Synthetic Methods

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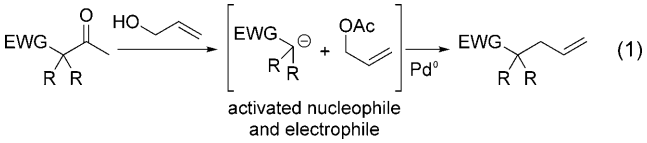
Deacylative Allylation of Nitroalkanes: Unsymmetric Bisallylation by a Three-Component Coupling**

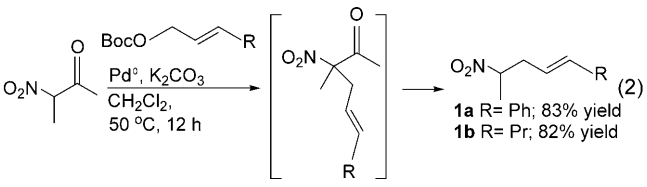
*Alexander J. Grenning and Jon A. Tunge**

Catalytic Tsuji–Trost allylation has become a ubiquitous method for the allylation of active methylene compounds.[1] Although monoallylation products are typically formed, the bisallylation of malonates and related ketone enolates leads to 1,6-dienes.[2] Given the utility of these 1,6-heptadienes in metal-catalyzed cycloisomerization reactions,[3] it would be beneficial if less stabilized carbon nucleophiles could be bisallylated in a controlled manner. Unfortunately, the one-pot bisallylation of other carbon nucleophiles is not well documented and usually requires harsh reaction conditions.[4] Moreover, the addition of two different allyl electrophiles to form unsymmetrical 1,6-dienes in a one-pot operation is exceedingly rare.[5] Herein, we describe the development of an unsymmetric bisallylation of carbon nucleophiles and introduce catalytic deacylative allylation as a new strategy for the tandem in situ generation and coupling of nucleophiles with allyl electrophiles [Eq. (1); EWG = electron-withdrawing group].[1]

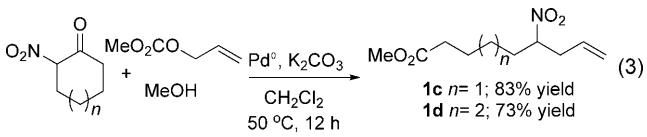


(1)

We began our pursuit of a three-component catalytic bisallylation reaction with the investigation of the deacylative allylation of nitroalkanes. The palladium-catalyzed allylation of nitroalkanes is a well-known, albeit nontrivial, process.[6,7] For example, as the monoallylation of nitromethane and primary nitroalkanes is complicated by competing bisallylation, excess nitroalkane is often required for successful monoallylation.[6] It was expected that we could take advantage of the ease of Tsuji–Trost allylation of highly stabilized nitroacetone nucleophiles to form allylated nitroketones [Eq. (2); Boc = *tert*-butoxycarbonyl].[8] Ballini and co-workers, and others, have shown that simple nitroalkanes can be generated by the deacylation of related nitroacetone derivatives.[9,10] Indeed, Tsuji–Trost reactions proceeded with deacylation in the presence of methanol and a base to selectively afford the monoallylated nitroalkanes [Eq. (2)]. Similar treatment of cyclic nitroketones provided clean monoallylated products containing a pendent ester [Eq. (3)]. Thus, the clean one-pot monoallylation of nitroalkanes is possible by a deacylative Tsuji–Trost reaction.[8,11]

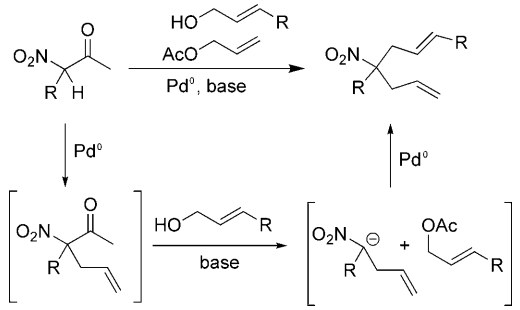


(2)



(3)

As in most other deacylative (retro-Claisen) reactions,[12] in our monoallylation reactions the acyl group is simply used as an activating group that can be readily removed. However, we hypothesized that an allylic alcohol could deacylate the intermediate α-nitroketone to simultaneously generate a nitronate anion and an allylic acetate electrophile [Eq. (1)]. Such a process would enable a selective three-component bisallylation with nitroacetones, an allylic acetate or carbonate, and an allylic alcohol (Scheme 1). Because allylic alcohols are relatively nonreactive toward palladium catalysts, the nitroacetone was expected to undergo rapid, selective Tsuji–Trost allylation with the allylic acetate. The resulting nitroketone would be able to undergo further allylation only through a deacylative allylation process. Ultimately, it was



Scheme 1. Proposed bisallylation through deacylative allylation.

[*] A. J. Grenning, J. A. Tunge
Department of Chemistry, University of Kansas
1251 Wescoe Hall Drive, Lawrence, KS 66045-7582 (USA)
Fax: (+1) 785-864-5396
E-mail: tunge@ku.edu
Homepage: http://www.tunge.ku.edu

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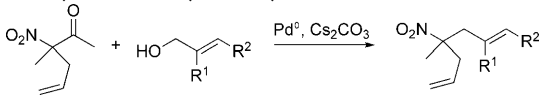
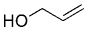
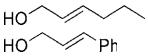
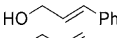
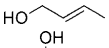
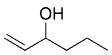
anticipated that these kinetically distinct steps could be combined to afford a three-component unsymmetric bisallylation reaction.

The proposed coupling hinged on the hypothesis that an allylic alcohol could deacylate an α-nitroketone to generate an allylic acetate and a nitronate anion in situ. To begin, we synthesized a model allylated nitroacetone by a Tsuji–Trost allylation and examined its reactivity under a variety of reaction conditions. We were pleased to find that various primary allylic alcohol derivatives participated in $[Pd(PPh_3)_4]$-catalyzed deacylative allylation when 1 equivalent of the base Cs_2CO_3 was added (Table 1). The allylation proceeded well with 2-hexenol as well as with cinnamyl alcohol to provide the linear allylation products **2b** and **2c**, respectively (Table 1, entries 2 and 3). However, the coupling of cinnamyl alcohol required a higher palladium-catalyst loading of 10 mol% for the reaction to proceed in high yield. The higher catalyst concentration promotes the desired C-allylation of the intermediate nitronate at the expense of problematic vinylogous Hass–Bender oxidation of cinnamyl acetate to cinnamaldehyde.[7b,13] When crotyl alcohol was the coupling partner, a decrease in selectively for the linear over the branched allylation product was observed (3.8:1; Table 1, entry 5). A similar drop in regioselectivity was noted in the decarboxylative allylation of nitroacetates with crotyl alcohol derivatives.[7b] The deacylative allylation appears to have a steric limitation; whereas the primary alcohol derivatives provided the products in good to excellent yields, a secondary allylic alcohol provided the desired product in poor yield (Table 1, entry 6).

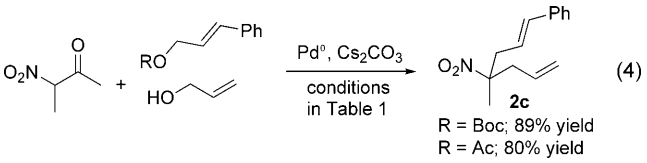
Table 1: Scope of the deacylative allylation.[a]



Entry	Allylic alcohol	Product	Yield [%]
1		**2a**	87
2		**2b**	79[b]
3[c]		**2c**	89[b]
4		**2d**	92
5		**2e**	79[d]
6		**2b**	25[b]

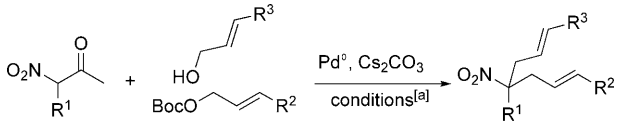
[a] Reaction conditions: $[Pd(PPh_3)_4]$ (2.5 mol%), allylic alcohol (1.2 equiv), Cs_2CO_3 (1 equiv), $CH_2Cl_2/ClCH_2CH_2Cl$ (1:1), 80°C, 12 h. [b] Linear/branched >19:1. [c] The reaction was carried out with 10 mol% of $[Pd(PPh_3)_4]$. [d] *E*/*Z* 5.6:1, linear/branched 3.8:1.

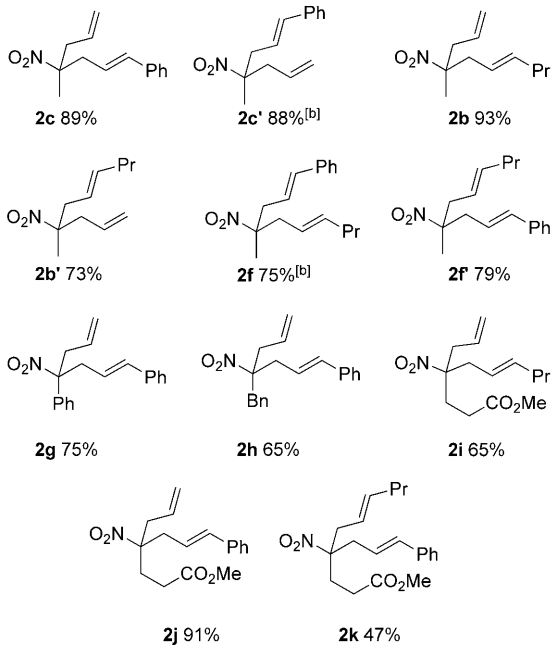
Having demonstrated the requisite deacylative allylation, we turned our attention to the three-component bisallylation of an α-nitroketone. Indeed, the treatment of α-methylnitroacetone with an allylic carbonate (or acetate) and allyl alcohol selectively produced the desired nitro-substituted 1,6-diene **2c** in high yield [Eq. (4)]. Importantly, attempts to synthesize the same product directly from nitroethane gave rise to a complex mixture of allylated products. Thus, deacylative allylation provides a unique avenue to unsymmetrically substituted 1,6-dienes.



(4)

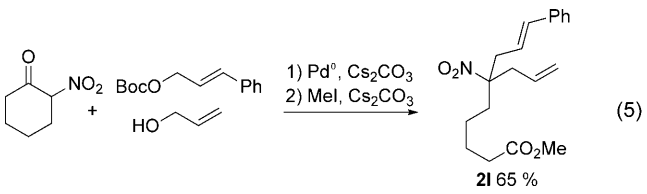
Since the allylic carbonate provided **2c** in higher yield than the allylic acetate [Eq. (4)], subsequent exploration of the reaction scope focused on the coupling of allylic carbonate derivatives (Scheme 2).[14] A comparison of **2c** (derived from allyl alcohol) and **2c′** (derived from cinnamyl alcohol) suggests that the allylic carbonate and alcohol partners can be reversed with little or no change in yield. With regard to the nitroketone substrate, α-phenyl and α-alkyl ketones were viable coupling partners. Notably, an α substituent with a base-sensitive methyl ester moiety survived the reaction conditions, and the functionalized products **2i–k** were formed. The fact that the methyl ester remains intact shows that acyl substitution of nitroacetones by





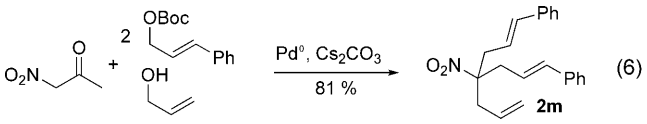
Scheme 2. Three-component unsymmetric bisallylation. [a] $[Pd(PPh_3)_4]$ (2.5 mol%), allylic carbonate (1 equiv), allylic alcohol (1.2 equiv), Cs_2CO_3 (1 equiv), CH_2Cl_2/DCE (1:1), 80°C, overnight. [b] The reaction was carried out with 10 mol% of $[Pd(PPh_3)_4]$. Bn = benzyl.

allylic alcohols is more facile than acyl substitution of esters. Lastly, the reaction of a cyclic α-nitroketone provided the ring-opened product with a pendent carboxylic acid [Eq. (5)]. The carboxylic acid was obtained in good yield; however, it was necessary to convert it into the methyl ester to effect complete purification.



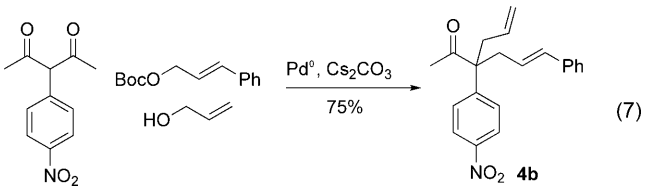
(5)

Whereas secondary nitroketones were required for the bisallylation reactions described above, trisallylation of a primary nitroketone was also possible with 2 equivalents of an allylic carbonate and 1.3 equivalents of allyl alcohol [Eq. (6)]. Thus, deacylative allylation enabled the selective synthesis of **2m** from four reactant molecules through the formation of three new C–C bonds in 81 % yield.



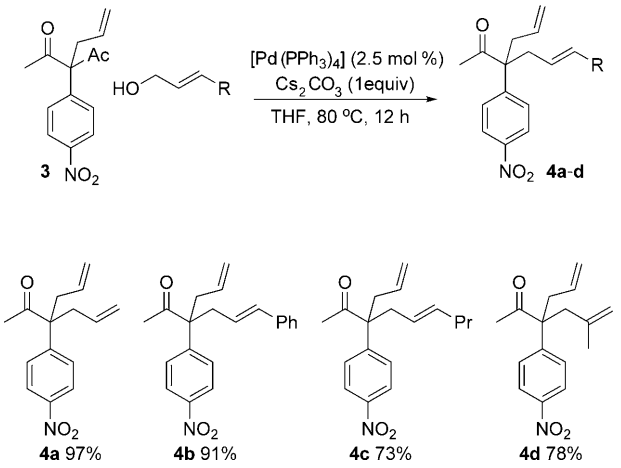
(6)

Besides the deacylative allylation of nitroketones, preliminary studies suggest that deacylative allylation will also enable the intermolecular allylation of activated ketones (Scheme 3). We and others have previously developed decarboxylative allylations of ketones which proceed through the formation of ketone enolates by C–C bond cleavage.[1c–f] Although these reactions have significant utility, their use is somewhat hampered by the need to incorporate the electrophile and nucleophile in the same molecular entity prior to decarboxylative coupling. The allylation reactions in Scheme 3 suggest that deacylative allylation may enable similar reactions to take place in an intermolecular fashion. Finally, ketone substrates that participate in deacylative allylation also undergo selective three-component coupling to form unsymmetrical heptadienes [Eq. (7)].



(7)

In closing, we have developed deacylative allylation as a synthetic strategy for the direct use of inexpensive, readily available allylic alcohols in electrophilic allylation reactions. Not only does deacylative allylation enable the selective monoallylation of nitronates, but it can also be used in tandem with the Tsuji–Trost allylation of stabilized nitronates to enable the controlled synthesis of unsymmetrical 1,6-dienes through a three-component coupling. Precise control of the kinetics of the coupling processes obviates many possible side reactions (e.g. homoallylation, allylation of alkoxide intermediates) and leads to a highly selective bisallylation. Similar strategies are expected to facilitate the selective multicomponent allylation of a wide variety of acyl pronucleophiles with allylic alcohols.



Scheme 3. Deacylative allylation of an acetyl acetone derivative.

Experimental Section

Representative deacylative allylation procedure: In a glove box under an argon atmosphere, $[Pd(PPh_3)_4]$ (14 mg, 0.0125 mmol) and Cs_2CO_3 (165 mg, 0.5 mmol) were placed in a flame-dried pressure vial equipped with a septum. Anhydrous DCE (1 mL) was added, and the vial was sealed. The vial was removed from the glove box, a solution of α-allyl-α-methylnitroacetone (47 mg, 0.3 mmol) and allyl alcohol (22 mg, 0.36 mmol) in dry CH_2Cl_2 (500 μL) was added with a syringe, and the vessel from which this solution was transferred was rinsed with CH_2Cl_2 (2×250 μL) to ensure complete transfer of the substrates to the reaction mixture. The pressure vial was then submerged in an oil bath at 80 °C, and the reaction mixture was stirred at this temperature for 12 h. The reaction vessel was then cooled to room temperature, and the resulting solution was diluted with 15 % Et_2O/pentane (ca. 5 mL) and eluted through a silica plug with excess 15 % Et_2O/pentane (ca. 50–75 mL). After removal of the volatiles by rotary evaporation, column chromatography (SiO_2; 2–4 % Et_2O/pentane) of the crude oil yielded pure **2a** (40 mg, 87 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.65$–5.55 (m, 2H), 5.12 (d, J=8.9 Hz, 2H), 5.09 (d, $J = 16.3$ Hz, 2H), 2.67 (dd, $J = 14.2$, 7.3 Hz, 2H), 2.48 (dd, $J = 14.2$, 7.3 Hz, 2H), 1.47 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 128.7$, 118.4, 88.3, 41.2, 19.6 ppm; MS: m/z 109.2 $[M-NO_2]^+$, 46.0 $[NO_2]^+$.

Representative bisallylation procedure: In a glove box under an argon atmosphere, $[Pd(PPh_3)_4]$ (14 mg, 0.0125 mmol) and Cs_2CO_3 (165 mg, 0.5 mmol) were placed in a flame-dried pressure vial equipped with a septum. Anhydrous DCE (1 mL) was added, and the was vial sealed. The vial was removed from the glove box, a solution of α-methylnitroacetone (58 mg, 0.5 mmol) and *tert*-butyl cinnamyl carbonate (124 mg, 0.5 mmol) in dry CH_2Cl_2 (500 μL) was

added with a syringe, and the vessel from which this solution was transferred was rinsed with CH_2Cl_2 (2×250 μL) to ensure complete transfer of the substrates to the reaction mixture. Allyl alcohol (36 mg, 0.6 mmol) was then added with a syringe, the pressure vial was submerged in an oil bath at 80 °C, and the reaction mixture was stirred overnight. The reaction vessel was then cooled to room temperature, and the resulting solution was diluted with 15% EtOAc/hexanes (ca. 5 mL) and eluted through a silica plug with excess 15% EtOAc/hexanes (ca. 50–75 mL). After removal of the volatiles by rotary evaporation, column chromatography (SiO_2; 2% EtOAc/hexanes) of the crude oil yielded pure **2c** (103 mg, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$–7.22 (m, 4H), 7.19–7.15 (m, 1H), 6.41 (d, $J = 15.7$ Hz, 1H), 5.96 (dt, $J = 15.3$, 7.5 Hz, 1H), 5.63 (m, 1H), 5.14 (d, $J = 9.2$ Hz, 1H), 5.11 (d, $J = 16.4$ Hz, 1H), 2.83 (ddd, $J = 14.2$, 7.3, 1.3 Hz, 1H), 2.72 (dd, $J = 14.2$, 7.3 Hz, 1H), 2.63 (ddd, $J = 14.2$, 7.7, 1.3 Hz, 1H), 2.52 (dd, $J = 14.2$, 7.7 Hz, 1H), 1.51 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 136.6$, 135.4, 130.8, 128.6, 127.8, 126.3, 122.1, 120.7, 90.9, 43.5, 42.6, 22.1 ppm; MS: *m*/*z* 231.2 $[M]^+$, 185.2 $[M-NO_2]^+$, 46.0 $[NO_2]^+$.

See the Supporting Information for full experimental procedures as well as ^{1}H and ^{13}C NMR spectroscopic data and GC–MS data for starting materials and compounds **1a–d**, **2a–n**, and **4a–d**.

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[1] a) U. Kazmaier, *Curr. Org. Chem.* **2003**, *7*, 317; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; c) J. A. Tunge, E. C. Burger, *Eur. J. Org. Chem.* **2005**, 1715; d) M. Braun, T. Meier, *Angew. Chem.* **2006**, *118*, 7106; *Angew. Chem. Int. Ed.* **2006**, *45*, 6952; e) S.-L. You, L.-X. Dai, *Angew. Chem.* **2006**, *118*, 5372; *Angew. Chem. Int. Ed.* **2006**, *45*, 5246; f) M. Austeri, F. Buron, S. Constant, J. Lacour, D. Linder, J. Müller, S. Tortoioli, *Pure Appl. Chem.* **2008**, *80*, 967.

[2] a) Y. Yamamoto, Y.-i. Nakagai, K. Itoh, *Chem. Eur. J.* **2004**, *10*, 231; b) B. C. Ranu, K. Chattopadhyay, L. Adak, *Org. Lett.* **2007**, *9*, 4595; c) S. G. Manjunatha, P. Chittari, S. Rajappa, *Helv. Chim. Acta* **1991**, *74*, 1071.

[3] a) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; b) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067; c) R. A. Widenhoefer, *Acc. Chem. Res.* **2002**, *35*, 905; d) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215; e) C. Böing, J. Hahne, G. Franciò, W. Leitner, *Adv. Synth. Catal.* **2008**, *350*, 1073.

[4] a) G. Rojas, T. W. Baughman, K. B. Wagener, *Synth. Commun.* **2007**, *37*, 3923; b) S. P. Chavan, A. N. Dhawane, U. R. Kalkote, *Synthesis* **2007**, 3827; c) H. Rieck, G. Helmchen, *Angew. Chem.* **1995**, *107*, 2881; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2687; d) Y. Horino, M. Naito, M. Kimura, S. Tanaka, Y. Tamaru, *Tetrahedron Lett.* **2001**, *42*, 3113.

[5] For one example of a two-component hetero(bis)allylation through allylation/decarboxylative allylation, see: I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1983**, *24*, 3865.

[6] a) P. Aleksandrowicz, H. Piotrowska, W. Sas, *Tetrahedron* **1982**, *38*, 1321; b) P. A. Wade, S. D. Morrow, S. A. Hardinger, *J. Org. Chem.* **1982**, *47*, 365; c) D. R. Deardorff, K. A. Savin, C. J. Justman, Z. E. Karanjawala, J. E. Sheppeck II, D. C. Harger, N. Aydin, *J. Org. Chem.* **1996**, *61*, 3616; d) B. M. Trost, J.-P. Surivet, *J. Am. Chem. Soc.* **2000**, *122*, 6291; e) B. M. Trost, J.-P. Surivet, *Angew. Chem.* **2000**, *112*, 3252; *Angew. Chem. Int. Ed.* **2000**, *39*, 3122; f) K. Maki, M. Kanai, M. Shibasaki, *Tetrahedron* **2007**, *63*, 4250.

[7] a) J. Tsuji, T. Yamada, I. Minami, M. Yuhara, M. Nisar, I. Shimizu, *J. Org. Chem.* **1987**, *52*, 2988; b) A. J. Grenning, J. A. Tunge, *Org. Lett.* **2010**, *12*, 740.

[8] J. P. Genet, D. Ferround, *Tetrahedron Lett.* **1984**, *25*, 3579.

[9] a) R. H. Fischer, H. M. Weitz, *Synthesis* **1980**, 261; b) R. Ballini, *Synlett* **1999**, 1009; c) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Tetrahedron* **2005**, *61*, 8971.

[10] "Alkylation, Acylation, and Halogenation of Nitro Compounds": N. Ono, *The Nitro Group in Organic Synthesis*, Wiley, New York, **2002**, Chap. 5.

[11] The direct allylation of stabilized C and N nucleophiles with allylic alcohols typically requires Lewis acid additives or acidic conditions: a) Y. Tamaru, Y. Horino, M. Araki, S. Tanaka, M. Kimura, *Tetrahedron Lett.* **2000**, *41*, 5705; b) N. T. Patil, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 3101; c) H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, *6*, 4085; d) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968; e) I. Satoh, M. Ikeda, M. Miura, M. Nomura, *J. Org. Chem.* **1997**, *62*, 4877.

[12] a) B. H. Brodsky, J. Du Bois, *Org. Lett.* **2004**, *6*, 2619; b) A. Kawata, K. Takata, Y. Kuninobu, K. Takai, *Angew. Chem.* **2007**, *119*, 7939; *Angew. Chem. Int. Ed.* **2007**, *46*, 7793; c) S. Biswas, S. Maiti, U. Jana, *Eur. J. Org. Chem.* **2010**, 2861; d) I. Deb, D. Seidel, *Tetrahedron Lett.* **2010**, *51*, 2945; e) C. He, S. Guo, L. Huang, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 8273; f) C. B. Rao, D. C. Rao, D. C. Babu, Y. Venkateswarlu, *Eur. J. Org. Chem.* **2010**, 2855; g) Y. Wei, J. Liu, S. Lin, H. Ding, F. Liang, B. Zhao, *Org. Lett.* **2010**, *12*, 4220; h) J. R. Schmink, N. E. Leadbeater, *Org. Lett.* **2009**, *11*, 2575.

[13] a) H. B. Hass, M. L. Bender, *J. Am. Chem. Soc.* **1949**, *71*, 1767; b) T. A. Klein, J. M. Schkeryantz, *Tetrahedron Lett.* **2005**, *46*, 4535.

[14] J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* **1982**, *23*, 4809.

