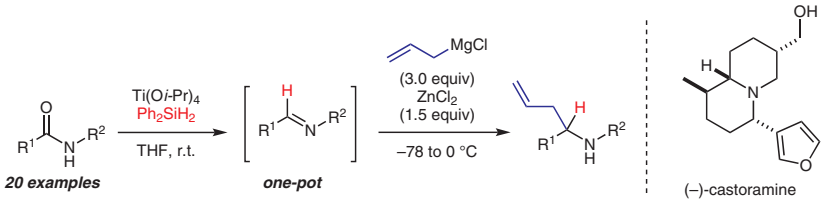
Synlett S. Itabashi et al. Letter

One-Pot Reductive Allylation of Amides by Using a Combination of Titanium Hydride and an Allylzinc Reagent: Application to a Total Synthesis of (–)-Castoramine

Suguru Itabashi
Masashi Shimomura
Manabu Sato
Hiroki Azuma
Kentaro Okano
Juri Sakata
Hidetoshi Tokuyama*

Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba 6-3, Aramaki, Aoba-ku, Sendai, 980-8578, Japan
tokuyama@m.tohoku.ac.jp

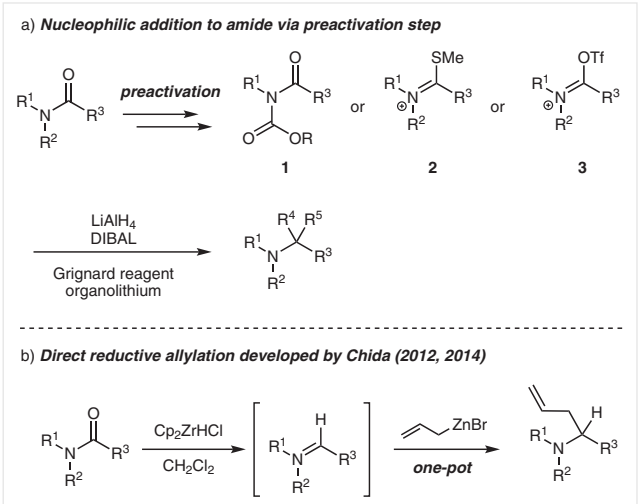


Received: 26.04.2018
Accepted after revision: 29.05.2018
Published online: 26.06.2018
DOI: 10.1055/s-0037-1610435; Art ID: st-2018-u0260-l

Abstract A one-pot direct reductive allylation protocol has been developed for the synthesis of secondary amines by using titanium hydride and an allylzinc reagent. This protocol is applicable to a broad range of substrates, including acyclic amides, benzamides, α,β-unsaturated amides, and lactams. The stereochemical outcome obtained from the reaction with crotylzinc reagent suggested that the allylation reaction proceeds through a six-membered cyclic transition state. A total synthesis of (–)-castoramine was accomplished by following this protocol for the highly stereoselective construction of contiguous stereocenters.

Key words amides, reduction, allylation, amines, total synthesis, alkaloids

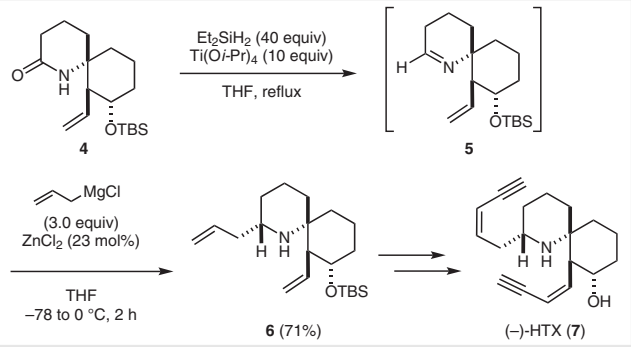
The amide group is a ubiquitous functional group that can be found in natural products, pharmaceutical agents, functional materials, and agrochemicals. In contrast to developments in protocols available for the formation of amides,[1] the conversion of the amide group into other functional groups, particularly amines, has not been thoroughly investigated. The most frequently used transformation of amides into amines is through reduction to the corresponding primary amines with $LiAlH_4$. The conversion into α- or α,α-branched amines by a one-pot sequential nucleophilic addition of a hydride anion and a carbon nucleophile is not straightforward due to the low nucleophilicity of the starting amides and the imine intermediates, together with the challenging control of each step of the reaction. To facilitate the nucleophilic addition to amides, preactivation of the starting amides as an imide **1**, thioamide **2**, or iminium triflate **3**, and the use of highly reactive nucleophiles such as DIBAL, $LiAlH_4$, Grignard reagents, or organolithium reagents are generally required (Scheme 1a).[2–4] Recently, Chida, Sato, and their co-workers reported a direct conversion of tertiary and secondary amides into α-allylated amines by using Schwartz's reagent and allylzinc halides; this method exhibited superior chemoselectivity to previously reported methods (Scheme 1b).[5–7] Currently, there is no useful method, in terms of functional-group compatibility and practical utility, for the large-scale conversion of amides into amines, and the development of an efficient protocol is still required.



Scheme 1 Conversion of amides into α-branched amines

During the course of our recent total synthesis of (–)-histrionicotoxin (HTX; **7**), we obtained preliminary results on a one-pot reductive allylation of a nonactivated secondary amide (Scheme 2).[8] In following Buchwald's protocol, the spirocyclic lactam **4** was exposed to titanium hydride, generated from Ti(O-*i*-Pr)$_4$(10 equiv) and diethylsilane (40 equiv), to give the partially reduced imine intermediate **5**;[9,10] subsequent allylation under Ishihara's conditions af-

forded the homoallylic amine **6** in a one-pot process (71%).[11,12] In the present study, this preliminary one-pot sequence was reinvestigated in detail for the optimization of both the selective partial reduction to the imine and the allylation, and its scope and limitations were explored. Here, we report the practical and chemoselective one-pot reductive allylation of nonactivated amides by using a combination of titanium hydride and an allylzinc reagent, and its application to a total synthesis of (–)-castoramine.



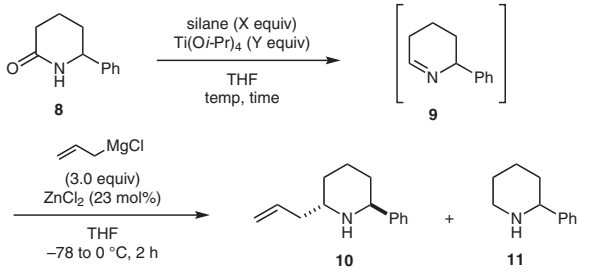
Scheme 2 Results of our previous studies

Initially, we investigated the optimization of the reduction conditions,[13] and the resultant imine was subsequently allylated under the conditions that were used for the synthesis of HTX (Table 1).[9] The reaction of the model substrate **8** with diethylsilane (40 equiv) and Ti(O-*i*-Pr)$_4$(10 equiv) gave the desired product **10** in 35% yield as a single diastereomer,[14] together with the over-reduction product **11** in 28% yield (Table 1, entry 1).

A series of experiments were then performed in an attempt to prevent the overreduction of **8**. Decreasing the amount of reducing agent proved ineffective (Table 1, entry 2), whereas lowering the reaction temperature suppressed the initial reduction (entry 3). By further screening, we found that the use of diphenylsilane was key to the suppression of the overreduction. When substrate **8** was treated with Ti(O-*i*-Pr)$_4$(1.5 equiv) and diphenylsilane (5 equiv), the reduction of lactam **8** reached completion even at room temperature, and the yield of **10** dramatically increased to 71%, along with a trace amount of the fully reduced amine **11** (entry 4). A further decrease in the amount of Ph_2SiH_2 was ineffective (entries 5 and 6), whereas the silanes Et_3SiH (entry 7) and Ph_3SiH (entry 8) did not promote the initial reduction at all.

With the optimal reduction conditions in hand, we next searched for a suitable allylating reagent (Table 2). The reaction with a zinc reagent freshly prepared from allylmagnesium chloride and $ZnCl_2$ (2:1) afforded the desired product **10** in a higher yield (Table 2, entry 2) than that obtained under the original conditions using a lower amount of $ZnCl_2$ (23 mol%) (entry 1). In the absence of $ZnCl_2$, the reaction

Table 1 Optimization of the Reduction Conditions

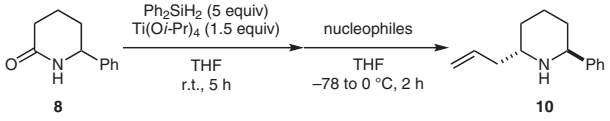


Entry	Silane	X[a]	Y[b]	Temp	Time (h)	Product [Yield[c,d] (%)]
1	Et_2SiH_2	40	10	reflux	1	**10** (35) **11** (28)
2	Et_2SiH_2	5	1.5	reflux	5	**10** (40) **11** (28)
3	Et_2SiH_2	5	1.5	r.t.	8	no reaction
4	Ph_2SiH_2	5	1.5	r.t.	5	**10** (71) **11** (6)
5	Ph_2SiH_2	3	1.5	r.t.	40	**10** (50) **11** (10)
6	Ph_2SiH_2	1	1.5	r.t.	96	no reaction
7	Et_3SiH	5	1.5	r.t.	22	no reaction
8	Ph_3SiH	5	1.5	r.t.	22	no reaction

[a] Equivalents of the silane.
[b] Equivalents of Ti(O-*i*-Pr)$_4$.
[c] In all cases, amine **10** was obtained as a single diastereomer.
[d] Isolated yield.

with allylmagnesium chloride gave product **10** in a slightly lower yield (entry 3), whereas allylzinc bromide did not give **10** at all (entry 4). Finally, allylpinacol boronate gave

Table 2 Optimization of the Allyl Nucleophile

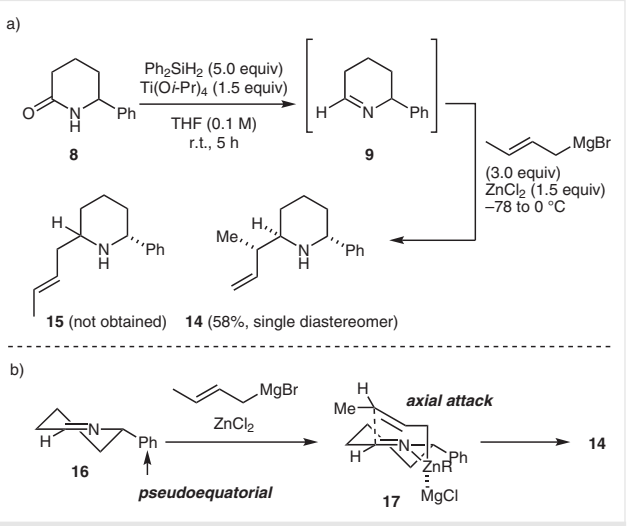


Entry	Nucleophiles	Yield[a,b] (%) of **10**
1	AllMgCl (3.0 equiv), $ZnCl_2$ (23 mol%)	71
2	AllMgCl (3.0 equiv), $ZnCl_2$ (1.5 equiv)	74[c]
3	AllMgCl (1.5 equiv)	56
4	AllZnBr (1.5 equiv)	0
5[d]	AllB(pin) (1.5 equiv)	66
6[d]	AllTMS (1.5 equiv), $TiCl_4$ (1.5 equiv)	0
7[d]	$AllSnBu_3$ (1.5 equiv), $Sc(OTf)_3$ (1.5 equiv)	0

[a] In all cases, amine **10** was obtained as a single diastereomer.
[b] Isolated yield.
[c] Amine **11** was obtained in 3% yield.
[d] Reaction temperature 25 °C.

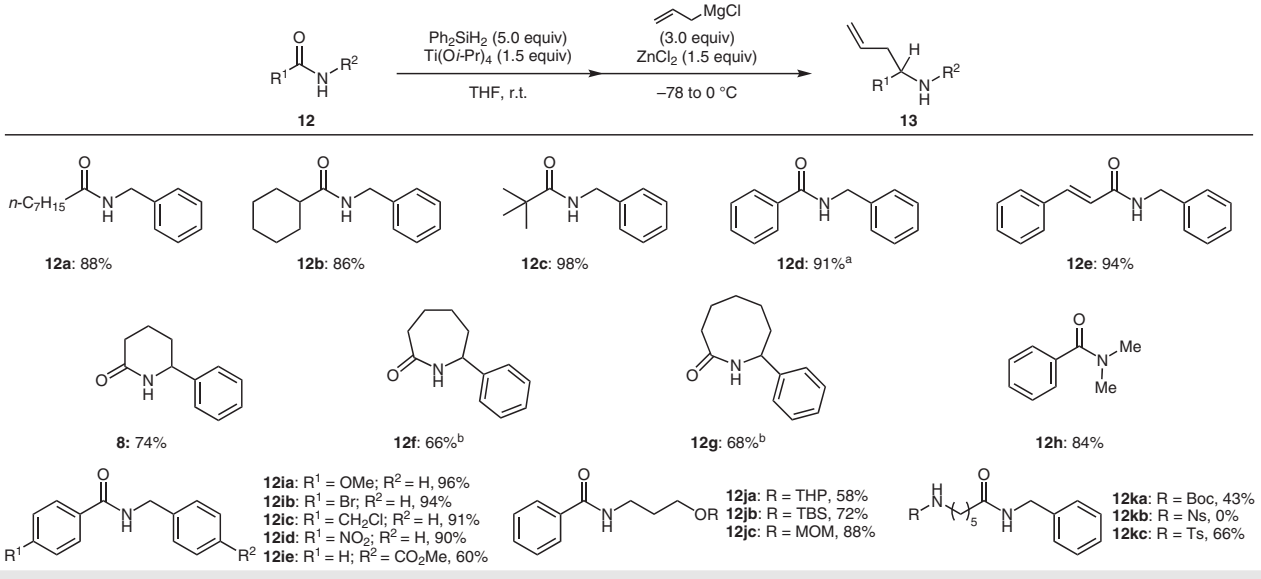
product **10** in a comparable yield (66%; entry 5), whereas allylsilane or allylstannane with Lewis acids proved unsuccessful (entries 6 and 7).

Having established the optimal conditions, we then investigated the generality, scope, and limitations of the method (Scheme 3).[15] A variety of benzylic amides derived from aliphatic or aromatic carboxylic acids **12a–d** were allylated in good to almost quantitative yield. The protocol was also practical and applicable to a gram-scale reaction. Thus, amide **12d** (1.0 g) was converted into the desired allylated compound in 91% yield without such precautions as the use of a glovebox to completely exclude oxygen or moisture.[16] In the case of the cinnamyl amide **12e**, no byproduct stemming from 1,4-reduction was observed. The reductive allylation proceeded smoothly for the six- to eight-membered lactam compounds **8**, **12f**, and **12g**.[17,18] We found that the present method was also applicable to the tertiary amide **12h** (84%). Furthermore, a number of functional groups were compatible with the one-pot allylation protocol. In addition, the electron-rich *N*-benzyl-4-methoxybenzamide (**12ia**) and the electron-deficient *N*-benzyl-4-bromobenzamide (**12ib**) and *N*-benzyl-4-(chloromethyl)benzamide (**12ic**) gave the corresponding products in excellent yields (96, 94, and 91%, respectively). Interestingly, despite bearing a sensitive nitro group, benzamide **12id** tolerated the reaction conditions, giving a 90% yield of the allylated product. Moreover, the aromatic methyl ester group in **12ie** remained intact during the chemoselective reduction and allylation (product yield: 60%). Various protecting groups for alcohols, including THP (**12ja**, 58%), TBS (**12jb**, 72%), and MOM (**12jc**, 88%) were also tolerated, as were two protecting groups for nitrogen, Boc carbamate **12ka** and Ts amide **12kc**, which gave the corresponding allylated compounds in low to good yields.



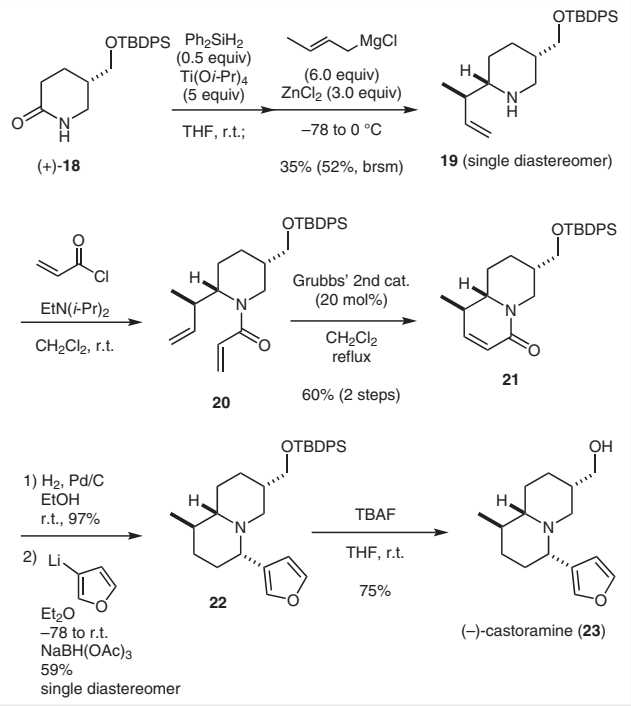
Scheme 4 Rationale for the observed stereoselectivity

To obtain some mechanistic insights into the allylation step, the reaction with a crotylzinc reagent was examined. Thus, crotylation of the imine intermediate **9** proceeded in a highly diastereoselective manner to give the branched product **14** exclusively in 58% yield Scheme 4a,[19] which strongly suggests the formation of a six-membered chair-like transition state on the half-chair conformation of the initially formed imine intermediate **16**. The axial attack by the crotylzinc reagent must occur via the six-membered transition state **17** to form the branched product **14** stereospecifically Scheme 4b.



Scheme 3 Generality, scope, and limitations of the reductive allylation [a] Gram-scale reaction. [b] Obtained as single diastereomer.

To demonstrate the utility of this highly diastereoselective reductive allylation protocol, we chose (–)-castoramine (**23**) as a target compound and we examined its synthesis (Scheme 5).[20] The reaction of lactam (+)-**18**[21] with Ti(O-*i*-Pr)$_4$ (5.0 equiv) and diphenylsilane (0.5 equiv), followed by addition of the crotylzinc reagent, resulted in the expected partial reduction to yield product **19** with perfect stereoselectivity.[22] The facial selectivity of the crotylation was completely controlled by the siloxymethyl group on the piperidine ring. Crotylation of **19** followed by ring-closing metathesis then gave the cyclic product **21**. After reduction of the double bond, a 3-furyl moiety was introduced by following Shenvi's procedure to give **22** in 59% yield as a single diastereomer.[23] Finally, removal of the TBDPS group afforded (–)-castoramine (**23**), whose physical properties were in agreement with the reported data.[20c]



Scheme 5 Application to the total synthesis of (–)-castoramine

In summary, we have established a highly chemoselective, one-pot, direct reductive allylation of a variety of secondary amides by using titanium hydride and a diallylic zinc reagent. The utility of this protocol was demonstrated by performing a stereocontrolled total synthesis of (–)-castoramine.

Funding Information

This work was financially supported by KAKENHI (16H01127, 16H00999, 26253001, 18H02549, 18H04231, 18H04379, 18K18462) and Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP18am0101100.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610435.

References and Notes

(1) For selected recent reviews on amide formation, see: (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447. (c) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (d) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (e) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (f) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (g) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453. (h) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714.

(2) For a review on nucleophilic addition to amides, see: Pace, V.; Holzer, W.; Olofsson, B. *Adv. Synth. Catal.* **2014**, *356*, 3697.

(3) For a review and a recent example through a thioamide, see: (a) Murai, T.; Mutoh, Y. *Chem. Lett.* **2012**, *41*, 2. (b) Murai, T.; Mutoh, N. *J. Org. Chem.* **2016**, *81*, 8131.

(4) For recent examples through iminium triflates, see: (a) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J.; Wang, Y.; Xia, X.-E. *J. Org. Chem.* **2015**, *80*, 2861. (b) Wang, A.-E.; Yu, C.-C.; Chen, T.-T.; Liu, Y.-P.; Huang, P.-Q. *Org. Lett.* **2018**, *20*, 999. (c) Chen, H.; Ye, J.-L.; Huang, P.-Q. *Org. Chem. Front.* **2018**, *5*, 943.

(5) (a) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950. (b) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. *Chem. Eur. J.* **2014**, *20*, 17565.

(6) For examples of direct reductive nucleophilic additions to amides by using Vaska's complex, see: (a) Xie, L.-G.; Dixon, D. J. *Chem. Sci.* **2017**, *8*, 7492. (b) Fuentes de Arriba, Á. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3655.

(7) For direct reductive nucleophilic additions to *N*-alkoxy amides, see: (a) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6369. (b) Yanagita, Y.; Nakamura, H.; Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Chem. Eur. J.* **2013**, *19*, 678. (c) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 512. (d) Sato, T.; Chida, N. *Org. Biomol. Chem.* **2014**, *12*, 3147. (e) Nakajima, M.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 1696. (f) Fukami, Y.; Wada, T.; Meguro, T.; Chida, N.; Sato, T. *Org. Biomol. Chem.* **2016**, *14*, 5486.

(8) When spirocyclic lactam **4** was treated with the Schwartz reagent, a fully reduced amine was detected as the major product.

(9) Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 1087.

(10) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515.

(11) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.

(12) For an example of a titanium hydride-mediated one-pot partial reduction/intramolecular Henry reaction of a tertiary amide, see: Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482.

(13) For details of the preparation of lactam **8**, see the Supporting Information.

(14) The relative stereochemistry (*trans*) of compound **10** was determined after conversion to the known compound; see the Supporting Information.

(15) The conditions of Table 2, entry 2 gave the allylated compounds in higher yields than those of Table 2, entry 1. For instance, the latter conditions gave **13a** (62%), **13b** (54%), **13ie** (0%), **13ka** (31%), and **13kc** (53%).

(16) ***N*-Benzyl-1-phenylbut-3-en-1-amine (13d): Gram-Scale Synthesis**

A 1.0 M solution of allylmagnesium chloride in THF (14.2 mL, 14.2 mmol) was added to a suspension of $ZnCl_2$ (1.00 g, 7.35 mmol) in THF (7.7 mL) at r.t., and the mixture was stirred for 1 h at r.t., before being used in the next reaction.

$Ti(O\text{-}i\text{-}Pr)_4$ (2.1 mL, 7.1 mmol) was added to a solution of amide **12d** (1.00 g, 4.74 mmol) and Ph_2SiH_2(4.4 mL, 24 mmol) in THF (47 mL) at r.t., and the mixture was stirred at r.t. for 7.5 h. The mixture was then cooled to –78 °C, and the freshly prepared allylzinc reagent was added at –78 °C. The resulting mixture was warmed to 0 ℃ and stirred at 0 ℃ for 1 h before the reaction was quenched with sat. aq NH_4Cl (100 mL). The mixture was then filtered through a pad of Celite, which was washed with EtOAc (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. The organic solvents were removed under reduced pressure to give a crude material that was purified by column chromatography [silica gel, hexanes–EtOAc (1:1)] to give a colorless oil; yield: 1.02 g (4.31 mmol, 91%); R_f = 0.75 (hexanes–EtOAc, 1:1). IR (neat): 3068, 3028, 2916, 2835, 1455, 1119, 916, 749, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 10 H), 5.76–5.65 (m, 1 H), 5.07 (d, *J* = 17.2 Hz, 1 H), 5.03 (d, *J* = 10.0 Hz, 1 H), 3.71-3.66 (m, 2 H), 3.52 (d, *J* = 13.2 Hz, 1 H), 2.45-2.35 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 140.6, 135.4, 128.34, 128.28, 128.1, 127.3, 127.0, 126.8, 117.5, 61.6, 51.4, 43.0. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{17}H_{20}N$: 238.1590; found: 238.1580.

Spectroscopic data were identical with those reported for this compound (see Ref. 5a).

(17) Four- and five-membered lactams were not suitable substrates for this protocol. Initial reduction of a four-membered lactam did not proceed at all, and in the case of a five-membered lactam, the reduction step was sluggish.

(18) The relative stereochemistry (*trans*) of compound **13f** was determined after conversion into the known compound; see the Supporting Information.

(19) The structure of compound **14** was determined by NOE experiments after several transformations; see the Supporting Information.

(20) For the isolation, see: (a) Valenta, Z.; Khaleque, A. *Tetrahedron Lett.* **1959**, *1*, 1(12): 1. For total syntheses, see: (b) Bohlmann, F.; Winterfeldt, E.; Laurent, H.; Ude, W. *Tetrahedron* **1963**, *19*, 195. (c) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207.

(21) For the preparation of amide **18**, see the Supporting Information.

(22) Under the optimal conditions, we obtained compound **19** (19%) together with a considerable amount of the over-reduced amine (18%).

(23) Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209.