Synthetic Methods

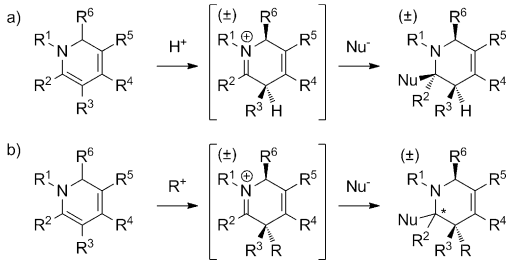
DOI: 10.1002/ange.201310517

Regio- and Stereoselective 1,2-Dihydropyridine Alkylation/Addition Sequence for the Synthesis of Piperidines with Quaternary Centers**

*Simon Duttwyler, Shuming Chen, Colin Lu, Brandon Q. Mercado, Robert G. Bergman, and Jonathan A. Ellman**

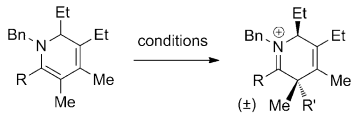
Abstract: *The first example of C alkylation of 1,2-dihydropyridines with alkyl triflates and Michael acceptors was developed to introduce quaternary carbon centers with high regio- and diastereoselectivity. Hydride or carbon nucleophile addition to the resultant iminium ion also proceeded with high diastereoselectivity. Carbon nucleophile addition results in an unprecedented level of substitution to provide piperidine rings with adjacent tetrasubstituted carbon atoms.*

Piperidines are valuable and prevalent substructures in biologically active natural products and in medicines which have been enormously important in managing disease.[1–3] As an entry to this important class of compounds, a number of powerful methods for the synthesis of 1,2-dihydropyridines have been developed.[4,5] In this context, we previously disclosed an approach to rapidly assemble highly substituted 1,2-dihydropyridines by a rhodium(I)-catalyzed C–H alkenylation/electrocyclization cascade from readily available α,β-unsaturated imines and alkynes.[6] We have also recently described that these 1,2-dihydropyridine products are versatile intermediates for the preparation of highly substituted tetrahydropyridines by regio- and diastereoselective protonation with subsequent hydride or carbon nucleophile addition (Scheme 1 a).[7–9] Herein, we demonstrate that C alkylation of 1,2-dihydropyridines, a reaction which to our knowledge has not previously been reported, can be achieved with alkyl triflates and Michael acceptors with high regio- and diastereoselectivity to provide quaternary carbon centers within the piperidine core (Scheme 1 b).[10–12] Moreover, reduction or carbon nucleophile addition to the resultant iminium ion can also be accomplished with high diastereoselectivity. In the case of carbon nucleophile addition, an unprecedented level of substitution is achieved to provide piperidine rings with adjacent tetrasubstituted carbon atoms.



Scheme 1. a) Previously reported 1,2-dihydropyridine protonation and nucleophilic addition sequence. b) Transformation developed in this study: Reaction with carbon electrophiles (R^+) followed by addition of hydride or carbon nucleophiles.

Table 1: Optimization of dihydropyridine alkylation conditions.



1 2

Entry	R	R′X	Solvent	*t* [h]	d.r.[a]	Conv. [%][b]
1	Me	MeOTf	toluene	16	–	>95
2	Me	EtOTf	toluene	14	>95	>95
3	H	MeOTf	toluene	18	–	>95
4	Me	MeOTf	CH_2Cl_2	1.5	–	>95
5	Me	EtOTf	CH_2Cl_2	1.5	>95	>95
6	H	MeOTf	CH_2Cl_2	1.5	–	>55
7	H	EtOTf	CH_2Cl_2	1.5	>95	>95
8	Me	BnCl	CH_2Cl_2	16	n.d.	<5
9	Me	BnBr	CH_2Cl_2	16	n.d.	<5
10[c]	Me	BnBr	CH_2Cl_2	2	>90	>95

[a] Where applicable, the reaction d.r. value was determined by ^{1}H NMR analysis. [b] The reaction conversion was established by ^{1}H NMR analysis. [c] With $ZrCl_4$ as a Lewis acid additive, −78 °C to RT.

We initially explored the addition of methyl iodide and dimethyl sulfate to the dihydropyridine **1** (R = Me; Table 1). However, methylation was not observed using a variety of solvents such as THF, toluene, and CH_2Cl_2 even with heating to 60 °C in a sealed reaction vessel (data not shown). We consequently evaluated the considerably more reactive methyl triflate, which resulted in complete conversion into the methylated iminium product at room temperature (entry 1). Successful alkylation with ethyl triflate demonstrated that less-reactive alkylating agents also couple efficiently (entry 2). Moreover, ethylation established that the reaction proceeds with very high diastereoselectivity. To

[*] S. Duttwyler, S. Chen, C. Lu, B. Q. Mercado, Prof. Dr. J. A. Ellman
Department of Chemistry, Yale University
225 Prospect St., New Haven, CT 06520 (USA)
E-mail: jonathan.ellman@yale.edu
Prof. Dr. R. G. Bergman
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720-1416 (USA)
and
Lawrence Berkeley National Laboratory
1 Cyclotron Road, Berkeley, CA 94720 (USA)

[**] This work was supported by the NIH Grant GM069559 (to J.A.E.). R.G.B. acknowledges funding from the DOE, DE-AC02-05CH11231.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201310517.

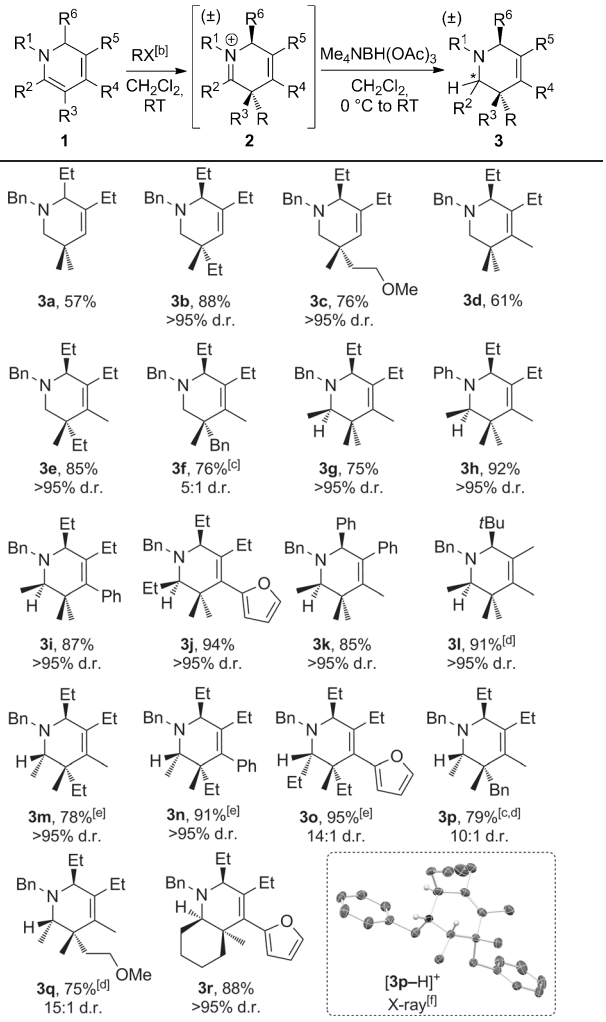
further test the generality of the alkylation protocol, the reactivity of **1**, where R = H, was investigated because it results in a more highly destabilized aldiminium product (entry 3). While generally complete and stereoselective alkylation was observed in toluene with a 14–18 h reaction time, at shorter reaction times using CH_2Cl_2 as the solvent proved to be more effective (entry 4–7). Given the instability of benzyl triflates, benzyl chloride and bromide were instead evaluated, but no alkylation was observed for either reagent (entries 8 and 9). Lewis-acid-mediated activation of benzyl bromide was therefore investigated, with $ZrCl_4$ providing the benzylated product in greater than 95% conversion within 2 hours at −78 °C to room temperature, and with good diastereoselectivity (entry 10).

With the feasibility of the key alkylation step established, we next focused on the preparation of the desired tetrahydropyridines **3** by reduction of the reactive iminium ion **2** (Table 2). We first explored the alkylation/reduction sequence for the 1,2-dihydropyridines **1**, which are unsubstituted at the R^2 position (R^2 = H), because this avoids introducing a stereocenter in the reduction step. After alkylation, $Me_4NBH(OAc)_3$ served as a mild and inexpensive reducing agent for the synthesis of the tetrahydropyridines **3a–f** in good to high overall yields. Notably, in the key alkylation step, methyl (**3a** and **3d**), ethyl (**3b** and **3e**), functionalized 2-methoxyethyl (**3c**), and benzyl (**3f**) groups were all successfully incorporated. The overall yields for the methylation products **3a** and **3d** were somewhat lower than for the other electrophiles because of competitive methylation at nitrogen when R^2 = H. However, for all of the other alkylating agents, which are less reactive than methyl triflate, no alkylation at nitrogen was detected and high diastereoselectivities were observed. For ethylation (**3b** and **3e**) and 2-methoxyethylation (**3c**), only a single diastereomer was obtained. Alkylation consistently occurs opposite to the R^6 group as rigorously established by X-ray structural analysis of **3e** as well as for multiple other alkylation products (**3g, 3m**, **3n**, **3p**, **6d**, and **6g**).[13] The Lewis-acid-mediated benzylation provided a more modest 5:1 ratio (**3f**).

We next investigated the alkylation/reduction sequence for 1,2-dihydropyridines substituted at the R^2 position, which introduces added complexity because a stereocenter is generated in the reduction step (**3g–r**; Table 2). The sequence was first performed by methylating the dihydropyridines **1**, where R^3 = Me, such that a stereocenter is only introduced in the reduction step (**3g–l**). In all cases only a single diastereomer was produced as determined by ^{1}H NMR analysis. Hydride addition opposite the R^6 group was rigorously established for **3g** by X-ray structural analysis and is consistent with the face selectivity observed for reduction in our previously reported protonation/reduction sequence.[7] The methylation/reduction sequence proceeded in excellent overall yields for a range of substituents with diverse steric and electronic properties (75–94%). For the R^1 group on the nitrogen atom both N benzyl (**3g**) and the comparatively deactivating N phenyl (**3h**) group provided high yields. The R^4 position could be substituted with alkyl (**3g**, **h**, **k**, and **l**), phenyl (**3i**), and furanyl (**3j**) groups, while alkyl and phenyl groups could be used for both R^5 and R^6 groups (**3g** versus **3k**). A 91% yield was observed when R^6 was a *tert*-butyl group (**3l**), although reduction with K(*i*PrO)$_3$BH at −78 °C instead of $Me_4NBH(OAc)_3$ at 0 °C was necessary to achieve high selectivity.

For the products **3m–r**, two stereocenters are introduced, the first in the alkylation step and the second in the reduction step. High overall yields and good stereoselectivities were observed for methylation (**3r**), ethylation (**3m** to **3o**), benzylation (**3p**), and introduction of the 2-methoxyethyl group (**3q**). Moreover, different R^2–R^4 groups were tolerated, including a bicyclic dihydropyridine which resulted in the *cis*-fused product **3r**. However, to achieve high reduction stereoselectivity for many of these substrates, it was necessary

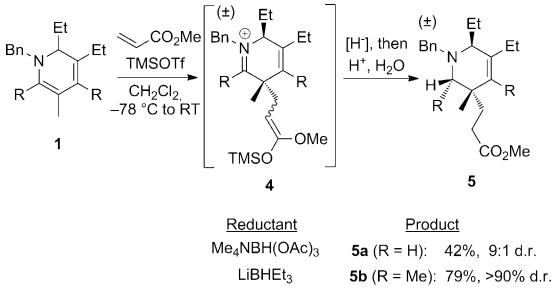
Table 2: One-pot dihydropyridine alkylation and reduction.[a]



[a] Yields are those of products isolated after purification by chromatography. Diastereoselectivities were determined by NMR analysis. [b] Unless otherwise indicated, alkylation was performed with the corresponding triflate (1.5–2 equiv). [c] Benzylation was accomplished using BnBr (2.5 equiv) and $ZrCl_4$ (1.7 equiv) at −78 °C with warming to RT. [d] Reduction was performed by addition of K(*i*PrO)$_3$BH in THF at −78 °C with warming to RT. [e] Reduction was performed by addition of $LiEt_3BH$ in THF at −78 °C with warming to RT. [f] For details and other crystal structures unequivocally establishing relative configurations of the products, see Figures S1–S7 in the Supporting Information.

to use more-reactive hydride reagents at −78 °C. In particular, for **3m–o**, reduction with $LiBEt_3H$ was optimal, and for **3l, 3p**, and **3q**, reduction with $K(iPrO)_3BH$ proved to be the most effective. The relative configurations of the two newly formed stereocenters were rigorously determined by X-ray structural analysis for the ethylation/reduction products **3m** and **3n** and the benzylation/reduction product **3p**.[13] These X-ray structures establish that upon introducing alkyl groups (R) larger than a methyl group, steric interactions, which result from the newly formed and adjacent quaternary stereocenter, control the face selectivity of reduction rather than the more distant R^6 substituent.

Michael additions to α,β-unsaturated esters were explored to introduce the ester group as a versatile functionality for further elaboration (Scheme 2). Direct addition of the



Reductant	Product
$Me_4NBH(OAc)_3$	**5a** (R = H): 42%, 9:1 d.r.
$LiBHEt_3$	**5b** (R = Me): 79%, >90% d.r.

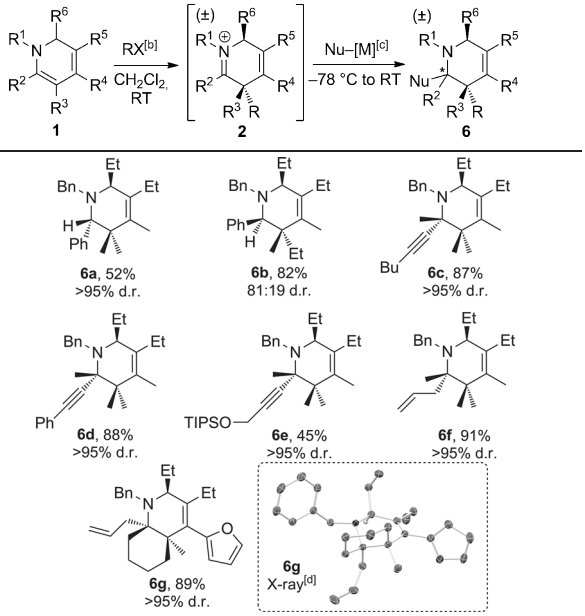
Scheme 2. Michael addition of dihydropyridines to methyl acrylate.

dihydropyridine to methyl acrylate did not proceed, but after evaluating a variety of Lewis acids, we established that TMSOTf results in high conversion into the silyl enol ether intermediate **4** as an approximately 1:1 *E*/*Z* isomer mixture. To obtain the tetrahydropyridine **5a**, reduction with $Me_4NBH(OAc)_3$ was most effective, while for **5b** $LiBHEt_3$ provided the highest diastereoselectivity and overall yield.

We next investigated the addition of carbon nucleophiles rather than hydride (Table 3). We first evaluated additions to the 1,2-dihydropyridines **1** unsubstituted at the R^2 position, because the iminium intermediate that is generated upon alkylation lacks α-hydrogen atoms and therefore cannot undergo competitive α-deprotonation. For these substrates phenyl Grignard adds cleanly to give **6a** and **6b**, with the yield for **6a** being somewhat lower because of the competitive N methylation of the dihydropyridine in the alkylation step (see previous discussion for **3a** and **3d**). While high diastereoselectivity was observed for **6a**, an attenuated 81:19 selectivity was observed for **6b**.

The remaining carbon nucleophile addition products (**6c–g**) were prepared from 1,2-dihydropyridines having carbon substituents as R^2, and results in adjacent tetrasubstituted stereocenters being introduced in the alkylation/nucleophilic addition sequence. Each of these substrates has the potential for competitive α-deprotonation in the carbon nucleophile addition step. For this reason, less basic and more covalent organometallic reagents were more effective. Phenyl-, alkyl-, and silyloxymethyl-substituted alkynyl Grignard reagents all added diastereoselectively and in good yields (**6a–e**).[14] Allyl cerium reagents also added in high yields and with excellent

Table 3: One-pot dihydropyridine alkylation and carbon nucleophile addition.[a]



[a] Yields are those of products isolated after purification by chromatography. Diastereoselectivities were determined by NMR analysis. [b] Alkylation was performed with the corresponding triflate (1.5–2 equiv). [c] PhMgBr in ether (7 equiv) was used to prepare **6a** and **6b**. AlkynylMgCl in ether (6–9 equiv) was used to prepare **6c–e**. Allylcerium chloride in THF (9 equiv) was used to prepare **6f** and **6g**. [d] For details and other crystal structures unequivocally establishing relative configurations of the products, see Figures S1–S7.

diastereoselectivities (**6f,g**),[15] including for the preparation of the *cis*-fused bicyclic piperidine **6g** with tetrasubstituted carbon atoms at the two bridgehead positions. Finally, X-ray structural analysis of **6d** and **6g**[13] establishes that when the alkylation step introduces a stereocenter the face selectivity for nucleophilic attack is controlled by steric interactions at this adjacent quaternary site and is consistent with that previously observed in the alkylation/reduction sequence.

In conclusion, a 1,2-dihydropyridine alkylation/nucleophile addition sequence has been developed and proceeds in good yields and with high levels of regio- and diastereoselectivity to provide piperidine derivatives with unprecedented levels of substitution, including products with adjacent tetrasubstituted ring carbon atoms. Because the 1,2-dihydropyridine starting materials are prepared in one step from simple precursors by a tandem C–H alkenylation/electrocyclization reaction cascade, the described alkylation/nucleophile addition sequence provides rapid access to densely substituted piperidines which would be extremely difficult to prepare by alternative methods.

Received: December 4, 2013
Published online: March 6, 2014

Keywords: alkylation · diastereoselectivity · heterocycles · reduction · synthetic methods

[1] For an analysis of the prevalence of piperidines in drugs, see: a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451 – 3479.

[2] The structural features of piperidines are consistent with renewed emphasis on the development of drug candidates having increased saturation and nonplanar display of functionality. See: a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752 – 6756; b) W. P. Walters, J. Green, J. R. Weiss, M. A. Murcko, *J. Med. Chem.* **2011**, *54*, 6405 – 6416; c) T. J. Ritchie, S. J. F. Macdonald, *Drug Discovery Today* **2009**, *14*, 1011 – 1020.

[3] For general reviews on piperidines, see: a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139 – 165; b) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701 – 1729; c) A. Mitchenson, A. Nadin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862 – 2892; d) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781 – 1813.

[4] For reviews on the synthesis and applications of 1,2-dihydropyridines, see: a) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642 – 2713; b) E. M. P. Silva, P. A. M. M. Varandas, A. M. S. Silva, *Synthesis* **2013**, 3053 – 3089; c) K. Tanaka, K. Fukase, S. Katsumura, *Synlett* **2011**, 2115 – 2139.

[5] For recent methods for the synthesis of 1,2-dihydropyridines, see: a) H. Mizoguchi, H. Oikawa, H. Oguri, *Nat. Chem.* **2014**, *6*, 57 – 64; b) S. T. Chau, J. P. Lutz, K. Wu, A. G. Doyle, *Angew. Chem.* **2013**, *125*, 9323 – 9326; *Angew. Chem. Int. Ed.* **2013**, *52*, 9153 – 9156; c) T. Yamakawa, N. Yoshikai, *Org. Lett.* **2013**, *15*, 196 – 199; d) K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 3699 – 3702; e) M. Amatore, D. Leboeuf, M. Malacria, V. Gandon, C. Aubert, *J. Am. Chem. Soc.* **2013**, *135*, 4576 – 4579; f) C. Nadeau, S. Aly, K. Belyk, *J. Am. Chem. Soc.* **2011**, *133*, 2878 – 2880; g) S. B. D. Jarvis, A. B. Charette, *Org. Lett.* **2011**, *13*, 3830 – 3833.

[6] D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645 – 3651.

[7] a) S. Duttwyler, C. Lu, A. L. Rheingold, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 4064 – 4067; b) S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman, J. A. Ellman, *Science* **2013**, *339*, 678 – 682; c) M. A. Ischay, M. K. Takase, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2013**, *135*, 2478 – 2481.

[8] For reviews on tetrahydropyridines, see: a) N. N. Mateeva, L. L. Winfield, K. K. Redda, *Curr. Med. Chem.* **2005**, *12*, 551 – 571; b) F. X. Felpin, J. Lebreton, *Curr. Org. Synth.* **2004**, *1*, 83 – 109.

[9] For recent methods for the preparation of highly substituted tetrahydropyridines, see: a) T. J. Martin, T. Rovis, *Angew. Chem.* **2013**, *125*, 5476 – 5479; *Angew. Chem. Int. Ed.* **2013**, *52*, 5368 – 5371; b) F. Shi, W. Tan, R.-Y. Zhou, G.-J. Xing, S.-J. Tu, *Adv. Synth. Catal.* **2013**, *355*, 1605 – 1622; c) X. Li, Y. Zhao, H. Qu, Z. Mao, X. Lin, *Chem. Commun.* **2013**, *49*, 1401 – 1403; d) G. Lemonnier, A. B. Charette, *J. Org. Chem.* **2012**, *77*, 5832 – 5837; e) D. X. Yang, G. C. Micalizio, *J. Am. Chem. Soc.* **2012**, *134*, 15237 – 15240; f) D. P. Harrison, D. A. Iovan, W. H. Myers, M. Sabat, S. S. Wang, V. E. Zottig, W. D. Harman, *J. Am. Chem. Soc.* **2011**, *133*, 18378 – 18387.

[10] For stereospecific 3-aza-Cope rearrangement of quaternary N-allyl enammonium salts to install quaternary centers in tetahydroisoquinolines, see: D. F. McComsey, B. E. Maryanoff, *J. Org. Chem.* **2000**, *65*, 4938 – 4943.

[11] For leading references on diastereoselective alkylations of α-carboxy or cyano-substituted hydrazones to introduce quaternary carbon stereocenters, see: a) D. Enders, A. Zmaponi, G. Raabe, J. Runsink, *Synthesis* **1993**, 725 – 728; b) D. Enders, A. Zamponi, T. Schafer, C. Nubling, H. Eichenauer, A. S. Demir, G. Raabe, *Chem. Ber.* **1994**, *127*, 1707 – 1721.

[12] For leading references on diastereolective enolate alkylations for the asymmetric synthesis of α,α-disubstituted α-hydroxy or amino acids, see: a) D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2881 – 2921; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708 – 2748; b) C. L. Hugelshofer, K. T. Mellem, A. G. Myers, *Org. Lett.* **2013**, *15*, 3134 – 3137.

[13] Synthetic details, characterization, and molecular structures obtained by X-ray structural analysis of compounds are described in the Supporting Information. CCDC 974855 (**3e**), 974821 (**3g**), 974854 (**3m**), 974857 (**3n**), 974819 (**3p**), 974856 (**6d**), and 974820 (**6g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] For diastereoselective, sequential addition of Grignard reagents and cyanide to *N*-methoxy-piperidin-2-ones to install a tetrasubstituted carbon center, see: M. Jäkel, J. Qu, T. Schnitzer, G. Helmchen, *Chem. Eur. J.* **2013**, *19*, 16746 – 16755.

[15] We previously observed that allyl cerium reagents minimize competitive iminium ion deprotonation. See Ref. [7b].

