Gomes, M. *Tetrahedron Lett.* **2005**, *46*, 563. (f) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381. (g) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397. (h) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683.

(11) (a) Petasis, N. A. *Multicomponent Reactions with Organoboron Compounds in Multicomponent Reactions*; Jieping, Z., Hugues, B., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 199. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169.

(12) (a) Vieira, A. S.; Fiorante, P. F.; Hough, T. L. S.; Ferreira, F. P.; Lüdtke, D. S.; Stefani, H. A. *Org. Lett.* **2008**, *10*, 5215. (b) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057. (c) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082. (d) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42. (e) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574.

(13) Taylor, C.; Bolshan, Y. *Org. Lett.* **2014**, *16*, 488.

(14) CCDC number for compound **3aa** is 1474607.

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