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Microwave Assisted Tandem Heck–Sonogashira Reactions of *N,N*-Di-Boc-Protected 6-Amino-5-iodo-2-methyl Pyrimidin-4-ol in An Efficient Approach to Functionalized Pyrido[2,3-*d*]Pyrimidines

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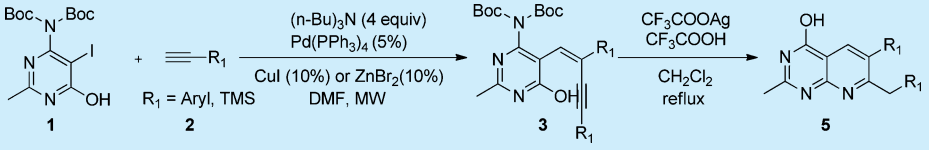
Supporting Information



ABSTRACT: A microwave assisted tandem Heck–Sonogashira cross-coupling reaction between 6-*N,N*-di-Boc-amino-5-iodo-2-methyl pyrimidin-4-ol and various aryl alkynyl substrates has been developed. This process generates novel 5-enynyl substituted pyrimidines, which can be transformed to novel functionalized pyrido[2,3-*d*]pyrimidines by way of a silver catalyzed cyclization reaction.

Pyrido[2,3-*d*]pyrimidine is a core structure that is found in a large variety of substances that exhibit important biological activities. For example, this heterocyclic structural motif is present in AZD8055 (A), a selective ATP-competitive PI3K-Akt-mTOR signaling pathway inhibitor used for the treatment of antitumor,[1] piritrexim (B), a lipid-soluble inhibitor of dihydrofolate reductase (DHFR) that displays high potency for the treatment of metastatic urothelial cancer,[2] and pyrido[2,3-*d*]pyrimidine derivative C that is a hepatitis C virus replicon inhibitor[3] (Figure 1). Also, substances that possess the pyrido[2,3-*d*]pyrimidine framework have other interesting biological properties such as anticardiovascular,[4] anti-inflammatory,[5] antibacterial,[6,7] and anti-Parkinson's activities.[8] The few methods thus far devised to prepare these substances involve condensation reactions of pyridine or pyrimidine[9] (Scheme 1), which are only applied with difficulty when diversified substitution patterns are required. Herein, we describe a novel palladium catalyzed microwave-assisted tandem Heck–Sonogashira reaction of 6-*N,N*-di-Boc-amino-5-iodo-2-methylpyrimidin-4-ol with terminal alkynes (HC≡CR, R = aryl group or TMS) that forms functionalized enyne (−C═C−C≡C−) substituted pyrimidines, which then undergo cyclization to generate novel diverse substituted pyrido[2,3-*d*]pyrimidines in good to excellent yields.

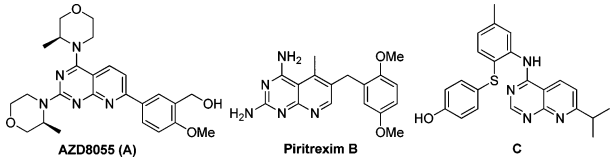
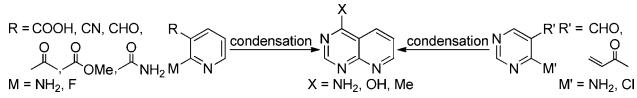
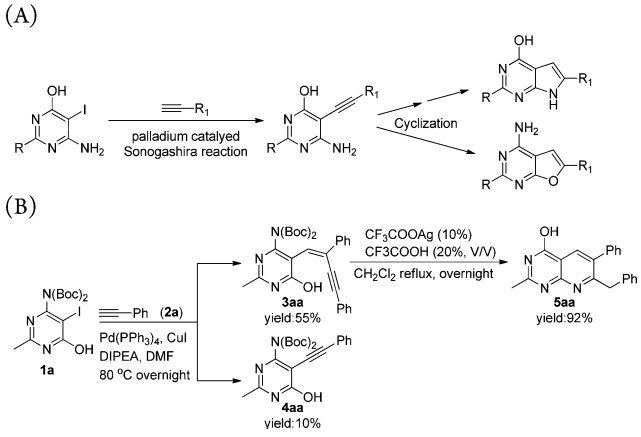


Figure 1. Representative bioactive pyrido[2,3-*d*]pyrimidines.

Scheme 1. Common Methods To Prepare Pyrido[2,3-*d*]pyrimidines



Scheme 2. Palladium Catalyzed Cross-Coupling of 2-Substituted-6-amino-5-iodopyrimidin-4-ols



Palladium catalyzed Sonogashira reactions of 2-substituted-6-amino-5-iodopyrimidin-4-ols (Scheme 2A) have been previously applied to the synthesis of functionalized heterocyclic pyrimidines.[10] However, the poor solubilities of 2-substituted-

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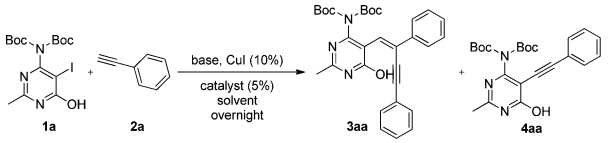
Table 1. Optimization of Reaction Conditions for the Formation of 5-Enynyl Substituted Pyrimidine 3aa[a]



				yield (%)[d]	
entry	temp	Pd-catalyst	base; solvent	3aa	4aa
1	80 °C	$Pd(PPh_3)_4$	DIPEA; MeCN	38	20
2	80 °C	$Pd(PPh_3)_4$	DIPEA; toluene	53	17
3	80 °C	$Pd(PPh_3)_4$	DIPEA; DMF	55	10
4	80 °C	$Pd(PPh_3)_4$	DIPEA; THF	43	15
5	80 °C	$Pd(PPh_3)_4$	Et_3N; DMF	40	18
6	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	67	5
7	80 °C	$Pd(PPh_3)_4$	DABCO; DMF	20	40
8	80 °C	$Pd(PPh_3)_4$	DBU; DMF	<5	45
9	80 °C	$PdCl_2(PPh_3)_2$	$(n\text{-}Bu)_3N$; DMF	40	32
10	80 °C	$Pd(OAc)_2$, PPh_3	$(n\text{-}Bu)_3N$; DMF	trace	
11	80 °C	Pd/C, PPh_3	$(n\text{-}Bu)_3N$; DMF	NR	
12	80 °C	$Pd_2(dba)_3$, PPh_3	$(n\text{-}Bu)_3N$; DMF	NR	
13	60 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	52	21
14	70 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	59	8
15	90 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	57	4
16	100 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	47	6
17[b]	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	NR	
18[c]	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	71	<5

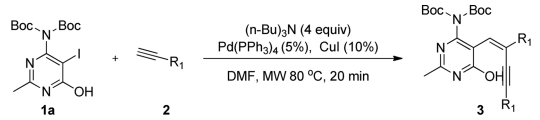
[a]Unless otherwise noted, reactions were carried out under standard conditions. [b]The reactions were carried out without CuI. [c]MW, 20 min. [d]Yield of isolated product based on **1a**.

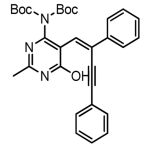
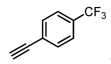
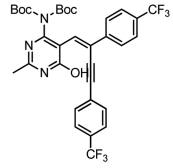
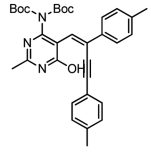
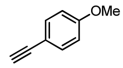
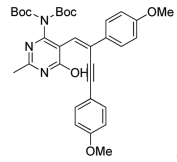
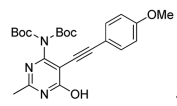
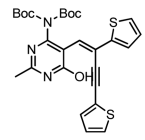
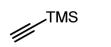
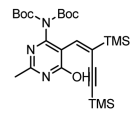
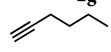
6-amino-5-iodopyrimidin-4-ols limit applications of this approach. By taking into account the fact that the solubilities of these substrates can be improved by introducing *N,N*-di-Boc amine protecting groups, we have explored the use of the protected aminopyrimidinol **1a** in palladium catalyzed Sonogashira cross-coupling reactions (Scheme 2B). Surprisingly, we observed that 6-*N,N*-di-Boc-amino-5-iodo-2-methyl pyrimidin-4-ol (**1a**) with ethynylbenzene **2a** undergoes tandem Heck−Sonogashira cross-coupling to form the unexpected and novel 5-enynyl substituted pyrimidine **3aa** as the major product (55%). In contrast, the expected Sonogashira cross-coupling product **4aa** is generated in this process in only a 10% yield. We also found that catalytic silver trifluoroacetate in trifluoroacetic acid promotes cyclization of **3aa** to form the novel pyrido[2,3-*d*]pyrimidine **5aa** in high yield.

The tandem Heck−Sonogashira reaction of terminal alkynes has been rarely described as a side reaction in the past.[11] Only few successful examples of this process, in which (thio)flavone, thiophene, naphthalene, and benzene rings react with a limited number of alkynes, have been reported.[12]

In the first phase of this effort, we examined the reaction of **1a** with ethynylbenzene **2a** using different conditions. The results show that, among a variety of different solvents such as acetonitrile, toluene, DMF, and THF (Table 1, entries 1−4), DMF is superior for this reaction. In addition, an exploration of different bases such as Et_3N, $(n\text{-}Bu)_3N$, DABCO, and DBU (Table 1, entries 5−8) uncovered the observation that the weak organic base $(n\text{-}Bu)_3N$ is more suitable for generation of enyne **3aa** while the reaction using the strong organic base DBU forms **4aa** preferentially. Among the different catalysts explored (Table 1, entries 9−12), the commonly used palladium catalyst

Table 2. Tandem Cross-Coupling Reactions of 1a with Various Alkynes 2[a]



entry	substrate	product	yield[b]
1	 **2a**	 **3aa**	71%
2	 **2b**	 **3ab**	58%
3	 **2c**	 **3ac**	60%
4	 **2d**	 **3ad**	30%
		 **4ad**	33%
5	 **2e**	 **3ae**	43%
6	 **2f**	 **3af**	73%
7	 **2g**	trace	
8	 **2h**	trace	

[a]Unless otherwise noted, reactions were carried out under the optimized conditions. [b]Yields of isolated product based on **1a**.

$Pd(PPh_3)_4$ is ideal and the reaction does not occur in the absence of CuI as a cocatalyst (Table 1, entry17). Finally, in the temperature range 60−100 °C (Table 1, entries 13−16), 80 °C is more suitable for this process. Finally, when the reaction is carried out under microwave irradiation at 80 °C for 20 min (Table 1, entry 18) instead of oil-heating overnight, **3aa** is generated efficiently (71%) and highly selectively. In summary, optimized conditions involve reaction in DMF at 80 °C for 20 min in the presence of 2.5 equiv of terminal alkyne, 4 equiv of $(n\text{-}Bu)_3N$, 0.05 equiv of $Pd(PPh_3)_4$, and 0.1 equiv of CuI under microwave irradiation.

To explore the alkyne substrate scope of the tandem Heck−Sonogashira process, various terminal alkynes **2** were reacted with **1a** using the optimized reaction conditions to generate 5-

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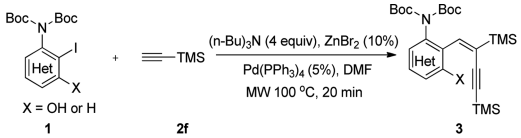
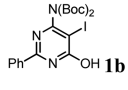
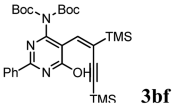
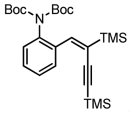
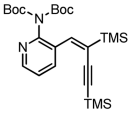
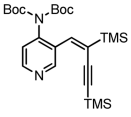
Table 3. Tandem Cross-Coupling Reactions of 2f with *o*-Iodo-*N,N*-di-Boc Aminoarenes 1[a]



entry	substrate	product	yield[b]
1	 **1b**	 **3bf**	63%
2	 **1c**	 **3cf**	65%
3	 **1d**	 **3df**	62%
4	 **1e**	 **3ef**	59%

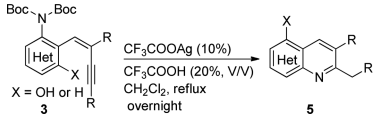
[a]Unless otherwise noted, reactions were carried out under standard conditions. [b]Yield of isolated product based on **1**.

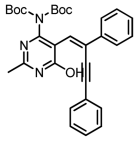
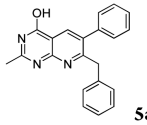
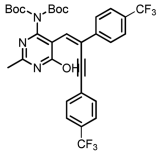
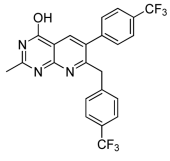
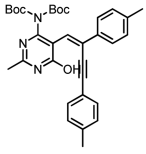
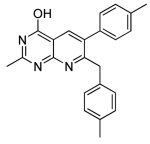
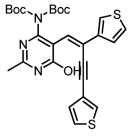
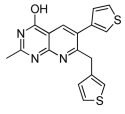
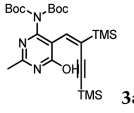
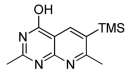
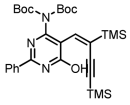
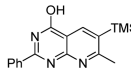
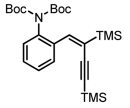
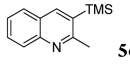
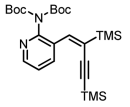
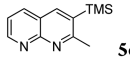
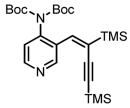
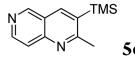
enynyl substituted pyrimidines **3** (Table 2). The results show that alkynes containing electron-withdrawing and weak electron-donating *para*-substituents on the aromatic ring react to form enyne products in modest yields (Table 2, entries 2 and 3). However, in the reaction with the *p*-methoxyphenyl alkyne **2d** was selective in that it produced **3ad** along with the normal Sonogashira coupling product **4ad** (Table 2, entry 4). Additionally, when the alkyne substituent is 2-thiophenyl (Table 2, entry 5) and trimethylsilyl (Table 2, entry 6), tandem processes occur to generate the respective enyne products **3ae** and **3af** in moderate to high yields. However, when the alkyne substrate possesses an alkyl substituent such as the *tert*-butyl or *n*-butyl group, the reaction is complicated by the production of a number of products, including those formed by double-Heck and Sonogashira reactions (Table 2, entries 7 and 8).

In a brief effort designed to probe the aryl iodide substrate range of the tandem coupling process, alkyne **2f** was reacted with other *o-iodo N,N*-di-Boc-aminoarenes. The results displayed in Table 3 show that tandem reactions of the 2-phenyl-6-*N,N*-di-Bocamino-5-iodo-pyrimidin-4-ol **1b**, protected-aminoiodobenzene **1c**, and pyridines **1d**−**e**, using $ZnBr_2$[13] in place of CuI as the cocatalyst and a higher temperature of 100 °C, led to high yielding production of the desired enyne products (Table 3, entries 1−4).

In order to demonstrate the importance of the novel tandem Heck−Sonogashira coupling process, we have explored cyclization reactions of the eneyne products promoted by catalytic silver trifluoroacetate in trifluoroacetic acid. Nearly all of the 5-enynyl substituted pyrimidines **3** and related benzene and pyridines are efficiently transformed to the novel substituted pyrido[2,3-*d*]pyrimidines **5** (Table 4 entries 1−9). Surprisingly, treatment of **3ad** under these conditions leads to production of a complicated mixture of products. Interestingly, under the cyclization reaction conditions desilylation takes

Table 4. Synthesis of Novel Functionalized Pyrido[2,3-*d*]pyrimidines[a]



entry	substrate	product	yield[b]
1	 **3aa**	 **5aa**	92%
2	 **3ab**	 **5ab**	77%
3	 **3ac**	 **5ac**	92%
4	 **3ae**	 **5ae**	93%
5	 **3af**	 **5af**	95%
6	 **3bf**	 **5bf**	91%
7	 **3cf**	 **5cf**	89%
8	 **3df**	 **5df**	82%
9	 **3ef**	 **5ef**	80%

[a]Unless otherwise noted, the reactions were carried out under standard conditions. [b]Yields of isolated products based on **3**.

place at the terminal alkyne position, leading to generation of 2-methyl-3-trimethylsilyl-pyridine-fused aromatic products (Table 4, entries 5−9).

It is noteworthy that Boc protecting groups play an important role in guiding the operation of the tandem Heck−Sonogashira process. In the mechanistic route followed in this reaction, arylpalladium species **M1** is likely the first intermediate generated by the oxidative addition of Pd (0) species with the 5-iodo pyrimidine (Scheme 3). **M1** undergoes syn addition to the triple bond of the alkyne to provide the crucial Pd−C σ-bonded vinylpalladium species **M2**, which

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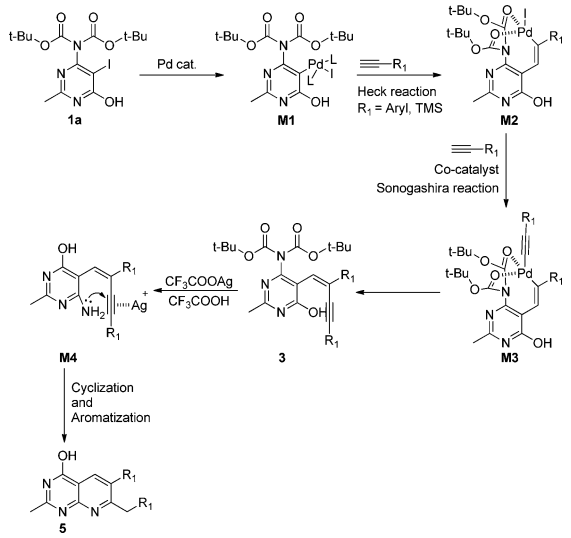
Scheme 3. A Proposed Mechanism



could be stabilized by a carbonyl oxygen of the Boc protecting group. Subsequent insertion into the second terminal alkyne followed by reductive elimination then gives the enyne **3**.

In conclusion, in the effort described above we have developed a novel microwave-assisted tandem Heck−Sonogashira reaction of 6-*N*,*N*-di-Boc-amino-5-iodo-2-methylpyrimidin-4-ol that forms functionalized enyne (−C═C−C≡C−) substituted pyrimidines. The products of this process undergo ready cyclization to generate novel substituted pyrido[2,3-*d*]pyrimidines in good to excellent yields. Notably, the enyne forming and cyclization sequence is applicable to the synthesis of a variety of novel highly functionalized fused pyridines. Further studies are underway to show that this chemistry is applicable to the preparation of heterocycle libraries for high throughput screening efforts.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds and crystal structure data for **3af** in CIF format. 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) Liu, Q. S.; Chang, J. W.; Wang, J. H.; Kang, S. A.; Thoreen, C. C.; Markhard, A.; Hur, W.; Zhang, J. M.; Sim, T.; Sabatini, D. M.; Gray, N. S. *J. Med. Chem.* **2010**, *53*, 7146−7155.

(2) Lassiter, L. K.; Tummala, M. K.; Hussain, M. H.; Stadler, W. M.; Petrylak, D. P.; Carducci, M. A. *Clin. Genitourin. Cancer* **2008**, *6*, 31−35.

(3) Krueger, A. C.; Madigan, D. L.; Beno, D. W.; Betebenner, D. A.; Carrick, R.; Green, B. E.; He, W. P.; Liu, D. C.; Maring, C. J.; McDaniel, K. F.; Mo, H. M.; Molla, A.; Motter, C. E.; Pilot-Matias, T. J.; Tufano, M. D.; Kempf, D. J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2212−2215.

(4) Fjellstrom, O.; Deinum, J.; Sjogren, T.; Johansson, C.; Geschwindner, S.; Nerme, V.; Legnehed, A.; McPheat, J.; Olsson, K.; Bodin, C.; Paunovic, A.; Gustafsson, D. *J. Biol. Chem.* **2013**, *288*, 873−885.

(5) (a) Gong, H. W.; Qi, H.; Sun, W.; Zhang, Y.; Jiang, D.; Xiao, J. H.; Yang, X. H.; Wang, Y.; Li, S. *Molecules* **2012**, *17*, 9961−9970. (b) El-Gazzar, A. R. B. A.; Hafez, H. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3392−3397.

(6) (a) Narayana, B. L.; Rao, A. R. R.; Rao, P. S. *Eur. J. Med. Chem.* **2009**, *44*, 1369−1376. (b) Bheemanapalli, L. N.; Akkinepally, R. R.; Pamulaparthy, S. R. *Chem. Pharm. Bull.* **2008**, *56*, 1342−1348.

(7) Saundane, A. R.; Vijaykumar, K.; Vaijinath, A. V.; Walmik, P. *Med. Chem. Res.* **2013**, *22*, 806−817.

(8) Wendt, J. A.; Deeter, S. D.; Bove, S. E.; Knauer, C. S.; Brooker, R. M.; Augelli-Szafran, C. E.; Schwarz, R. D.; Kinsora, J. J.; Kilgore, K. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5396−5399.

(9) (a) Lin, S. W.; Han, F. B.; Liu, P.; Tao, J.; Zhong, X. C.; Liu, X. J.; Yi, C. Q.; Xu, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 790−793. (b) Goto, T.; Shiina, A.; Yoshino, T.; Mizukami, K.; Hirahara, K.; Suzuki, O.; Sogawa, Y.; Takahashi, T.; Mikkaichi, T.; Nakao, N.; Takahashi, M.; Hasegawa, M.; Sasaki, S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3325−3328. (c) Tseng, H. W.; Zong, R.; Muckerman, J. T.; Thummel, R. *Inorg. Chem.* **2008**, *47*, 11763−11773. (d) Orfi, L.; Waczek, F.; Pato, J.; Varga, I.; Hegymegi-Barakonyi, B.; Houghten, R. A.; Keri, G. *Curr. Med. Chem.* **2004**, *11*, 2549−2553. (e) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523−1526. (f) Perandones, F.; Soto, J. L. *J. Heterocycl. Chem.* **1998**, *35*, 413−419. (g) Degraw, J. I.; Tagawa, H. *J. Heterocycl. Chem.* **1982**, *19*, 1461−1463. (h) Vercek, B.; Leban, I.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1979**, *44*, 1695−1699. (i) Althuis, T. H.; Moore, P. F.; Hess, H. J. *J. Med. Chem.* **1979**, *22*, 44−48.

(10) (a) Gibson, C. L.; Huggan, J. K.; Kennedy, A.; Kiefer, L.; Lee, J. H.; Suckling, C. J.; Clements, C.; Harvey, A. L.; Hunter, W. N.; Tulloch, L. B. *Org. Biomol. Chem.* **2009**, *7*, 1829−1842. (b) Liu, Z. D.; Li, D. W.; Li, S. K.; Bai, D. L.; He, X. C.; Hu, Y. H. *Tetrahedron* **2007**, *63*, 1931−1936. (c) Mayasundari, A.; Fujii, N. *Tetrahedron Lett.* **2010**, *51*, 3597−3598.

(11) (a) Carpita, A.; Ribecai, A. *Tetrahedron Lett.* **2009**, *50*, 204−207. (b) Olivier, J. H.; Camerel, F.; Ziessel, R.; Retailleau, P.; Amadou, J.; Pham-Huu, C. *New J. Chem.* **2008**, *32*, 920−924. (c) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782−1792.

(12) (a) Arsenyan, P.; Rubina, K.; Vasiljeva, J.; Belyakov, S. *Tetrahedron Lett.* **2013**, *54*, 6524−6528. (b) Pal, M.; Dakarapu, R.; Parasuraman, K.; Subramanian, V.; Yeleswarapu, K. R. *J. Org. Chem.* **2005**, *70*, 7179−7187. (c) Chen, Y.-J.; Lee, G.-H.; Peng, S.-M.; Yeh, C.-Y. *Tetrahedron Lett.* **2005**, *46*, 1541−1544; Corrigendum: *Tetrahedron Lett.* **2005**, *46*, 3265. (d) González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, *63*, 2854−2857. (e) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Šaman, D.; Fiedler, P. *Tetrahedron* **1998**, *54*, 11209−11234.

(13) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111−3113.