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Tertiary Alcohols by Tandem β-Carbolithiation and N→C Aryl Migration in Enol Carbamates

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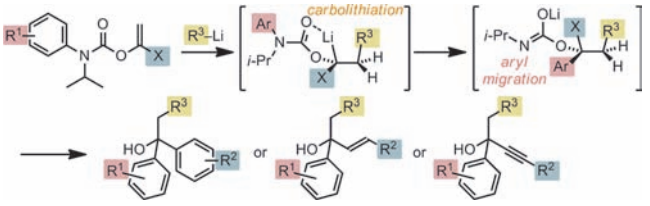
ABSTRACT



Enol carbamates (*O*-vinylcarbamates) derived from aromatic or α,β-unsaturated compounds and bearing an *N*-aryl substituent undergo carbolithiation by nucleophilic attack at the (nominally nucleophilic) β position of the enol double bond. The resulting carbamate-stabilized allylic, propargylic, or benzylic organolithium rearranges with N→C migration of the N-aryl substituent, creating a quaternary carbon α to O. The products may be readily hydrolyzed to yield multiply branched tertiary alcohols in a one-pot tandem reaction, effectively a polarity-reversed nucleophilic β-alkylation–electrophilic α-arylation of an enol equivalent.

We have recently uncovered a previously unnoticed facet of the reactivity of organolithiums stabilized by *N*-arylcarbamoyl groups, namely their tendency to undergo migration of the *N*-aryl ring to the carbanion center in what amounts to an intramolecular nucleophilic substitution even on an electron-rich aromatic ring.[1,2] In the case of *N*-aryl-*O*-benzylic carbamates,[2] lithiation at the benzylic carbon induces a stereochemically invertive intramolecular N→C aryl transfer and provides a route to α-arylated tertiary alcohols[2a] in an enantiomerically enriched form.[2b] A challenge to the extension of this mechanistically remarkable method into a more general synthesis of hindered and/or electron-rich alcohols is the fact that the deprotonation step needed to generate the intermediate benzyllithium is relatively slow. However, Hoppe[3a] and Snieckus[3b] have shown that α-aryl-*O*-alkenylcarbamates are receptive substrates for β-carbolithiation, presumably owing to a complex induced proximity effect[4] arising from coordination of the organolithium to the carbamate donor, and the stability of the benzylic anion preventing polymerization.[5] We have shown that *N*-alkenyl-*N*′-aryl ureas likewise undergo addition of organolithiums to their otherwise nucleophilic β-carbons and that the benzylic organolithiums that result undergo a tandem N→C aryl transfer.[6] A related reaction of *O*-vinylcarbamates would provide a remarkable connective route to tertiary alcohols involving two new C–C bond-forming reactions in a single pot.

Judging that the carbolithiation would require some degree of stabilization of the product anion,[7] we used α-aryl, alkynyl, alkenyl, and silyl-*O*-vinylcarbamates as

(1) (a) Clayden, J.; Dufour, J.; Grainger, D.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (b) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567. (c) Bach, R.; Clayden, J.; Hennecke, U. *Synlett* **2009**, 421. (d) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. *Org. Lett.* **2010**, *12*, 5442.

(2) (a) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410. (b) Fournier, A. M.; Brown, R. A.; Farnaby, W.; Miyatake-Ondozabal, H.; Clayden, J. *Org. Lett.* **2010**, *12*, 2222.

(3) (a) Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, *3*, 381. (b) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 6061.

(4) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (c) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Scheleyer, P. R. *J. Org. Chem.* **1981**, *46*, 4108.

(5) (a) Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1996**, 187. (b) Wei, P.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109.

(6) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.

(7) Hogan, A.-M. L.; O'Shea, D. F. *Chem. Commun.* **2008**, 3839.

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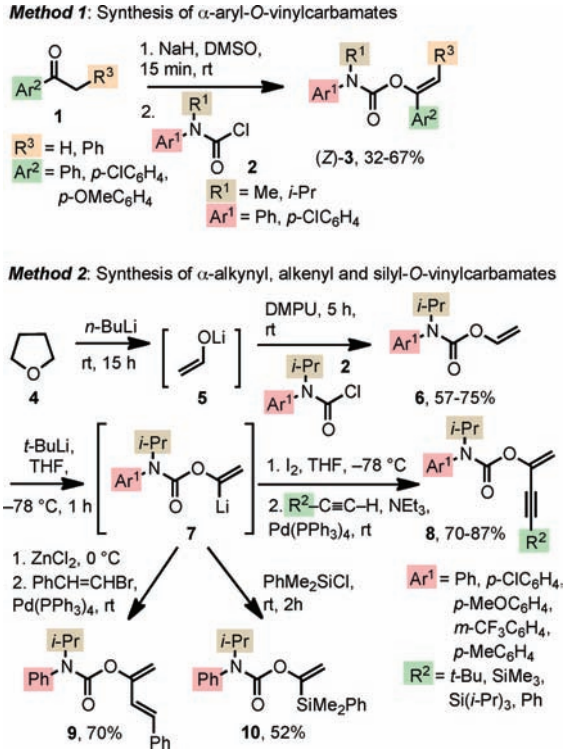
substrates. α-Aryl-*O*-vinylcarbamates **3** were accessible from ketones **1** by formation of their sodium enolates with NaH in DMSO, followed by *O*-acylation with carbamoyl chlorides **2** (Method 1, Scheme 1).[8] The carbamates **3** were formed in moderate yields, and in the case of R^3 = Ph a single geometrical isomer was formed which the X-ray crystal structure of **3g** (R^3 = Ar^1 = Ar^2 = Ph, R^1 = *i*-Pr) indicated to have *Z* geometry (see Supporting Information, SI).

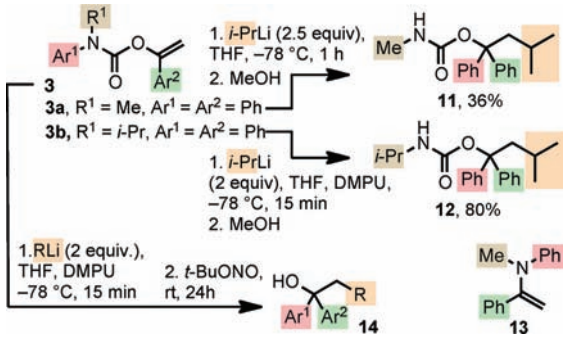
Scheme 1. Synthesis of *O*-Vinylcarbamates



The more versatile Method 2 was used to prepare α-alkynyl, alkenyl, and silyl-*O*-vinylcarbamates (Scheme 1). The lithium enolate **5** of acetaldehyde was generated by cleavage of THF **4** using *n*-BuLi,[9] and *O*-carbamoylation[10] gave simple *O*-vinylcarbamates **6** in good yields. Under standard metalation conditions (*t*-BuLi, THF, −78 °C),[11] **6** underwent α-lithiation and the resulting α-lithio species **7** were trapped with I_2 or $PhMe_2SiCl$ to form vinyl iodides or vinyl silanes with perfect control of regiochemistry. The alkynyl groups of **8** were introduced in excellent yields by a Sonogashira reaction,[12] and the alkenyl group of **9** by the *in situ* conversion of **7** into the corresponding zinc species ($ZnCl_2$) and subsequent Pd-catalyzed cross-coupling with bromostyrene in 70% yield.

In an initial study, *N*-methyl-α-aryl-*O*-vinylcarbamate **3a** (Scheme 2) was treated with *i*-PrLi in THF at −78 °C for 1 h. β-Carbolithiation occurred, followed by N→C migration of the *N*-phenyl ring, to return the product **11** (Scheme 2) in moderate yield (36%). The principal by-product was **13** presumably resulting from a pathway initiated by carbamate cleavage. Replacement of the *N*-methyl group with an *N*-isopropyl substituent improved the yield significantly. Repeating the carbolithiation–

Scheme 2. Optimization and Synthesis of Diarylalkylalcohols



rearrangement in a mixture of THF and DMPU[1,2,13] for 15 min allowed us to isolate **12** in 80% yield.

Cleavage of the carbamate group of **11** under standard conditions[1b,2b] was accompanied by dehydration, but by quenching the carbolithiation–rearrangement reactions with *tert*-butyl nitrite (to form an *N*-nitroso carbamate *in situ*) and stirring the resulting basic reaction mixture for 24 h at rt, diarylalkylalcohols **14** could be obtained from **3** in a one-pot reaction (Scheme 2; Table 1). Addition reactions worked best with primary and secondary alkyllithiums and gave **14** in good to excellent yields (Table 1, entries 1–13) while *tert*-butyllithium (entries 14–17) gave lower yields in some cases.[14] N→C aryl migration proceeded regardless of the electronic nature of aryl rings Ar^1 and Ar^2.

In an attempt to induce asymmetry in the carbolithiation step, the reaction in entry 8 was performed in the presence of (−)-sparteine. However, only moderate enantiofacial differentiation was observed, with the greatest *er* in the addition product being 72:28.[3a,15]

Attempted β-carbolithiation of the β-substituted *O*-vinylcarbamate **3f** with *i*-PrLi (2.5 equiv) in THF at −78 °C gave the alkene **15** in 57% yield, presumably resulting from N→C aryl migration initiated by a γ-deprotonation followed by γ-carbolithiation of *i*-PrLi and subsequent

(8) Jiang, X.-B.; van der Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223. *E*-Alkenylcarbamates have also been made by stereoselective carbometallation of alkynylcarbamates; see: Chechik-Lankin, H.; Marek, I. *Org. Lett.* **2005**, *5*, 5087.

(9) (a) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560. (b) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, *43*, 3791. (c) Clayden, J.; Yasin, S. A. *New J. Chem.* **2002**, *26*, 191.

(10) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680.

(11) Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 2047.

(12) Chedid, R. B.; Brummer, M.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 3131.

(13) The coordinating cosolvent DMPU typically accelerates nucleophilic attack of organolithiums on aromatic rings. See ref 1.

(14) Phenyllithium, vinyllithium, and ethoxyvinyllithium failed to add to **3b**.

(15) For examples of the use of (−)-sparteine to induce asymmetric carbolithiation, see: (a) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (b) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem.—Eur. J.* **1999**, *5*, 2055. (c) Hogan, A.-M. L.; O'Shea, D. F. *J. Org. Chem.* **2008**, *73*, 2503.

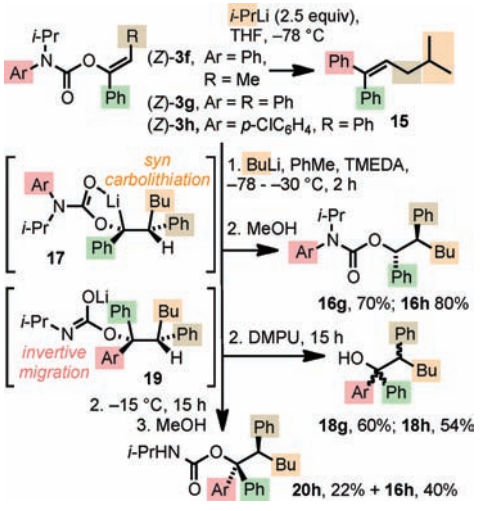
Table 1. Carbolithiation–N→C Aryl Migration of **3** To Give **14**

entry	S.M. **3** (R^1 = *i*-Pr; R^3 = H)	Ar^1	Ar^2	R	**14**, yield (%)
1	**3b**	Ph	Ph	*n*-Bu	**14a**, 57
2	**3c**	*p*-ClC_6H_4	Ph		**14b**, 77
3	**3d**	Ph	*p*-ClC_6H_4		**14b**, 55
4	**3e**	Ph	*p*-$MeOC_6H_4$		**14c**, 68
5	**3b**	Ph	Ph	$PhCH_2$[a]	**14d**, 53[b]
6	**3b**	Ph	Ph	*i*-Pr	**14e**, 73
7	**3c**	*p*-ClC_6H_4	Ph		**14f**, 65
8[c]	**3d**	Ph	*p*-ClC_6H_4		**14f**, 51
9	**3e**	Ph	*p*-$MeOC_6H_4$		**14g**, 81
10	**3b**	Ph	Ph	*sec*-Bu	**14h**, 64
11	**3c**	*p*-ClC_6H_4	Ph		**14i**, 67[d]
12	**3d**	Ph	*p*-ClC_6H_4		**14i**, 51[d]
13	**3e**	Ph	*p*-$MeOC_6H_4$		**14j**, 64[d]
14	**3b**	Ph	Ph	*tert*-Bu	**14k**, 71
15	**3c**	*p*-ClC_6H_4	Ph		**14l** 27
16	**3d**	Ph	*p*-ClC_6H_4		**14l**, 36
17	**3e**	Ph	*p*-$MeOC_6H_4$		**14m**, 67

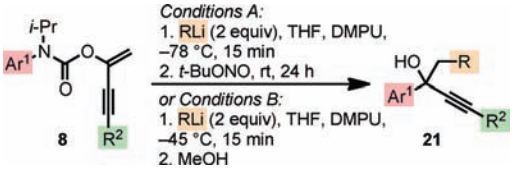
[a] Obtained by metalation of toluene at rt in the presence of (−)-sparteine. [b] After deprotection of the crude rearranged product by treatment with *n*-BuLi in THF followed by *tert*-butyl nitrite quench. [c] Reaction in the presence of (−)-sparteine (2 equiv) in cumene at −50 °C for 2 h gave the addition product in 18% yield and 72:28 *er*. [d] 1:1 mixture of diastereoisomers.

β-elimination of the lithium carbamate (Scheme 3). β-Carbolithiation was successful however when γ-deprotonation was blocked by a phenyl group. A single diastereoisomer of the addition products **16** was isolated in good yield when **3g** or **3h** was treated with *n*-BuLi/TMEDA in toluene, quenching with methanol at −30 °C. The relative configuration of **16g** was proved by an X-ray crystal structure (see SI). The stereochemistry of the product is consistent with *syn*-addition of the organolithium followed by retentive protonation, in agreement with Hoppe's related observations.[3a] This result suggests that the substituted benzyllithium intermediate **17** is configurationally stable[16] in toluene/TMEDA on the time scale of the reaction. Coordinating solvents accelerate both the aryl migration step and inversion at the lithium center,[2] and accordingly adding DMPU to enforce rearrangement after the carbolithiation was complete led to the formation of the alcohols **18g** and **18h** but as a mixture of diastereoisomers.[17] Avoiding DMPU and instead warming the reaction slowly to −15 °C and stirring for 15 h gave a 35:65 mixture of the single addition product **16h** and the rearranged product **20h** in a 95:5 diastereoisomeric ratio. The relative stereochemistry of **20h** was not determined, but previous aryl migrations in lithiated carbamates have been shown to be invertive.[2]

Scheme 3. Stereospecificity in the Carbolithiation of **3g**



Scheme 4. Carbolithiation-Aryl Migration of **8**

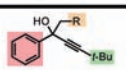
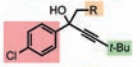
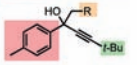
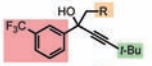
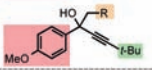
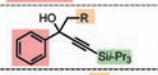
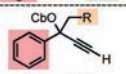
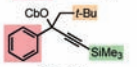
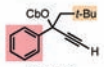
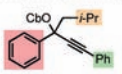
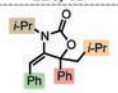


The series of related α-alkynyl-*O*-vinylcarbamates **8** were subjected to the conditions shown to induce β-carbolithiation and N→C aryl migration in α-aryl-*O*-vinylcarbamates **3** (Scheme 4). The alkyllithium was added either in THF in the presence of DMPU at −78 °C for 15 min, followed by a *tert*-butyl nitrite quench, or at −45 °C, with an *in situ* carbamate deprotection occurring in the presence of excess alkyllithium. The resulting alcohols **21** were isolated from this one-pot reaction in moderate to good yields (Table 2).

The migration of both electron-rich and -poor migrating rings took place cleanly. The reaction tolerated *tert*-butyl and triisopropylsilyl groups as acetylenic substituents, but trimethylsilyl and phenyl groups were prone to subsequent reactions. Treating *O*-vinylcarbamate **8g** with either *n*-BuLi or *i*-PrLi in THF at −78 °C gave the products **22a** and **22b** of carbolithiation, N→C aryl migration, and loss of the TMS group (Table 2, entry 7), and *tert*-BuLi gave a mixture of **23** and desilylated product **22c** (Table 2, entry 8). Treating *O*-vinylcarbamate **8h** with *i*-PrLi in THF at −78 °C led to carbolithiation, N→C aryl migration, and cyclization of the resulting carbamate anion of **24** onto the triple bond to yield the benzylidene oxazolidinone **25** (Table 2, entry 9).

(16) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.
(17) The lithium-coordinating additive DMPU decreases the configurational stability of *O*-substituted benzyllithiums. See ref 2b.

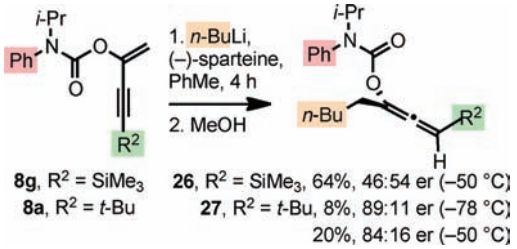
Table 2. Carbolithiation-Aryl Migration of **8**

entry	S.M.	R^2	product	**21**, R = , yield (%) (conditions)
1	**8a**			**21a**, *n*-Bu, 71 (A) **21b**, *i*-Pr, 74 (A) **21c**, *t*-Bu, 67 (A)
2	**8b**	*t*-Bu		**21d**, *n*-Bu, 40 (A) **21e**, *i*-Pr, 43 (A) **21f**, *t*-Bu, 47 (A)
3	**8c**			**21g**, *n*-Bu, 34 (A) **21h**, *i*-Pr, 44 (A)
4	**8d**			**21i**, *i*-Pr, 55 (A) **21j**, *t*-Bu, 26 (A)
5	**8e**			**21k**, *n*-Bu, 40 (B) **21l**, *i*-Pr, 47 (B)
6	**8f**	$Si(i\text{-}Pr)_3$		**21m**, *n*-Bu, 76 (A) **21n**, *s*-Bu, 58 (A) **21o**, *t*-Bu, 63 (A)
7	**8g**			**22a**, *n*-Bu, 72 **22b**, *i*-Pr, 51
8	**8g**	$SiMe_3$[a]	 **23**, 41	 **22c**, 13
9	**8h**	Ph[a]	 **24**, 30	 **25**, 28

[a] Cb = C(=O)N*i*-PrPh. Conditions: (1) RLi, THF/DMPU, −78 °C, 15 min; (2) MeOH.

As observed before, avoiding DMPU resulted in products of carbolithiation only, and treatment of the alkynyl-*O*-vinylcarbamates **8g** and **8a** with *n*-BuLi in THF at −78 °C (Scheme 5) gave allenes **26** and **27** on protonation. When **8g** was treated with *n*-BuLi in the presence of (−)-sparteine in toluene at −78 °C for 4 h, **26** was returned as a racemate, presumably because the silyl group stabilizes a negative charge which facilitates racemization.[18a] In contrast, under the same conditions, **8a** afforded **27** in 89:11 *er*, but in a low yield (8%) due to an incomplete conversion. Raising the temperature to −50 °C increased the yield to 20% with a slight erosion in the *er* (84:16). Longer reaction times lowered the enantioselectivity, presumably due to epimerization of the lithiated intermediate.[18,19]

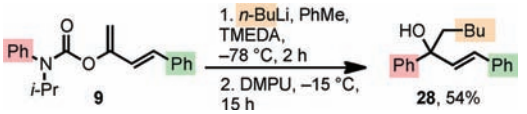
Scheme 5. Formation of Enantioenriched Allenes[a]



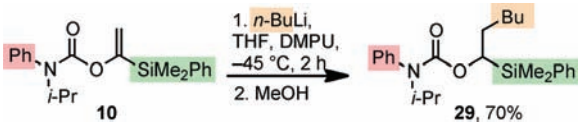
[a] Absolute stereochemistry not determined.

Under the conditions used previously for carbolithiation-N→C aryl migration of α-aryl and α-alkynyl-*O*-vinylcarbamates (THF/DMPU, −78 °C), α-alkenyl-*O*-vinylcarbamate **9** failed to react (Scheme 6). However, the corresponding alcohol **28** was obtained in 54% yield by carrying out the carbolithiation in toluene at −78 °C in the presence of TMEDA, thus increasing the reactivity of the organolithium, then adding DMPU, and increasing the temperature to −15 °C to enforce N→C aryl transfer after the carbolithiation was complete. Notably, carbolithiation was regioselective for the enol double bond rather than the styrene double bond.[15b] Carbolithiation of α-silyl-*O*-vinylcarbamate **10** gave only the addition product **29** in 70% yield upon treatment with *n*-BuLi in THF/DMPU at −45 °C (Scheme 7). We were unable to induce N→C aryl transfer of the intermediate, perhaps because of its inability to form a solvent separated ion pair[2a] under the conditions of the reaction.

Scheme 6. Carbolithiation-Aryl Migration of **9**



Scheme 7. Addition of *n*-BuLi to **10**



In summary, the β-carbolithiation of a range of *N*-aryl-*N*-isopropyl-*O*-vinylcarbamates, coupled with tandem N→C aryl migration, nitrosation, and deprotection, provides a method for the construction of branched tertiary benzylic, propargylic, and allylic alcohols in a single pot from simple precursors.

Acknowledgment. We are grateful to GlaxoSmithKline and the EPSRC for a studentship and to Dr. Christopher Nichols of GlaxoSmithKline for helpful discussions.

Supporting Information Available. Characterization and experimental details for all new compounds. X-ray data for **3g** and **16g**. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) (a) Dreller, S.; Dyrbusch, M.; Hoppe, D. *Synlett* **1991**, 397. (b) Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221.
(19) Tomida, Y.; Nagaki, A.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2011**, *133*, 3744.