Organic LETTERS

Letter

pubs.acs.org/OrgLett

Control of Chemo-, Regio-, and Enantioselectivity in Copper Hydride Reductions of Morita–Baylis–Hillman Adducts

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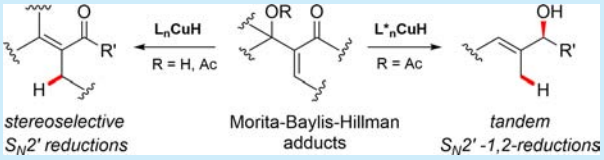
Supporting Information

ABSTRACT: Nonracemically ligated copper hydride can be used to effect tandem S_N2'/1,2-reductions of racemic Morita–Baylis–Hillman (MBH) acetates to access enantioenriched chiral allylic alcohols with defined olefin geometry. MBH esters, including those with β-substitution, can be transformed to stereodefined enoates by taking advantage of a bulky, oligomeric, in situ generated trialkoxysiloxane leaving group. Finally, an atypical conversion of easily arrived at MBH alcohol derivatives to nonracemic allylic alcohols is disclosed.

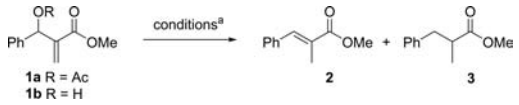


Morita–Baylis–Hillman (MBH) adducts are well-known, versatile intermediates in synthesis owing to their multiple electrophilic sites.[1] Their potential for use in reactions with copper hydride (CuH), especially nonracemically ligated CuH, has yet to be realized. Since Stryker's seminal reports,[2a−c] CuH-mediated methods for numerous types of reduction have reached considerable sophistication in recent years, with catalytic systems allowing for highly chemo- and enantioselective 1,2- or 1,4-reductions under mild conditions.[3a−g] While substitution reactions based on copper have been extensively developed for carbon-, boron-, and silicon-type nucleophiles,[4a−d] substitutions involving *hydride* have been far less studied.[5a−d]

Examining simple MBH acetate **1a** (Table 1) immediately poses the interesting question of regioselectivity, where CuH (prepared from $Cu(OAc)_2$ and a silane) could, in principle, deliver hydride to the activated allylic site or add hydride in a 1,4-sense to the enoate as a Michael acceptor. CuH reductions are widely believed to give rise to an O–Cu enolate after 1,4-hydride delivery,[6a,b,7] and a 1,4-addition pathway in this case could potentially lead to a silyl ketene acetal or undergo *anti*-elimination to give rise to a new enoate, **2**. Subjecting **1a** to CuH (THF, rt) led to only enoate **2** and the corresponding over-reduced ester **3**, the former with 8:1 *E*/*Z* selectivity. These results suggest that allylic substitution, in this case, is faster than 1,4-reduction. The difficulty in separating the *E*-enoate from both its *Z* isomer and over-reduced product **3** would likely preclude use of this chemistry as a general method to arrive at α-substituted enoates. Therefore, the process was optimized to minimize formation of **3** and improve *E*/*Z* selectivity.[8]

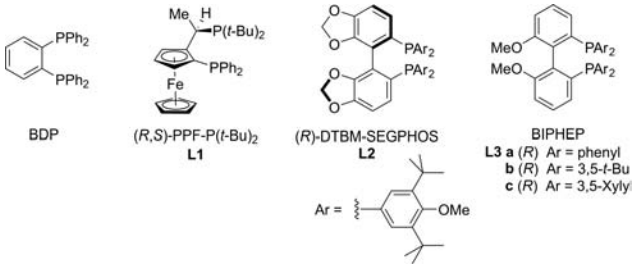
Control experiments revealed that the reaction is not induced by silane alone, nor does a silane in the presence of catalytic phosphine ligand lead to reduction; copper is clearly required for conversion (Table 1, entries 1–3). Attempts to mitigate over-reduction by varying temperature, time, and leaving group were unsuccessful. Several of the commonly used ligands for CuH either behaved sluggishly or led to an undesirable amount of over-reduced product (entries 5–7). Ligand **L3a**, on the other hand, gave rise to the desired enoate **2** in 6:1 *E*/*Z* selectivity; no detectable over-reduction (entry 8) was observed even in the presence of excess silane or prolonged reaction times. The use of less expensive PMHS, as opposed to DEMS, gave comparable results.[9] Although in the absence of a leaving group it was

Table 1. Optimization Studies



entry	R	$Cu(OAc)_2{\cdot}H_2O$ (mol %)	ligand (mol %)	silane (H^- equiv)	temp [°C]	time [h]	2 [%][b]	3 [%][b]
1	Ac	3	BDP (3)	DEMS (2)	rt	2	81 (8:1 *E*/*Z*)	18
2	Ac	0	none (0)	DEMS (2)	rt	18	0	0
3	Ac	0	BDP (3)	DEMS (2)	rt	72	0	0
4	Ac	3	BDP (3)	DEMS (2)	-25	13	80	7
5	Ac	3	L1 (3)	DEMS (2)	rt	2	69	5
6	Ac	3	L2 (3)	DEMS (2)	rt	2	21	0
7	Ac	3	L3b (3)	DEMS (2)	rt	2	22	1
8	Ac	3	L3a (3)	DEMS (2)	rt	2	100	0
9	Ac	3	L3a (3)	PMHS (4)	rt	2	100 (6:1 *E*/*Z*)	0
10	**H**	**3**	**L3a (3)**	**PMHS (4)**	**rt**	**2**	**100 (>20:1 *E*/*Z*)[c]**	**0**

[a]Reactions were performed under an inert atmosphere at 0.4 M in THF. [b]Determined by GCMS of the crude reaction mixture. [c]Determined by ^1H NMR of the pure product. DEMS = diethoxymethylsilane. PMHS = polymethylhydrosiloxane

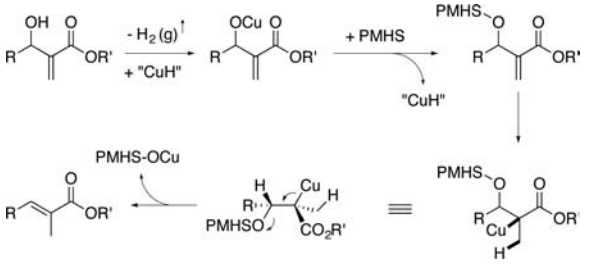


Received: November 20, 2016
Published: January 11, 2017

DOI: 10.1021/acs.orglett.6b03464
Org. Lett. 2017, 19, 328–331

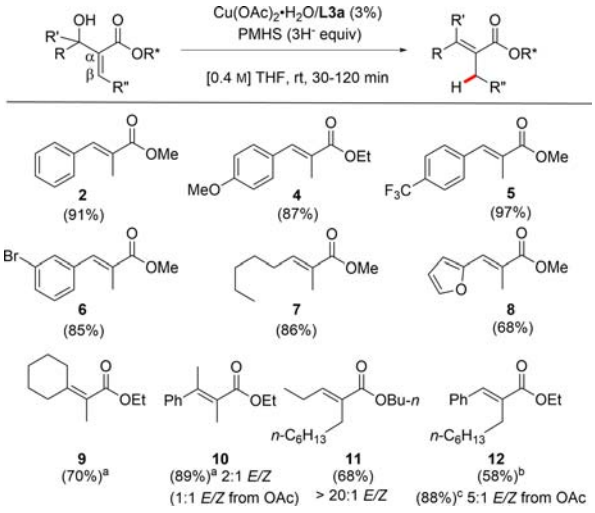
expected that 1,4-reduction would predominate, to our surprise, with *alcohol* **1b** as substrate, vigorous gas evolution was noted and product enoate **2** was obtained quantitatively and with dramatically higher (>20:1) *E*/*Z* selectivity (entry 10). This result implies that the reaction of **1b** initially proceeded through a dehydrogenative silylation[10] to afford a PMHS-bound silyl ether where 1,4-addition and subsequent elimination gives rise to the desired product. The higher *E*/*Z* selectivity can be rationalized given the much larger size of the oligomeric[11] O-PMHS-bound leaving group, forcing a highly *anti*-selective elimination (Scheme 1).

Scheme 1. Proposed Reaction Mechanism



These encouraging results prompted us to examine the scope of these reductions for several MBH alcohols (Scheme 2). In general, isolated yields were quite good for most examples. In all cases, *E*/*Z* selectivity for 2° alcohols was observed to be >20:1, with no detectable over-reduction.

Scheme 2. Stereoselective Reductions of MBH Esters*

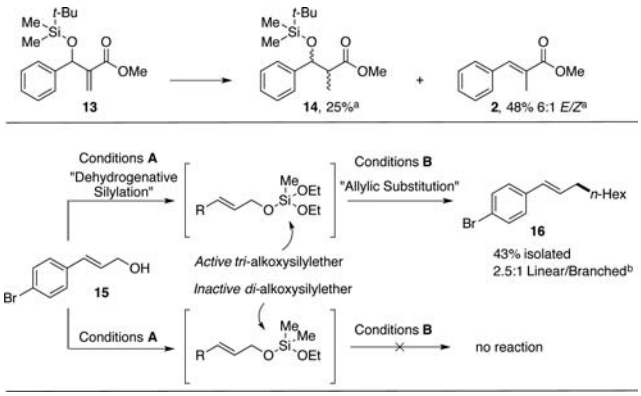


*Yields in parentheses are the percentage of product isolated after chromatography. [a]Reaction time 18 h. [b]Reaction time 24 h. [c]With 3 equiv of *t*-BuOH and reaction time 72 h.

Most methodology developed for functionalization of MBH adducts relies on substrates accessible from traditional conditions. (e.g., acrylate, aldehyde, DABCO). On the other hand, Ramachandran's hydroalumination of ynoates[13] significantly expands the scope of MBH derivatives that can be prepared, including adducts possessing both tertiary alcohols and those with *β*-substitution. Accordingly, four different MBH adducts were prepared by this method and tested as the alcohol or as the corresponding acetate. The reactions with tertiary MBH alcohols are particularly interesting cases, as despite their congested nature at the alcohol site, dehydrogenative silylation remains kinetically favored over 1,4-addition, thus providing a comparatively mild albeit nontraditional method to access tetrasubstituted olefins such as **9** and **10**. Educts possessing substitution at the *β*-site of the Michael acceptor were also tested, giving rise to enoates **11** and **12**. While both were obtained uneventfully with high levels of stereocontrol, addition of *t*-BuOH[14] was needed to enhance catalyst regeneration.

Since silyl ethers are not traditionally thought of as competent leaving groups in substitution chemistry, we questioned whether the high reaction efficiency might be a result of the electronics of the proposed trialkoxysilyl ether intermediate and/or the activated nature of MBH adducts. The reaction of CuH on TBS ether **13** (Scheme 3) gave a mixture of 1,4-reduction

Scheme 3. Probing Silyl Ethers as Leaving Groups*



*Conditions A: 6 mol % of Xantphos/$Cu(OAc)_2 \cdot H_2O$, 1.25 equiv of $(EtO)_2MeSiH$ or $EtO(Me)_2SiH$ (0.2 M), Et_2O, rt, 2 h. Conditions B: 1.35 equiv of *n*-HexMgBr, −78 °C to rt, overnight. [a]Determined by GCMS of crude reaction mixture. [b]Determined by ^1H NMR of pure product.

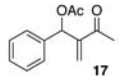
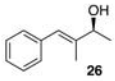
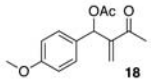
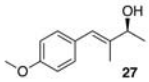
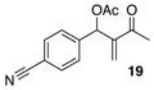
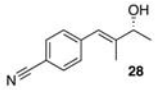
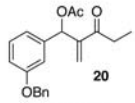
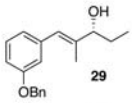
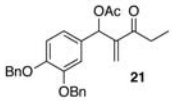
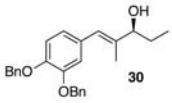
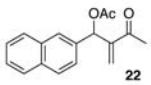
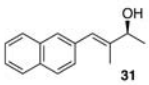
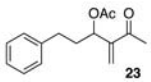
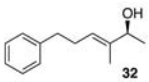
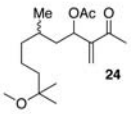
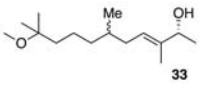
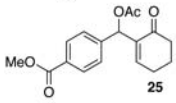
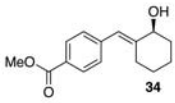
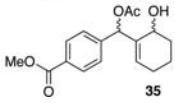
product **14**, allylic substitution product **2**, and starting material as confirmed by GCMS, suggesting that steric bulk alone of the silyl ether is insufficient for substitution.[15] Likewise, copper-catalyzed dehydrogenative silylation[10] on *p*-bromocinnamyl alcohol using either DEMS or dimethylethoxysilane was carried out. Once the intermediate silyl ether was fully formed, the solutions were treated at cryogenic temperature with Grignard reagent to effect a copper-catalyzed allylic alkylation. Only DEMS, which gives rise to a trialkoxysilyl ether intermediate, gave allyllic substitution product as a mixture of linear and branched regioisomers, lending support to our hypothesis that a trialkoxysilyl ether is crucial for these displacement reactions.[12a,b]

With various substitution patterns on MBH esters having been examined, we turned our attention to the much more intriguing question of regioselectivity with MBH *ketones*, since we had previously shown that enones bearing an *α*-substituent can redirect nonracemically ligated CuH to react in a 1,2-sense to arrive at chiral allylic alcohols.[3c,f] Hence, if CuH could be directed to react in a sense similar to that seen with MBH esters (vide supra), the resulting *α*-substituted enone would subsequently be expected to undergo further asymmetric 1,2-reduction to ultimately arrive at a nonracemic allylic alcohol. This seemed plausible, as the BIPHEP series of ligands are competent for use in these reductions of MBH esters and had already been shown to be highly enantioselective for the anticipated 1,2-reductions. Indeed, subjecting acetate **17** to previously developed conditions with ligand **L3c** led to allylic alcohol **26** in 92% isolated yield and

DOI: 10.1021/acs.orglett.6b03464
Org. Lett. 2017, 19, 328−331

93% ee with 100% control of olefin geometry (Table 2).[16] Thus, as is the case with MBH esters, allylic reduction is a much faster process than 1,4-reduction, and in this case, 1,2-reduction notwithstanding the α-substituent in the starting material. No isomerization of the product allylic alcohols was detected.

Table 2. Enantioselective Reductions of MBH Ketones

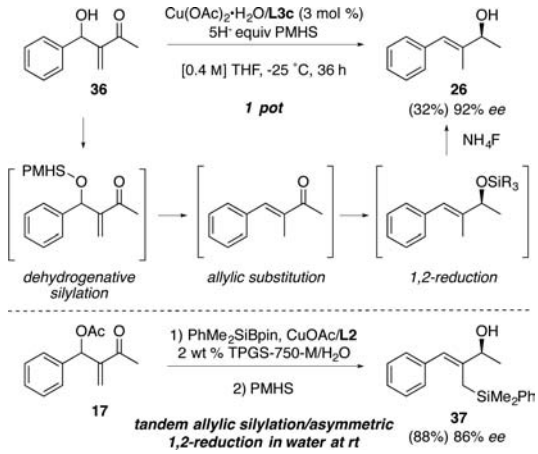
entry	substrate	ligand time (h)	product	yield[a] (% isolated)
1	 17	L3c 24	 26	(92%) 93% *ee* (91%)[b] 76% *ee*
2	 18	L3c 24	 27	(87%) 84% *ee*
3	 19	*ent*-L3c 24	 28	(93%) 89% *ee*
4	 20	*ent*-L3c 24	 29	(74%) 94% *ee*
5	 21	L3c 24	 30	(92%) 99% *ee*
6	 22	L3c 24	 31	(91%) 89% ee
7	 23	L3c 24	 32	(87%) 83% *ee*
8	 24	*ent*-L3c 36	 33	(70%) 22.1:16.5:1.5:1 *dr* (88% *de*)
9	 25	L3c 24	 34	(83%) 55% *ee*
10	------	*rac*-L2 24	 35	(73%) 1.2:1 *dr*

[a]Conditions: 3 mol % of $CuOAc_2$, 3 mol % of **L3c**, 4 equiv of DEMS, Et_2O (0.4 M), −25 °C, then quench NH_4F/MeOH. [b]Reaction conducted at rt in aqueous TPGS-750-M using PMHS as H-source.

The scope of this tandem allylic substitution/asymmetric 1,2-reduction was then further examined (Table 2). Electron-rich **18** was reduced uneventfully, as was electron-deficient **19**. Ethyl ketones **20** and **21** possessing benzyl-protected phenols displayed remarkable enantioselectivity, with the latter product obtained in essentially enantiopure form. Naphthyl and hydrocinnamyl substrates reacted smoothly to form products **31** and **32**. Diastereomeric substrate **24** was converted to **33** with high diastereoselectivity, implying that the influence of the distal methyl group was not significant. While the *s-cis* conformation of enones has been previously suggested to favor 1,2-reduction by CuH in the presence of bulky biaryl bis-phosphines such as **L2**,[3f] employing cyclic substrate **25** with an *s-trans* conformation led predominantly to the 1,2-adduct **35**. Remarkably, **L3c** completely reversed the mode of reduction back to the expected allylic substitution/1,2-reduction pathway, affording **34** albeit in substantially reduced enantioselectivity (55% ee). That regioselectivity can be completely inverted by modest alterations in ligand architecture highlights the subtleties associated with substrate recognition where the reactive functionality is forced into close proximity.

With the successful implementation of the tandem S_N2'/1,2-reductions of MBH acetates, the functionality in the MBH adducts seemed to offer good prospects for multiple manipulations. In particular, a three-step process might include a preliminary dehydrogenative silylation to activate the alcohol, prior to double reduction. Although CuH could potentially react with **36** in either a 1,4 or 1,2-sense, or at the alcohol, only an initial silylation would arrive at the requisite leaving group for further substitution (Scheme 4, top). In the event, subjecting **36**

Scheme 4. Enantioselective Tandem Reactions



to our standard conditions afforded allylic alcohol **26** as the major product in essentially the same level of enantioselectivity as seen using the corresponding acetate as educt. Thus, in terms of an overall transformation, a racemic and readily available substrate, and lacking alkene stereochemistry, was transformed over three consecutive steps (68% average yield per step) by a single catalyst to an enantioenriched allylic alcohol with defined double-bond geometry.

Lastly, to further demonstrate the potential of this methodology to prepare chiral synthons, and for its use under green chemistry conditions, we subjected MBH acetate **17** to Suginome's silylborane under micellar conditions followed by addition of PMHS to accomplish both introduction of a stereodefined allylic silane and enantioselective 1,2-reduction in water at room temperature to arrive at **37** in good yield (Scheme 4, bottom).[17,18a,b]

In summary, by harnessing each of the three major reactivity modes of CuH (i.e., dehydrogenative silylation, 1,4-addition, and 1,2-addition), racemic MBH adducts can be efficiently transformed into stereodefined enoates or nonracemic allylic alcohols via controlled tandem reduction sequences. Evidence is provided that an atypical, in situ generated trialkoxysilyl ether as leaving group is important for efficient substitution. When derived from oligomeric PMHS, excellent stereocontrol of the resulting alkenyl derivatives can be obtained, presumably due to the steric demand of these -O-PMHS ethers. The versatility of CuH has been further extended to include a previously unknown and potentially very useful sequence that converts a racemic MBH

DOI: 10.1021/acs.orglett.6b03464
Org. Lett. 2017, 19, 328−331

alcohol into a nonracemic allylic alcohol with defined olefin geometry. Further subtleties and applications associated with CuH chemistry will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03464.

Detailed experimental procedures along with analytical and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSF (SusChEM-1561158) for support of this work. R.L. warmly thanks Dr. Nicholas Isley (Scripps) for helpful discussions.

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(6) The initially formed copper enolate can also be quenched with other electrophiles (e.g., carbonyl compounds) to perform a net reductive aldol. See: (a) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378. (b) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292.

(7) If the copper enolate is trapped as the silyl ketene acetal, it can be regenerated in the presence of $(EtO)_3SiF$ and CuF for use in a subsequent aldol reaction. See: Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644.

(8) While these educts could be prepared by established olefination chemistry, it should also be noted that α-substitution in Horner–Emmons reactions does not as a rule give isomerically pure *E*-enoates, and variable *E*/*Z* ratios are often observed. See: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(9) Aldrich prices as of Apr 13, 2016: PMHS [cat. no. 176206] was calculated at \$0.11/mmol H^- vs DEMS [cat. no. 66612] \$2.27/mmol H^-, assuming 60 g mol^{-1} of effective hydride for PMHS.

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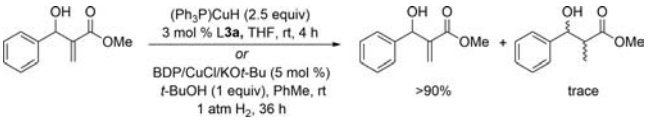
(12) (a) We ascribe the appearance of the branched isomer to the involvement of the soluble Cu(I) catalyst, as formation of branched products are relatively rare in the absence of copper, with Alexakis' NHC ligands being a notable exception. See: Jackowski, O.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3346. (b) Further experimentation showed that the yield of this reaction could be improved to 56% with exclusively linear product being formed by switching the ligand to BDP.

(13) While there are numerous protocols in the literature developed to accommodate additional functionality/substitution in MBH adducts, many of these required lengthy syntheses, specialty catalysts, or gave unreliable results. By contrast, Ramachandran's hydroalumination protocol uses readily available reagents and in our hands has proven quite reliable and easy to perform. See: Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310.

(14) *t*-BuOH is confirmed to accelerate 1,4-reductions by a more rapid quenching of a copper enolate. See: Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (b) Its role in this particular substitution is less clear and other modes of acceleration may be operative, as the copper enolate presumably leads to rapid loss of the O-PMHS silyl ether and catalyst regeneration is quite facile for reactions of simpler MBH alcohols.

(15) Reaction of MBH alcohol under silane-free conditions with either stoichiometric PPh_3CuH and catalytic **L3a** or catalytic BDP/CuCl/KO-*t*-Bu under 1 atm of H_2 gas gave predominantly recovered starting material along with traces of the 1,4-reduction product, suggesting that the intermediate copper alkoxide does not function as a leaving group and hinders further reduction.



(16) The use of low-temperature conditions for reactions of the acetates of MBH ketones is apparently satisfactory for high *E*-selectivity in the initial substitution step.

(17) (a) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647. (b) During the course of this study, another group independently reported a similar silylation of MBH alcohols. See: Xuan, Q.-Q.; Zhong, N.-J.; Ren, C.-L.; Liu, L.; Wang, D.; Chen, Y.-J.; Li, C.-J. *J. Org. Chem.* **2013**, *78*, 11076.

(18) CuH reductions in aqueous surfactant have been described previously. See: (a) Huang, S.; Voigtritter, K. R.; Unger, J. B.; Lipshutz, B. H. *Synlett* **2010**, *2010*, 2041. (b) We found the use of smaller TMS-terminated PMHS oligomers (average M_n = 390, CAS: 63148-57-2) produced much more reliable results by reducing excessive foaming/clumping of the reaction mixture that was problematic with the higher oligomers.

DOI: 10.1021/acs.orglett.6b03464
Org. Lett. 2017, 19, 328–331