Organic LETTERS

Letter

pubs.acs.org/OrgLett

Silyllithium-Initiated Coupling of α-Ketoamides with *tert*-Butanesulfinylimines for Stereoselective Synthesis of Enantioenriched α-(Silyloxy)-β-amino Amides

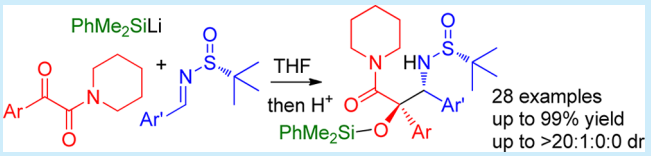
Zhao Sun,[†] Hui Liu,[‡] Yong-Ming Zeng,[†] Chong-Dao Lu,*[,†,‡] and Yan-Jun Xu*[,‡]

[†]Department of Chemistry and Applied Chemistry, Changji University, Changji 831100, China

[‡]The Key Laboratory of Plant Resources and Chemistry of Arid Zones, Xinjiang Technical Institute of Physics & Chemistry, Chinese Academy of Sciences, Urumqi 830011, China

Supporting Information

ABSTRACT: A silyllithium-initiated coupling of α-ketoamides with *tert*-butanesulfinylimines was developed for the efficient, stereoselective synthesis of enantioenriched α-(silyloxy)-β-amino amides. Nucleophilic addition of silyllithium to α-ketoamides, followed by 1,2-Brook rearrangement, generates nucleophilic enolates, which are then intercepted by chiral imines to provide three-component coupling products. Use of α-ketoamides is critical for achieving high yields and diastereoselectivities in the resulting α-hydroxy-β-amino acid derivatives.

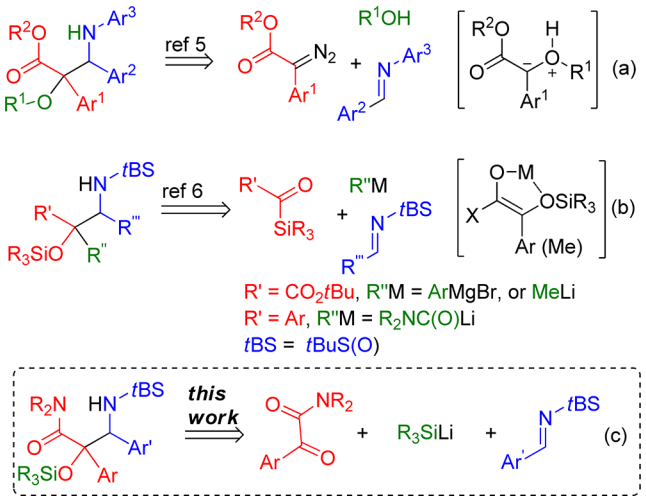


Enantioenriched α-hydroxy-β-amino acids are important building blocks in bioactive molecules such as taxoid anticancer agents.[1,2] A straightforward way to generate these subunits is by directly coupling α-hydroxy acid derivatives or their equivalents to suitable azomethines.[3] This strategy also allows for the preparation of β-amino acid derivatives containing an α-tertiary carbinol center.[4] Such derivatives are sometimes obtained with moderate diastereoselectivity when chiral imines are used as coupling partners.

In situ formation of reactive equivalents of α-hydroxy acid derivatives has recently been achieved. Hu and co-workers used a cooperative catalytic system of rhodium(II) salt and chiral phosphoric acid to achieve enantioselective three-component coupling of α-diazoesters, alcohols and imines. In this approach, rhodium carbenoids and alcohols react to generate alcoholic oxonium ylides, which behave analogously to α-substituted glycolic esters by undergoing Mannich addition to imines (Scheme 1a).[5] Our laboratory has developed alternative three-component protocols[6] in which imines are coupled with α-substituted α-silyloxy enolate intermediates; these intermediates are generated in situ via an acylsilane addition/1,2-silyl migration, also known as a 1,2-Brook rearrangement[7,8] (Scheme 1b). Since this approach requires the relatively tedious preparation of acylsilanes, we wondered whether adding nucleophilic silyl reagents to α-ketoacid derivatives could initiate a similar silyl migration/Mannich coupling cascade. If so, this would provide a simpler and faster method for constructing α,α-disubstituted α-silyloxy-β-amino amides (Scheme 1c).

First, we examined whether phenyldimethylsilyllithium (**1**),[9,10] a nucleophilic silyl reagent that is easy to prepare and handle, would react with α-ketoester **2** and *tert*-butanesulfinylimine **3a** (Scheme 2a).[11−13] Adding **3a** to the reaction mixture of 3 equiv of **1** and **2** afforded the three-component coupling

Scheme 1. Buildup of α,α-Disubstituted α-Hydroxy-β-amino Acid Derivatives by Three-Component Coupling Involving Alcoholic Oxonium Ylides (a) and Silyloxy Enolates (b and c)

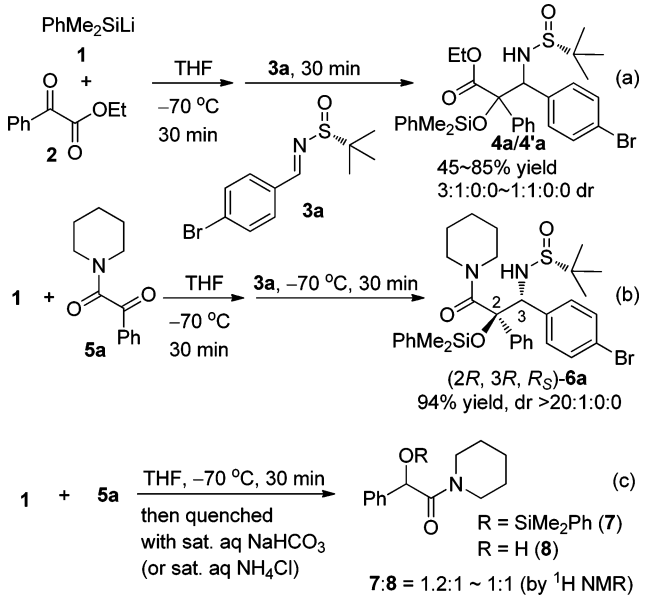


products **4a**/**4′a**, although yields varied substantially (45−85%), as did diastereoselectivities (3:1:0:0−1:1:0:0 dr). Both yield and dr were found to depend on the batch of $PhMe_2SiLi$, reaction temperature, and other unexplained factors. This variability did not improve by introducing Lewis acids such as $BF_3{\cdot}Et_2O$ into the reaction.[14] In contrast, modifying the structure of the α-ketoacid derivative by using α-ketoamide **5a** rather than α-ketoester **2** dramatically improved the reaction

Received: January 2, 2016

DOI: 10.1021/acs.orglett.6b00006
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Examination of the Silyllithium-Initiated Coupling of α-Keto Acid Derivatives with *tert*-Butanesulfinylimines



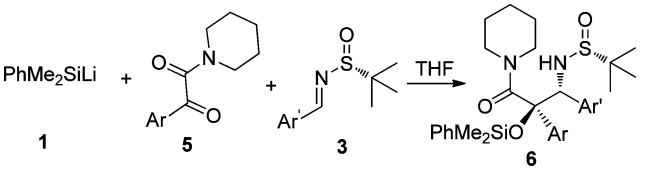
outcomes. This allowed the reproducible formation of coupling product **6a** in 94% yield and >20:1:0:0 dr (Scheme 2b).[15] The procedure was scaled up to 1 g of **6a** with even higher yield of 99% and excellent dr (Table 1, entry 1). The absolute configuration of **6a** was assigned to be (2*R*,3*R*,R_S) based on analysis of its desilylation product.[16]

Excess amounts of silyllithium and α-ketoamide (2.0−3.0 equiv) are necessary for achieving high yield. Control experiments suggested that the undesired reduction of α-ketoamide occurs in the presence of $PhMe_2SiLi$: quenching the reaction of **1** and **5a** with aqueous solutions led to a mixture of addition/silyl migration product **7** and reduction product **8** in ratios of 1.2:1−1:1 (Scheme 2c).[17]

Next, we assessed the suitability of various aryl imines and aryl α-ketoamides in this three-component coupling reaction (Table 1). Aryl imines bearing electron-rich, -poor, and -neutral substituents reacted smoothly, yielding the desired products in high yields and with excellent diastereocontrol in most cases. Aryl imines functionalized at the *ortho*-, *meta*-, and *para*-positions were well tolerated. Imines derived from heteroaromatic 2-carboxaldehydes provided the corresponding α-hydroxy-β-amino amides **6q−s** in good total yields, albeit with diminished dr values (entries 17−19). Imines derived from enolizable or nonenolizable aliphatic aldehydes such as EtCHO, BnCHO, and *t*-BuCHO did not react, leaving the imines intact.

Several electron-rich aryl α-ketoamides **5b−h** participated in the cascade transformations (entries 20−27), while other aryl α-ketoamides **5** did not (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 2-MeC_6H_4, 1-naphthyl, 2-pyridyl, *trans*-PhCH═CH). In the latter case, silyllithium **1** reacted with the α-ketoamides **5** to give complex mixtures of uncharacterized products, and most of the imine was recovered. Using enolizable piperidine pyruvamide gave no detectable three-component coupling product; instead, silyllithium-initiated pinacol homocoupling of this α-ketoamide predominated. Like $PhMe_2SiLi$, the silyllithium reagent $Ph_2MeSiLi$[18] initiated the coupling reaction, giving the desired product in high yield and excellent dr (entry 28).

Table 1. Substrate Scope of Three-Component Coupling of Silyllithiums, α-Ketoamides, and *tert*-Butanesulfinylimines[a]



entry	amide **5** (Ar)	imine **3** (Ar′)	product **6**, yield[b] (%) (dr)[c]
1	**5a** (Ph)	**3a** (4-BrC_6H_4)	**6a**, 99% (>20:1:0:0)[d]
2	**5a** (Ph)	**3b** (Ph)	**6b**, 94% (>20:1:0:0)
3	**5a** (Ph)	**3c** (4-ClC_6H_4)	**6c**, 98% (>20:1:0:0)
4	**5a** (Ph)	**3d** (4-FC_6H_4)	**6d**, 99% (>20:1:0:0)
5	**5a** (Ph)	**3e** (4-MeC_6H_4)	**6e**, 77% (>20:1:0:0)
6	**5a** (Ph)	**3f** (4-$MeOC_6H_4$)	**6f**, 77% (>20:1:0:0)
7	**5a** (Ph)	**3g** (4-$CF_3C_6H_4$)	**6g**, 99% (>20:1:0:0)[e]
8	**5a** (Ph)	**3h** (4-*t*-BuC_6H_4)	**6h**, 80% (>20:1:0:0)[e]
9	**5a** (Ph)	**3i** (4-CNC_6H_4)	**6i**, 85% (6:1:0:0)
10	**5a** (Ph)	**3j** (3-BrC_6H_4)	**6j**, 99% (>20:1:0:0)
11	**5a** (Ph)	**3k** (3-MeC_6H_4)	**6k**, 92% (>20:1:0:0)
12	**5a** (Ph)	**3l** (2-BrC_6H_4)	**6l**, 99% (>20:1:0:0)
13	**5a** (Ph)	**3m** (2-ClC_6H_4)	**6m**, 92% (>20:1:0:0)
14	**5a** (Ph)	**3n** (2-MeC_6H_4)	**6n**, 47% (>20:1:0:0)
15	**5a** (Ph)	**3o** (2-naphthyl)	**6o**, 92% (>20:1:0:0)
16	**5a** (Ph)	**3p** (3-pyridine)	**6p**, 98% (>20:1:0:0)
17	**5a** (Ph)	**3q** (2-thienyl)	**6q**, 98% (2.5:1:0:0)
18	**5a** (Ph)	**3r** (2-furyl)	**6r**, 83% (2:1:0:0)[e]
19	**5a** (Ph)	**3s** (2-pyridine)	**6s**, 87% (4:1:1:0)
20	**5b** (4-MeC_6H_4)	**3a** (4-BrC_6H_4)	**6t**, 91% (>20:1:0:0)
21	**5c** (4-*t*-BuC_6H_4)	**3a** (4-BrC_6H_4)	**6u**, 98% (>20:1:0:0)
22	**5d** (3-MeC_6H_4)	**3a** (4-BrC_6H_4)	**6v**, 99% (>20:1:0:0)
23	**5e** (3,4-$Me_2C_6H_3$)	**3a** (4-BrC_6H_4)	**6w**, 98% (>20:1:0:0)
24	**5f** (4-$MeOC_6H_4$)	**3a** (4-BrC_6H_4)	**6x**, 89% (11:1:0:0)
25	**5g** (3-MeO C_6H_4)	**3a** (4-BrC_6H_4)	**6y**, 79% (15:1:0:0)[e]
26	**5h** (2-naphthyl)	**3a** (4-BrC_6H_4)	**6z**, 96% (>20:1:0:0)
27	**5i** (2-thienyl)	**3a** (4-BrC_6H_4)	**6zz**, 99% (>20:1:0:0)
28	**5a** (Ph)	**3a** (4-BrC_6H_4)	**6a′**, 99% (>20:1:0:0)[f]

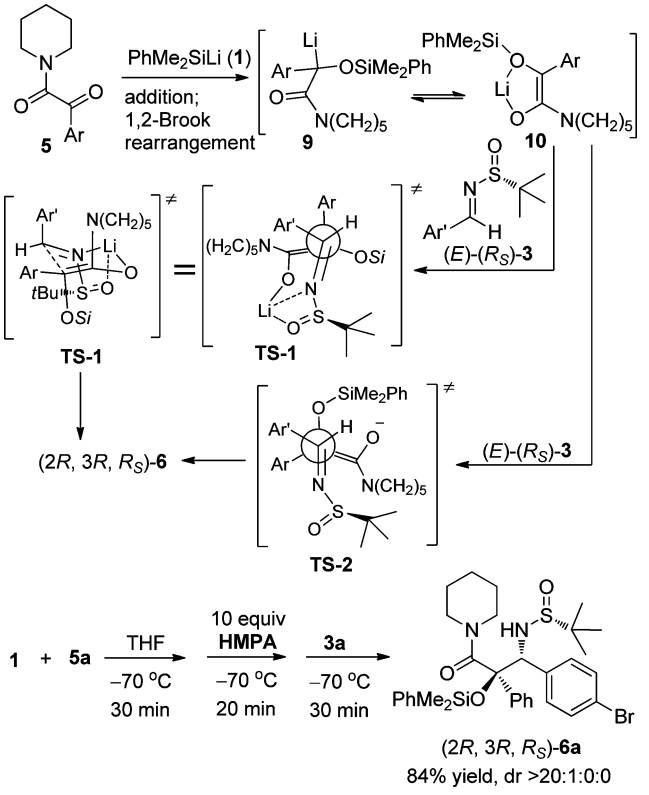
[a]$PhMe_2SiLi$ (0.60 mmol), ketoamide (0.60 mmol), and imine (0.20 mmol) in anhydrous THF under argon at −70 °C unless otherwise noted. [b]Isolated yield. [c]Ratios were determined by ^1H NMR analysis of crude reaction mixtures. [d]2.0 mmol scale (1.28 g scale in the case of **6a**). [e]Product and α-hydroxyamide **8** were inseparable, necessitating silylation of the resulting mixture (using Et_3SiCl/imidazole/DMAP/CH_2Cl_2), followed by column chromatography. [f]$Ph_2MeSiLi$ was used.

Purifying products **6g**, **6h**, or **6r** via silica gel column chromatography proved impossible because their R_f values are identical to those of α-hydroxy amide **8**. We managed to achieve complete removal of **8** by using Et_3SiCl/imidazole/DMAP/CH_2Cl_2 to silylate it in the mixture obtained from the first column chromatography, after which we performed a second column chromatography. Purifying **6y** required the same procedure.

We propose the following mechanism for the three-component coupling (Scheme 3): addition of silyllithium reagents to α-ketoamides and subsequent 1,2-Brook rearrangement generate the α-silyloxy (*Z*)-enolates[19] **10**, which are trapped by (*E*)-(R_S)-*tert*-butanesulfinylimines **3** via a well-known Ellman's chairlike 6/4-membered bicyclic transition state[20] **TS-1** to afford the (2*R*,3*R*,R_S)-products. We also envisioned the possibility of a nonbonding transition state **TS-2**, in which nonbonding interactions among the *t*-BS group

DOI: 10.1021/acs.orglett.6b00006
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Plausible Models of Stereoselection and a Control Experiment

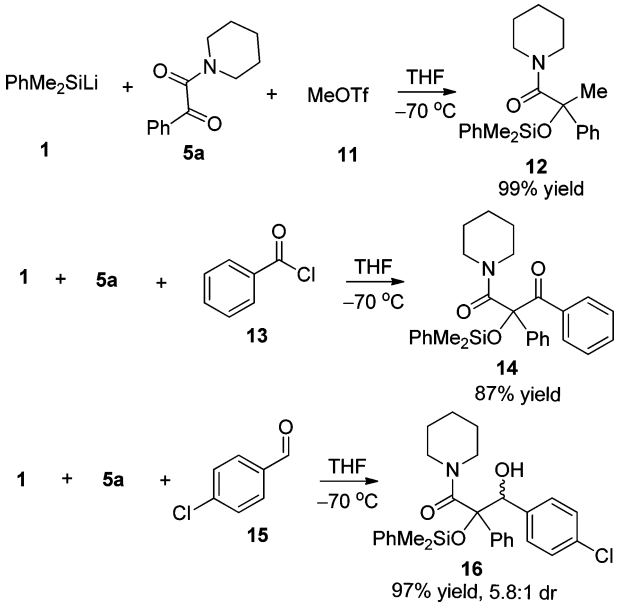


of the imine and the silyloxy and amide groups of the enolate are minimized. In the case of **TS-2**, imine attack on the *Si* face predominates to avoid repulsion between the enolate and *tert*-butyl groups of *t*-BS. A control experiment supports the rationality of **TS-2**: the same diastereomer **6a** was obtained in high yield with excellent dr with or without the addition of excess HMPA to solvate lithium cations in the reaction of **1** and **5a** before addition of imine **3a** to the reaction mixture (Scheme 2b). Although the proposed transition-state models can explain the observed stereochemical outcomes, why the α-ketoester **2** is associated with such poor diastereocontrol (Scheme 2a) remains unclear.[21]

Finally, we examined the feasibility of using other electrophiles to trap the reactive intermediate generated from the reaction of silyllithium and α-ketoamide. We succeeded in methylating the intermediate using MeOTf, acylating it using BzCl, and causing it to undergo aldol coupling with 4-ClC_6H_4CHO, all in high yield (Scheme 4). Diastereoselectivity was only moderate in the aldol process.

In conclusion, we have developed an efficient method for synthesizing enantioenriched α,α-disubstituted α-hydroxy-β-amino acid derivatives via three-component coupling of silyllithiums, α-ketoamides, and chiral *t*-BS-imines. Use of α-ketoamides ensures high diastereocontrol. These nucleophilic silyl group-triggered reductive couplings of two electrophiles proceed in good yield with high diastereoselectivity, allowing the placement of a silyl group on the oxygen atom of the keto group of α-ketoamides via an addition/1,2-silyl migration cascade.

Scheme 4. Trapping Reactive Intermediates via Methylation, Acylation, and Aldol Reactions



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00006.

Experimental details and characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: clu@ms.xjb.ac.cn.
*E-mail: xuyj@ms.xjb.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21572262, U1403301, and 21372255), the YCSTTC Project of Xinjiang Uygur Autonomous Region (2013711017), the Recruitment Program of Global Experts (Xinjiang Program), and the Director Foundation of XTIPC (2015RC014). Z.S. is grateful for support from The Graduate Innovation Projects of Changji University (2015YJSYB05).

■ REFERENCES

(1) For reviews of β-amino acids: see: (a) Spiteller, P., von Nussbaum, F. β-Amino Acids in Natural Products. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley & Sons: Hoboken, NJ, 2005; p 19. (b) Liu, M.; Sibi, M. *Tetrahedron* **2002**, *58*, 7991. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.

(2) For a recent review of the synthesis of the side chain of taxoids, see: Borah, J. C.; Boruwa, J.; Barua, N. C. *Curr. Org. Synth.* **2007**, *4*, 175.

(3) For selected examples of enantioselective preparation of α-hydroxy-β-amino acid derivatives (or their analogues) via direct coupling of α-hydroxy acid derivatives (or their equivalents) with imines, see: (a) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe,

DOI: 10.1021/acs.orglett.6b00006
Org. Lett. XXXX, XXX, XXX−XXX

L. R. *J. Org. Chem.* **1991**, *56*, 1681. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (c) Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588. (d) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. A. *Org. Lett.* **2008**, *10*, 841.

(4) (a) Guerrini, A.; Varchi, G.; Daniele, R.; Samori, C.; Battaglia, A. *Tetrahedron* **2007**, *63*, 7949. (b) Guerrini, A.; Varchi, G.; Samori, C.; Daniele, R.; Arturo, B. *Tetrahedron Lett.* **2007**, *48*, 5081. (c) Guerrini, A.; Varchi, G.; Battaglia, A. *J. Org. Chem.* **2006**, *71*, 6785. (d) Ha, H.-J.; Ahn, Y.-G.; Woo, J.-S.; Lee, G. S.; Lee, W. K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1667. For representative examples of nonenantioselective version, see: (e) Clerici, A.; Pastori, N.; Porta, O. *J. Org. Chem.* **2005**, *70*, 4174. (f) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955.

(5) (a) Lu, C.-D.; Liu, H.; Chen, Z.-Y.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2005**, *7*, 83. (b) Huang, H.; Guo, X.; Hu, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337. (c) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (d) Qian, Y.; Jing, C.; Ji, J.; Tang, M.; Zhou, J.; Zhai, C.; Hu, W. *ChemCatChem* **2011**, *3*, 653. (e) Guo, X.; Hu, W. *Acc. Chem. Res.* **2013**, *46*, 2427.

(6) (a) Jiang, J.-L.; Yao, M.; Lu, C.-D. *Org. Lett.* **2014**, *16*, 318. (b) Lin, C.-Y.; Ma, P.-J.; Sun, Z.; Lu, C.-D.; Xu, Y.-J. *Chem. Commun.* **2016**, *52*, 912.

(7) For reviews of Brook rearrangement and its synthetic applications, see: (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (d) Boyce, G. R.; Greszler, S. N.; Johnson, J. S.; Linghu, X.; Malinowski, J. T.; Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Steward, K. M. *J. Org. Chem.* **2012**, *77*, 4503. (e) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175.

(8) For selected examples of Brook rearrangement mediated multicomponent coupling to construct diverse building blocks in organic chemistry, see: (a) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294. (b) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 8805. (c) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281. (d) Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689. (e) Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 17393. (f) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930. (g) Smirnov, P.; Mathew, J.; Nijs, A.; Katan, E.; Karni, M.; Bolm, C.; Apeloig, Y.; Marek, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 13717.

(9) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403. (c) Fleming, I. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 257. (d) Weickgenannt, A.; Oestreich, M. *Chem. - Eur. J.* **2010**, *16*, 402.

(10) For recent applications of $PhMe_2SiLi$, see: (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727. (b) Herrmann, A. T.; Martinez, S. R.; Zakarian, A. *Org. Lett.* **2011**, *13*, 3636.

(11) For reactions of $PhMe_2SiLi$ with amides, see: (a) Fleming, I.; Ghosh, U. *J. Chem. Soc., Perkin Trans. 1* **1994**, 257. (b) Fleming, I.; Ghosh, U.; Mack, S. R.; Clark, B. P. *Chem. Commun.* **1998**, *29*, 711. (c) Fleming, I.; Mack, S. R.; Clark, B. P. *Chem. Commun.* **1998**, 713. (d) Buswell, M.; Fleming, I. *ARKIVOC* **2002**, *2002* (vii), 46. (e) Fleming, I.; Russell, M. G. *Chem. Commun.* **2003**, 198. (f) Buswell, M.; Fleming, I. *Chem. Commun.* **2003**, 202. (g) Buswell, M.; Fleming, I.; Ghosh, U.; Mack, S.; Russell, M.; Clark, B. P. *Org. Biomol. Chem.* **2004**, *2*, 3006. (h) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977. For reactions of $PhMe_2SiLi$ with esters, aldehydes, ketones, and nitriles, see ref 11a and: (i) Chenede, A.; Abd.Rahman, N.; Fleming, I. *Tetrahedron Lett.* **1997**, *38*, 2381. (j) Saito, S.; Shimada, K.; Yamamoto, H.; Martinez de Marigorta, E.; Fleming, I. *Chem. Commun.* **1997**, 1299. (k) Fleming, I.; Marangon, E.; Roni, C.; Russell, M. G.; Taliansky Chamudis, S. *Chem. Commun.* **2003**, 200. (l) Fleming, I.; Marangon, E.; Roni, C.; Russell, M. G.; Taliansky Chamudis, S. *Can. J. Chem.* **2004**, *82*, 325. (m) Fleming, I.; Solay, M.; Stolwijk, F. *J. Organomet. Chem.* **1996**, *521*, 121.

(12) For reactions of silyllithium with *tert*-butanesulfinylimines, see: (a) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403. (b) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035. (c) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145. (d) Hernandez, D.; Mose, R.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 732.

(13) For selected reviews of *tert*-butanesulfinylimines and *tert*-butanesulfinamide, see: (a) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(14) For examples of sulfinylimine activation using boron trifluoride etherate, see: (a) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396. (b) Fernandez-Salas, J. A.; Maestro, M. C.; Rodriguez-Fernandez, M. M.; Garcia-Ruano, J. L.; Alonso, I. *Org. Lett.* **2013**, *15*, 1658.

(15) We examined the reactivity of PhCH=NTs and PhCH=NP(O)Ph_2 in coupling with **1** and **5a**; these reactions gave respective yields of 99% and 87%, as well as >20:1 dr. We also tested other amides bearing different secondary amino groups for their ability to react with **1** and **3a**. Replacing the 1-piperidinyl group of **5a** with dimethylamino, 4-morpholinyl, 1-pyrrolidinyl, or diisopropylamino groups resulted in three-component couplings with high yields (80−98%) and respective diastereoselectivities of 7:1:0:0 dr, >20:1:0:0 dr, 8:3:1:0 dr, and 7:1:0:0 dr.

(16) The desilylation product of **6a** was found to be identical to the compound reported in ref 6b.

(17) For reduction of ketones using alkyllithium, see: (a) Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904. For reduction of imines using silyllithium via single-electron transfer, see: (b) Hwu, J. R.; Tseng, W. N.; Patel, H. V.; Wong, F. F.; Horng, D.-N.; Liaw, B. R.; Lin, L. C. *J. Org. Chem.* **1999**, *64*, 2211.

(18) (a) Gilman, H.; Lichtenwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 607. (b) George, M. V.; Peterson, D. J.; Gilman, H. J. *J. Am. Chem. Soc.* **1960**, *82*, 403.

(19) Johnson and co-workers have rigorously documented the preferential formation of (*Z*)-lithium silyloxy enolates in lithium enolate-triggered Brook rearrangements of silyl glyoxylates in: Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944. Also see ref 7d.

(20) (a) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.

(21) A possible reason might be that, compared to esters, acyclic tertiary amides are more likely to form (*Z*)-enolates due to the steric hindrance of nitrogen substituents with the double bond substituent. Minko, Y.; Marek, I. *Chem. Commun.* **2014**, *50*, 12597.

DOI: 10.1021/acs.orglett.6b00006
Org. Lett. XXXX, XXX, XXX−XXX