Organic LETTERS

Letter

pubs.acs.org/OrgLett

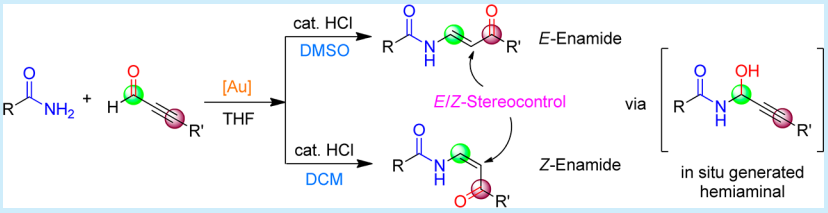
Gold(I)-Catalyzed, Stereocontrolled Enamide Synthesis from Primary Amides and Propargyl Aldehydes Using a Tandem Strategy

Sang Min Kim, Dabon Lee, and Soon Hyeok Hong*

Center for Nanoparticle Research, Institute for Basic Science (IBS), Gwanak-gu, Seoul 151-742, Republic of Korea

Department of Chemistry, College of Natural Sciences, Seoul National University, 599 Gwanak-ro, Gwanak-gu, Seoul 151-747, Republic of Korea

Supporting Information



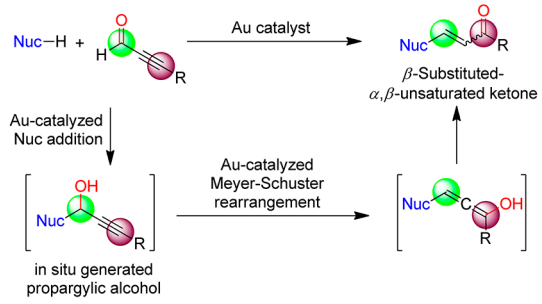
ABSTRACT: A novel strategy for enamide synthesis from primary amides and propargyl aldehydes via Au(I)-catalyzed tandem amide addition and Meyer−Schuster rearrangement is described. In situ generated hemiaminals were successfully converted to the desired products under the optimized conditions. Enamide stereochemistry was controlled simply by changing solvents and adding a catalytic amount of acid. The developed synthetic strategy provides a new method to synthesize various β-substituted α,β-unsaturated carbonyl compounds.

Enamides are very common organic compounds and encompass numerous natural products and drug candidates.[1] In addition, enamides are highly valuable synthetic intermediates for the synthesis of chiral amines,[2] heterocycles,[3] and cross-coupling reagents.[4] Several synthetic methods for the preparation of enamides have already been developed, such as the dehydration of hemiaminals,[5] condensation of compounds containing carbonyl functional groups with amides,[6] and acylation of imines;[7] however, these conventional methods require harsh reaction conditions and provide poor stereoselective control. Recently, diverse transition metal-catalyzed reactions have been developed utilizing Ru,[8,9] Rh,[8] Fe,[8] Pd,[10] Au,[11] and Cu,[12] which provide significant advantages over traditional methods. Nevertheless, these reactions are also limited due to difficulties in preparing the necessary starting materials, requirement of particular reaction conditions, and confined scope of the enamide products. Therefore, new, simple synthetic strategies are still needed.

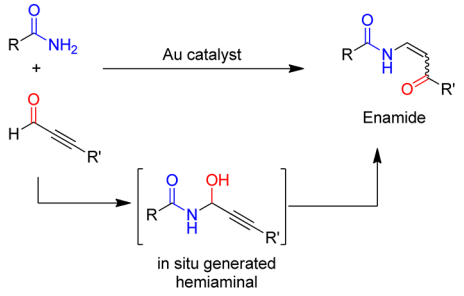
The Meyer−Schuster rearrangement of propargylic alcohols is a powerful tool to make α,β-unsaturated ketones,[13] allowing for the synthesis of many β-functionalized compounds from diverse substrates. Within the past decade, many Au(I)- and Au(III)-catalyzed Meyer−Schuster rearrangement reactions have been developed.[14] However, the propargylic alcohols are mostly confined to alkyl or aryl substitution at the propargylic position. Applying this reaction to the more inherently unstable substrates with a carbon-heteroatom bond at the propargylic position, such as propargylic hemiaminal, would significantly extend the synthetic possibilities. To overcome the limitation, we envisioned the use of in situ generation of heteroatom-substituted propargylic alcohols from readily available nucleophiles and propargyl aldehydes (Scheme 1). In this regard,

Scheme 1. Novel Synthetic Strategy for β-Substituted α,β-Unsaturated Ketones via Tandem Nucleophilic Addition and Meyer−Schuster Rearrangement

a. Tandem Strategy : Nucleophilic addition and Meyer-Schuster rearrangement



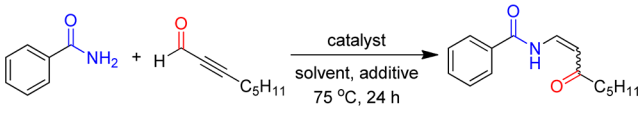
b. Enamide synthesis from primary amides and propargyl aldehydes



Received: October 18, 2014

   dx.doi.org/10.1021/ol503055x | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



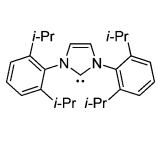
1a **2a** **3aa + 4aa**

3aa; *Z*-enamide

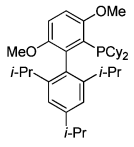
4aa; *E*-enamide

entry	catalyst	additive	solvent	yield[b] (%)	Z/E[b]
1	$AuCl_3$		THF	19	5.6
2	AuCl		THF	29	5.4
3	AuCl/AgOTf		THF	40	4.8
4	(IPr)AuCl/AgOTf		THF	44	4.8
5	Ph_3PAuCl/AgOTf		THF	56	4.7
6	BrettPhosAuCl/AgOTf		THF	55	5.2
7	LAuCl/AgOTf		THF	69	4.9
8	LAuCl/AgOTs		THF	71	6.6
9	LAuCl/$AgBF_4$		THF	56	5.7
10	LAuNTf$_2$		THF	43	5.7
11	LAuCl/AgOTf		DCM	38	19
12	LAuCl/AgOTf		DMF	29	0.7
13[c]	LAuCl/AgOTf	1.0 equiv of H_2O and 0.5 equiv of EtOH	THF	89	4.9
14[c]	LAuCl/AgOTs	1.0 equiv of H_2O and 0.5 equiv of EtOH	THF	85	5.0

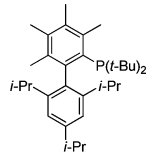
[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (0.25 mmol, 1.0 equiv), catalyst (5 mol %), solvent (0.5 mL), 24 h. [b]Yield of isomeric mixtures and Z/E ratio determined by ^{1}H NMR. Mesitylene was used as an internal standard. [c]**2a** (0.30 mmol, 1.2 equiv) was used.



IPr

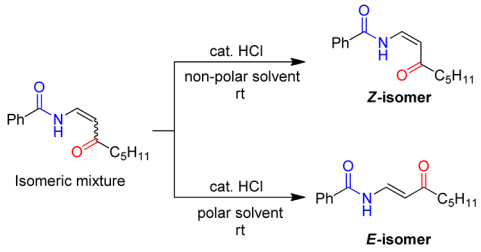


BrettPhos



L, Me$_4$*t*BuXPhos

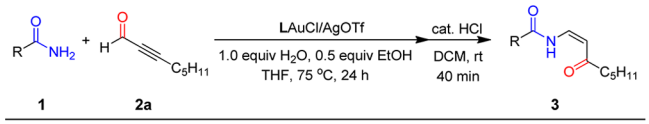
Table 2. Stereocontrolled Isomerization of Enamides



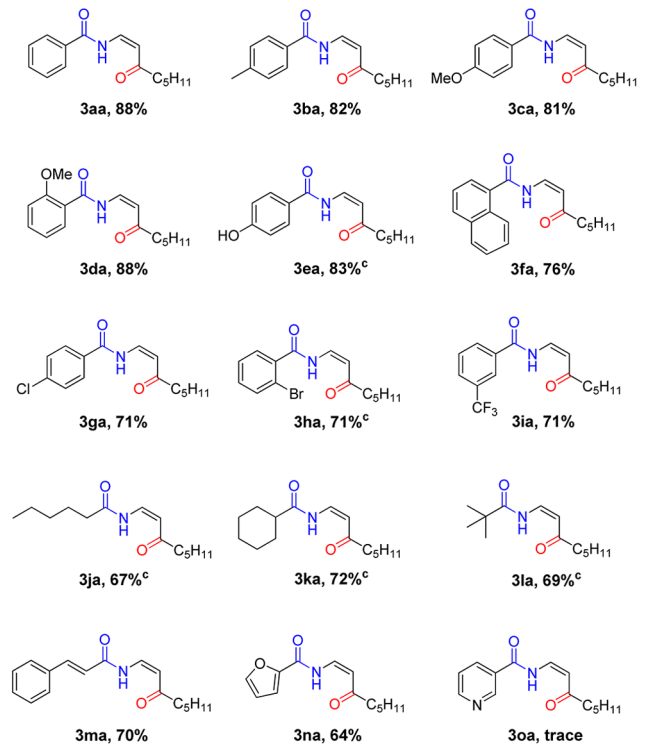
entry	solvent	Z/E[a]
1	DCM	19:1
2	THF	5:1
3	MeOH	1.1:1
4	DMA	1:1.3
5	DMF	1:1.5
6	DMSO	1:8.6

[a]Z/E ratio was determined by ^{1}H NMR.

Scheme 2. Amide Substrate Scope[a,b]



1 **2a** **3**



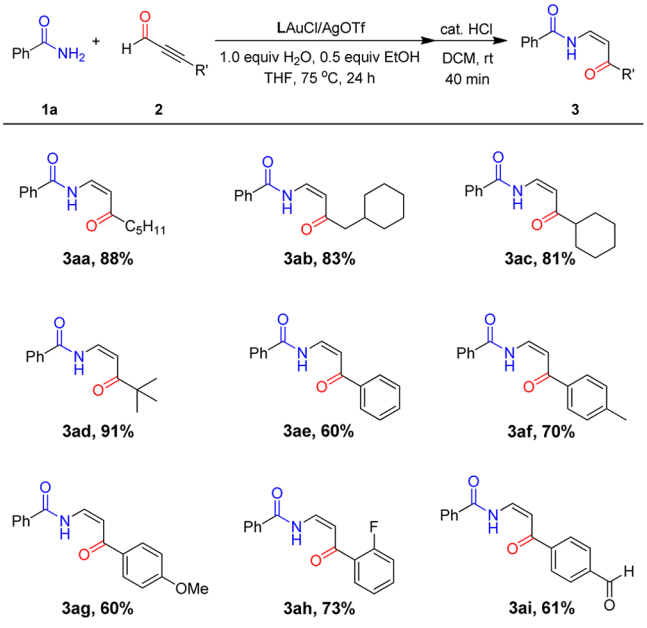
[a]Reaction conditions: (step 1) **1** (0.25 mmol, 1.0 equiv), **2a** (0.30 mmol, 1.2 equiv), LAuCl (0.0125 mmol, 5 mol %), AgOTf (0.0125 mmol, 5 mol %), H_2O (0.25 mmol, 1.0 equiv), EtOH (0.125 mmol, 0.5 equiv), THF (0.5 mL), 75 °C, 24 h; (step 2) 4 M HCl in dioxane (0.0125 mmol, 5 mol %), DCM (0.5 mL), room temperature, 40 min. [b]Isolated yield. [c]**2a** (0.50 mmol, 2.0 equiv) was used.

the rearrangement of propargylic hemiaminals synthesized from primary amides and propargyl aldehydes would yield particularly valuable enamides. Au catalysis appeared to be most promising to achieve this goal, given that it can activate propargyl aldehydes to yield more electrophilic species[15] and also can mediate the Meyer−Schuster rearrangement of propargylic alcohols.[14]

A model reaction between benzamide (**1a**) and 2-octynal (**2a**) was first used to determine the required catalytic conditions (Table 1), beginning by determining the ideal Au catalyst. The simpler Au(I) and Au(III) chloride catalysts showed low activity (entries 1 and 2), while the addition of AgOTf increased the yield slightly to 40% (entry 3). While the N-heterocyclic carbene (NHC)-based Au catalyst (IPr)AuCl did not result in a meaningful improvement in yield (entry 4), Ph_3PAuCl showed significantly greater activity, producing the enamide in 56% yield (entry 5). This result suggested that phosphine-based Au complexes might provide the best results; testing of several of these catalysts identified Me$_4$-*t*-BuXPhosAuCl (LAuCl) as the best candidate (entries 6 and 7). Further testing of the Ag additive confirmed triflate and tosylate to be the best counterions (entries 7−10). Meanwhile, solvent testing revealed that THF gave the highest yields (entries 7, 11, and 12). Interestingly, decreasing solvent polarity increased the Z/E ratio of the product; while DCM yielded the highest ratio of 19 (entry 11), DMF gave the *E*-enamide as the major isomer (entry 12). Water and ethanol additives increased the yield to 89%, an observation that is consistent with previous results;[14] because AgOTf gave a slightly better yield than AgOTs under

dx.doi.org/10.1021/ol503055x | Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Aldehyde Substrate Scope[a,b]



[a]Reaction conditions: (step 1) **1a** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), LAuCl (0.0125 mmol, 5 mol %), AgOTf (0.0125 mmol, 5 mol %), H_2O (0.25 mmol, 1.0 equiv), EtOH (0.125 mmol, 0.5 equiv), THF (0.5 mL), 75 °C, 24 h; (step 2) 4 M HCl in dioxane (0.0125 mmol, 5 mol %), DCM (0.5 mL), room temperature, 40 min. [b]Isolated yield.

the optimized conditions, it was selected for further study (entries 13 and 14).

Given the observed stereoselective solvent dependency in the screening experiments, additional solvents were tested to further improve the reaction utility (Table 2). A catalytic amount of HCl was added to facilitate isomerization through protonation of the carbonyl oxygen. As previously reported, DCM predominantly gave the *Z*-isomer due to intramolecular hydrogen bonding between the amide proton and the carbonyl oxygen of the ketone group;[10e] unfortunately, less polar solvents could not be tested due to solubility issues. On the other hand, polar solvents, particularly DMSO, disrupted that intramolecular hydrogen bond by competing with the substrate, favoring the *E*-isomer as a result. Chang and co-workers reported that some *E*-enamides could be obtained by photoisomerization of the corresponding *Z*-enamides with moderate efficiency and selectivity by using 350 nm UV light.[10e] In our case, a simple workup involving catalytic addition of HCl and careful solvent selection produce a similar, more selective result without any loss of the enamide product.

With the above results in hand, we investigated substrate scope with a one-pot procedure including Au-catalyzed enamide synthesis and enamide isomerization to obtain *Z*-enamide selectively. First, amide substrate scope with **2a** was examined (Scheme 2). Several substituted benzamides afforded *Z*-enamides in reasonably high yields, including both those that contained electron-donating and electron-withdrawing groups (**3aa**–**ia**). Hydroxy and halide substituents were both well tolerated by the reaction (**3ea**,**ga**–**ha**), while aliphatic amides gave good yields when two equivalents of aldehyde were used (**3ja**–**la**). While cinnamamide and furanamide afforded moderate yields (**3ma**–**na**), nicotinamide showed no reactivity (**3oa**).

Next, aldehyde substrate scope was investigated with benzamide (Scheme 3). As opposed to the amides, aliphatic substitution gave higher yields than aryl substitution, even for sterically hindered substrates (**3aa**–**ad**); aryl propargyl aldehydes only gave yields up to 73% (**3ae**–**ai**). Notably, the aryl aldehyde 4-(3-oxo-1-propyn-1-yl)benzaldehyde (**2i**) only allowed for reaction at the propargyl aldehyde site (**3ai**).

The developed isomerization method was then applied to obtain *E*-enamides from the various *Z*-enamides (Table 3).

Table 3. *E*-Selective Enamide Isomerization[a]

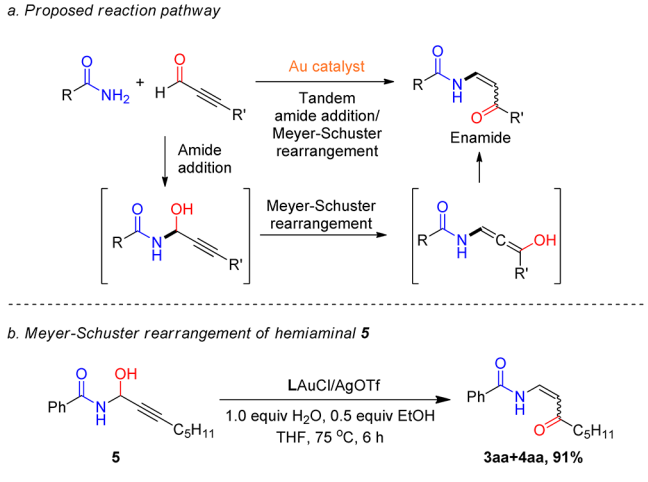
entry	R	R′	E/Z[b]
1	Ph	*p*-$MeOC_6H_4$	3.4
2	Ph	*t*-Bu	4.0
3	Ph	Ph	6.2
4	Ph	*n*-C_5H_{11}	8.6
5	Ph	*o*-FC_6H_4	9.9
6	*t*-Bu	*n*-C_5H_{11}	3.8
7	*p*-$MeOC_6H_4$	*n*-C_5H_{11}	7.0
8	*n*-C_5H_{11}	*n*-C_5H_{11}	11
9	*m*-$CF_3C_6H_4$	*n*-C_5H_{11}	17

[a]Reaction conditions: *Z*-enamide (1.0 equiv), 4 M HCl in dioxane (10 mol %), DMSO (0.5 mL), 6 h. [b]Determined by ^1H NMR.

As expected, all chosen enamides showed good *E*-selectivity in DMSO. Generally, electron-deficient enamides gave higher E/Z ratios, presumably due to weaker intramolecular hydrogen bonding.

Finally, the reaction pathway was investigated to confirm that hemiaminals are produced as intermediates in this reaction (Scheme 4). An isolable hemiaminal (**5**) afforded the desired

Scheme 4. Proposed Reaction Pathway and Intermediate Study



enamide product in 91% yield after 6 h under the optimized conditions, providing further support for the proposed mechanism.

In summary, a novel enamide synthesis has been developed that combines primary amides and propargyl aldehydes via Au(I)-catalyzed tandem amide addition and Meyer–Schuster

dx.doi.org/10.1021/ol503055x | *Org. Lett.* XXXX, XXX, XXX–XXX

rearrangement. Enamide stereoselectivity was controlled simply by changing solvents and through the addition of a catalytic amount of acid. The developed synthetic strategy provides a new approach by which to synthesize various β-substituted α,β-unsaturated carbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedure and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: soonhong@snu.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF-2014R1A2A1A11050028) and the Institute for Basic Science (IBS-R006-D1), funded by the Korean Government.

■ REFERENCES

(1) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.
(2) (a) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363. (c) Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708. (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.
(3) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801.
(4) Roff, G. J.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem. Soc.* **2004**, *126*, 4098.
(5) (a) Wang, X.; Porco, J. A. *J. Org. Chem.* **2001**, *66*, 8215. (b) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665.
(6) (a) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (b) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832.
(7) (a) Boeckman, R. K.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.
(8) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.
(9) (a) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413. (b) Gooβen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042. (c) Gooβen, L. J.; Salih, K. S.; Blanchot, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492.
(10) (a) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (b) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (c) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. (d) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229. (e) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, *128*, 12954. (f) Panda, N.; Mothkuri, R. *J. Org. Chem.* **2012**, *77*, 9407.
(11) Kimber, M. C. *Org. Lett.* **2010**, *12*, 1128.
(12) (a) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679. (b) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109.
(13) (a) Meyer, K. H.; Schuster, K. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 819. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149. (c) Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015.
(14) (a) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027. (b) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107. (c) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 0949. (d) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437. (e) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988. (f) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867. (g) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767. (h) Ramón, R. n. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665. (i) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479. (j) Gómez-Suárez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013**, *32*, 1106. (k) Hansmann, M. M.; Hashmi, A. S. K.; Lautens, M. *Org. Lett.* **2013**, *15*, 3226.
(15) Bhunia, S.; Abu Sohel, S. M.; Yang, C.-C.; Lush, S.-F.; Shen, F.-M.; Liu, R.-S. *J. Organomet. Chem.* **2009**, *694*, 566.