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Hydrogen-Bond-Activated Palladium-Catalyzed Allylic Alkylation via Allylic Alkyl Ethers: Challenging Leaving Groups

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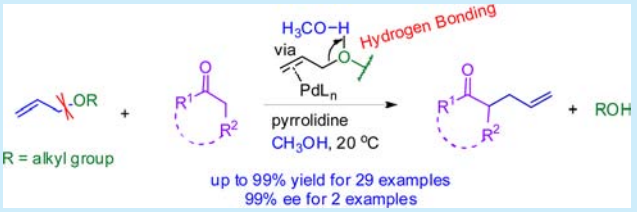
Supporting Information

ABSTRACT: C−O bond cleavage of allylic alkyl ether was realized in a Pd-catalyzed hydrogen-bond-activated allylic alkylation using only alcohol solvents. This procedure does not require any additives and proceeds with high regioselectivity. The applicability of this transformation to a variety of functionalized allylic ether substrates was also investigated. Furthermore, this methodology can be easily extended to the asymmetric synthesis of enantiopure products (99% ee).

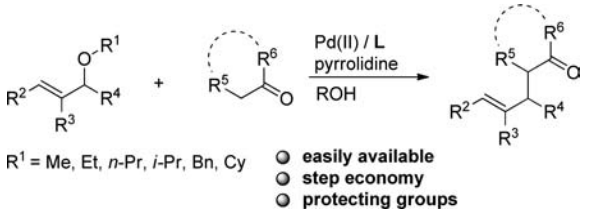


Palladium-catalyzed allylic alkylation is a reliable and widely used method for the formation of multiple types of bonds and has been extensively used in total synthesis.[1,2] Tremendous progress has been made toward the development of increasingly elaborate nucleophiles and catalysts to facilitate the aforementioned reaction.[3] However, despite significant advances, Pd-catalyzed allylic substitution reactions are still limited predominantly to substrates possessing good leaving groups (i.e., allylic acetates and carbonates);[2,3] unactivated leaving groups such as ethers and amines remain difficult to utilize. More recently, allylic amines have been successfully employed in the Tsuji−Trost reaction by utilizing strong acids,[4] minicyclic tension,[5] and hydrogen bond activation.[6] Unfortunately, a facile method for the direct use of the accessible allylic alkyl ethers remains a challenge.

O-Based compounds are ubiquitous in nature and synthetic systems;[7] thus, metal-catalyzed cleavage of the C−O bond of ethers remains a topic of interest.[8−11] Importantly, the high stability of the C−O bond of allylic ethers means the substrates are compatible with most reaction conditions (e.g., $LiAlH_4$, *n*-BuLi, Grignard reagents, oxidants, etc.). However, allylic ethers are not commonly used in Pd-catalyzed allylic alkylation reactions because their high stabilities often require the use of stoichiometric quantities of strong Lewis acids[10] or special substrates,[11] such as vinyl epoxides and allylic aryl ethers. These substrates suffer from limited substrate scope, thus limiting their potential use in organic synthesis. We therefore believed it would be beneficial if simple allylic alkyl ethers such as −OMe, −OEt, or −OCy could be directly used in Pd-catalyzed allylic alkylation reactions under mild conditions.

Our group recently introduced a strategy employing allylic amines (LG = $-NR^1R^2$) as allylic reagents in Pd-catalyzed allylic alkylation reactions in the presence of pyrrolidine with alcohol solvents.[6,12] Considering that allylic alkyl ethers are comparatively more accessible and compatible with a wider range of reaction conditions than allylic amines, we herein report a general and convenient method for the direct use of allylic alkyl ethers in Pd-catalyzed allylic alkylations via hydrogen bond activation (Scheme 1).

Scheme 1. Challenging Leaving Groups



We first carried out the reaction using allyl propyl ether as the substrate, an enamine generated in situ as the nucleophile, and a $[Pd(\eta^3\text{-allyl})Cl]_2$/dppf catalytic system (Table 1). The effects of solvent on the reaction were first explored. The results suggested that protic solvents (MeOH, EtOH, and *n*-PrOH) could promote the reaction (entries 1−3). However, when aprotic solvents (toluene, DMSO, and DMF) were used, the reaction was unsuccessful. Lowering the acidity of the protic solvents led to decreased reactivity and prolonged reaction times. Use of low reaction temperatures or different amounts of cyclohexanone and pyrrolidine were also investigated (entries 4−6). Taking multiple factors into consideration, the optimal reaction conditions were determined to be as follows: 1 equiv of pyrrolidine, $[Pd(\eta^3\text{-allyl})Cl]_2$/dppf as a catalyst in MeOH at 20 °C.

In order to clarify the role of methanol in hydrogen bond participation, $Pd_2(dba)_3$ was used to prevent the generation of

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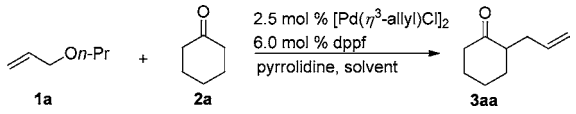
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	temp (°C)	solvent	pK_a[b]	t (h)	yield (%)[c]
1	20	MeOH	15.5	3	95
2	20	EtOH	15.9	12	95
3	20	*n*-PrOH	16.1	18	95
4	0	MeOH	15.5	18	35
5[d]	20	MeOH	15.5	4	95
6[e]	20	MeOH	15.5	48	89
7[f]	20	MeOH	15.5	12	92
8[g]	20	MeOH	15.5	12	93

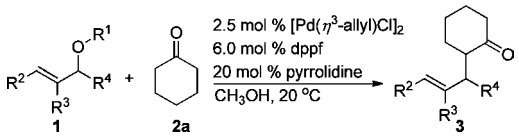
[a]Reactions of **1a** (0.50 mmol) with **2a** (1.50 mmol) were performed in 1.0 equiv of pyrrolidine using 6.0 mol % of dppf and 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in solvent (2 mL) at 20 °C; [b]See ref 15. [c]Isolated yields. [d]20 mol % of pyrrolidine. [e]1.5 equiv of **2a**. [f]$Pd_2(dba)_3$ instead of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ under reflux. [g]3.0 equiv of enamine was used. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

HCl from the catalyst precursor. No change in reaction yield was observed (entry 7), thus indicating this reaction is not affected by catalytic amounts of HCl. In addition, *N*-allylpyrrolidine was detected by GC−MS during the reaction. As the reaction proceeds, *N*-allylpyrrolidine is completely converted into the desired product.[6] It has been reported that the allylammonium cation can promote the deallylation of allylic ethers.[13] In order to avoid the formation of the allylammonium cation, an enamine was used in this reaction, smoothly providing the desired product (entry 8). These results suggested that our reaction conditions are not significantly affected by the presence of the allylammonium cation. Furthermore, a computational study suggested that MeOH plays a crucial role in the formation of the Pd−allyl complex by lowering the activation energy and stabilizing the resulting hydroxide and alkyloxide ion.[14]

Several substituted allylic ethers were subjected to the optimized conditions described above (Table 2). The reactions of linear allylic alkyl ethers with cyclohexanone proceeded smoothly, with comparable reaction activity and high yields (entries 1−3). In contrast, the use of branched substrates, phenyl ether, and benzyl ether resulted in decreased reaction activity. Nevertheless, the desired products were still obtained by using longer reaction times and/or by using an equivalent amount of pyrrolidine (entries 4−7). 2-Methylallylic ether was also amenable to the reaction conditions, giving the desired product in high yield (entry 8). Notably, regioisomeric methyl- or phenyl-substituted allylic ethers gave identical products (entries 9−12). Additionally, high yields were also obtained by using 1,3-disubstituted allylic substrates with an equivalent of pyrrolidine (entries 13−15).

A broad range of carbonyl compounds were then investigated for the formation of C−C bonds in this reaction using allylic propyl ether (Table 3). The reactions with cyclopentanone and cyclohexanone proceeded smoothly with high activities and yields (entries 1−2). However, a prolonged reaction time and a higher temperature were required for the reaction using cycloheptanone (entry 3). The substituents at the 4-position of cyclohexanone did not appear to affect the reaction, and the ketones possessing acid-labile groups could also be used in our catalytic system (entries 4−6). In addition, a ketone possessing

Table 2. Substrate Scope of Allylic Alkyl Ethers[a]



1 2a 3

entry	1	t (h)	3	yield (%)[b]
1	On-Pr **1a**	4	**3aa**	95
2	OMe **1b**	4	**3ba**	91
3	OEt **1c**	4	**3ca**	93
4	O*i*-Pr **1d**	6	**3da**	92
5[c]	OCy **1e**	9	**3ea**	91
6[c]	OBn **1f**	24	**3fa**	93
7[c]	OPh **1g**	2	**3ga**	92
8	OEt, Me **1h**	7	**3ha**	95
9	OBn **1i**	8	**3ia**	93
10	OBn **1j**	8	**3ja**	96
11[c]	Ph, OEt **1k**	12	**3ka**	98
12[c]	OEt, Ph **1l**	12	**3la**	96
13[c]	OEt, Ph, Me **1m**	12	**3ma**	97[d]
14[c]	OEt, Ph, Ph **1n**	8	**3na**	99[d]
15[c]	O*i*-Pr, Ph, Ph **1o**	12	**3oa**	98[d]

[a]Reactions of **1** (0.50 mmol) with **2a** (1.50 mmol) were performed; all data are the average of two experiments. [b]Isolated yields. [c]1.0 equiv of pyrrolidine. [d]Products with 1:1 dr, determined by ^{1}H NMR.

a free hydroxyl group was also subjected to our reaction conditions, and the desired products were obtained in high yield (entry 7). Excellent yields were also obtained when using an aromatic ketone such as indone (entry 8). To expand the scope of our catalytic system, phenyl acetaldehyde was also used in the allylic alkylation reaction. The corresponding alcohols of the desired products were obtained in moderate yields (entry 9). These results suggested both ketones and aldehyde are suitable for this reaction.

When considering atom economy and the number of synthetic steps, it is important to exploit the inherent reactivity of functional groups.[16] Alkyl ethers may be the ideal functional groups for this purpose. The use of these groups may improve the overall efficiency of a synthetic route by reducing the need for protecting groups or exploiting new synthetic pathways. At first, we explored functional group compatibility of the allylic ether, (*E*)-1-bromo-4-(3-ethoxyprop-1-enyl)benzene, by subjecting it to different reactions such as a Suzuki coupling,[17] Bouveault aldehyde synthesis,[18] and oxidation and reduction reactions (Scheme 2, A). The allylic ether displayed excellent functional group tolerance. All the functionalized allylic ethers

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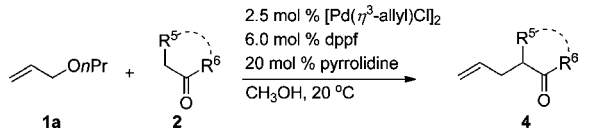
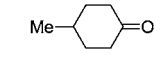
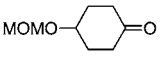
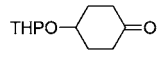
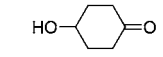
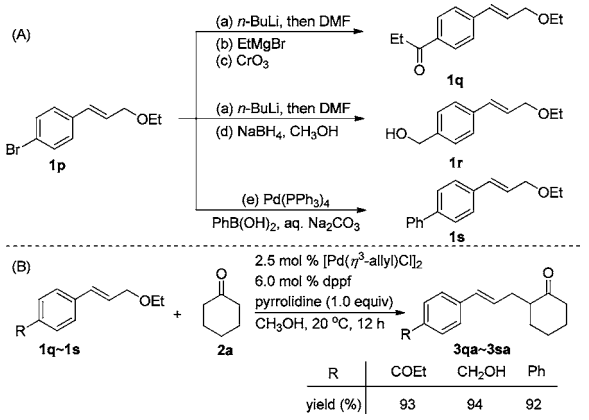
Table 3. Different Ketones and Aldehyde[a]



entry	2		t (h)	4	yield (%)[b]
1		2b	2.5	4ab	96
2		2a	4	4aa	95
3[c]		2c	18	4ac	95
4		2d	5	4ad	98
5		2e	2.5	4ae	96
6		2f	7	4af	96
7		2g	12	4ag	92
8		2h	4	4ah	96
9[d]		2i	18	4ai	62[e]

[a]Reactions of **1a** (0.50 mmol) with **2** (1.50 mmol) were performed with 20 mol % of pyrrolidine; all data are the average of two experiments. [b]Isolated yields. [c]1.0 equiv of pyrrolidine. [d]10.0 equiv of aldehyde was used in EtOH. [e]Yield of the corresponding alcohol from the desired product reduced with $NaBH_4$ for easy isolation.

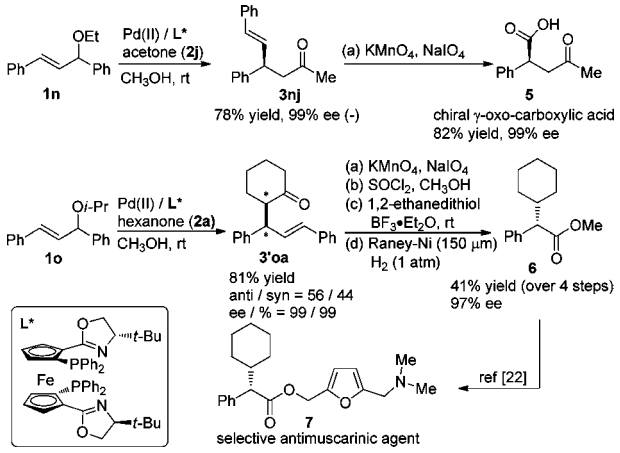
Scheme 2. Compatibility of Allylic Ethers



could be used in Pd-catalyzed allylic alkylation reactions, providing excellent yields (Scheme 2, B).

To further explore the applicability of this methodology, we applied our catalytic system to an enantioselective reaction using a chiral ferrocene-based phosphinooxazoline ligand (Scheme 3).[19] Allylic ethers **1n** and **1o** were studied in the Pd-catalyzed asymmetric allylic alkylation using acetone (**2j**) and **2a** as nucleophiles. The desired products were obtained in high yields and excellent enantioselectivities. The use of (*E*)-((pent-3-en-2-yloxy)methyl)benzene as a substrate was also explored, with the desired product being obtained in less than

Scheme 3. Asymmetric Transformation[a]



[a]Reagents and conditions: for the asymmetric allylic alkylation, see the Supporting Information.

20% yield, even under reflux conditions. The product **3nj** was successfully applied to the synthesis of chiral γ-oxocarboxylic acid, which is an important intermediate for the synthesis of various peptides, therapeutic agents, and bioactive natural products.[20] Although the product **3′oa** was obtained with a low degree of diastereoselectivity,[21] the chiral phenylacetic acid derivatives **6** (97% ee) can be readily obtained by oxidation, esterification, and reduction. The enantiopure motif **6** could then be used for the synthesis of the selective antimuscarinic agent **7**.[22]

To conclude, we have developed a hydrogen-bond-activated Pd-catalyzed allylic alkylation reaction of allylic alkyl ethers with carbonyl compounds. The procedure does not require any additives and proceeds with high regioselectivity. A series of allylic alkyl ethers could be utilized using this methodology, providing excellent results. This methodology can be extended to the synthesis of enantiopure intermediates which can be used for the synthesis of chiral γ-oxo-carboxylic acid and phenylacetic acid derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compounds characterization, HPLC spectra, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; p 585. (b) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (d) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (e) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476. (f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (g) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312. (h) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (i) Milhau, L.; Guiry, P. J. *Top. Organomet. Chem.* **2012**, *38*, 95.

(2) For its applications in organic synthesis, see: (a) Ernst, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4054. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580. (d) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395. (e) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952. (f) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228. (g) Du, C.; Li, L.; Li, Y.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7853. (h) Huters, A. D.; Styduhar, E. D.; Garg, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3758.

(3) (a) Ma, G.; Afewerki, S.; Deiana, L.; Palo-Nieto, C.; Liu, L.; Sun, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6050. (b) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626. (c) Du, L.; Cao, P.; Xing, J.; Lou, Y.; Jiang, L.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 420.

(4) (a) Hirao, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1982**, *236*, 409. (b) Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559. (c) Murahashi, S.-I.; Makabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5563. (d) Murahashi, S.-I.; Makabe, Y.; Kunita, K. *J. Org. Chem.* **1988**, *53*, 4489. (e) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (f) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516. (g) Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924.

(5) (a) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800. (b) Lowe, M. A.; Ostovar, M.; Ferrini, S.; Chen, C. C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6370.

(6) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354.

(7) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411.

(8) Recent reviews: (a) Houpis, I. N.; Lee, J. *Tetrahedron* **2000**, *56*, 817. (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (c) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (d) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

(9) Allylic ethers have been used in some metal-catalyzed coupling reactions; see the references in the Supporting Information.

(10) (a) Lu, X.; Jiang, X. *J. Organomet. Chem.* **1989**, *359*, 139. (b) Mukai, R.; Horino, Y.; Tanaka, S.; Tamaru, Y.; Kimura, M. *J. Am. Chem. Soc.* **2004**, *126*, 11138.

(11) (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (c) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (d) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907. (e) Hosokawa, T.; Kono, T.; Uno, T.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2191.

(12) For other related examples of combining enamine organocatalysis with palladium catalysis: (a) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952. (b) Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063. (c) Usui, I.; Schmidt, S.; Breit, B. *Org. Lett.* **2009**, *11*, 1453. (d) Jiang, G. X.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (e) Yasuda, S.; Kumagai, N.; Shibasaki, M. *Heterocycles* **2012**, *86*, 745.

(13) Mora, G.; Piechaczyk, O.; Le Goff, X. F.; Le Floch, P. *Organometallics* **2008**, *27*, 2565.

(14) For more details, see the Supporting Information.

(15) McMurry, J. E. *Organic Chemistry*, 6th ed.; Brooks/Cole: Belmont, CA, 2003.

(16) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (c) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.

(17) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(18) Bouveault, L. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1306.

(19) (a) Zhang, W.; Adachi, Y.; Hirao, T.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 451. (b) Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545.

(20) (a) Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Pergamon: Oxford, 1989. (b) Cregge, R. J.; Durham, S. L.; Farr, R. A.; Gallion, S. L.; Hare, C. M.; Hoffman, R. V.; Janusz, M. J.; Kim, H.-O.; Koehl, J. R.; Mehdi, S.; Metz, W. A.; Peet, N. P.; Pelton, J. T.; Schreuder, H. A.; Sunder, S.; Tradif, C. *J. Med. Chem.* **1998**, *41*, 2461.

(21) To improve the diastereoselectivity, chiral proline derivatives (such as proline, (*S*)-2-(diphenyl(trimethylsilyloxy) methyl)pyrrolidine, Macmillan catalysts, etc.) were used, but only trace amounts of product were obtained.

(22) Feriani, A.; Gaviraghi, G.; Toson, G.; Mor, M.; Barbieri, A.; Grana, E.; Boselli, C.; Guarneri, M.; Simoni, D.; Manfredini, S. *J. Med. Chem.* **1994**, *37*, 4278.