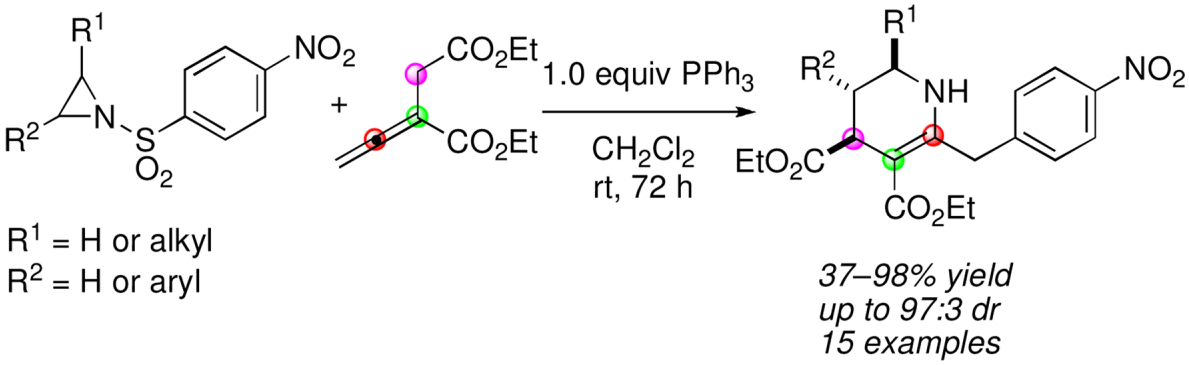
Published in final edited form as:
J Am Chem Soc. 2009 May 13; 131(18): 6318–6319. doi:10.1021/ja8097349.

Phosphine-Promoted [3 + 3] Annulations of Aziridines With Allenoates: Facile Entry Into Highly Functionalized Tetrahydropyridines

Hongchao Guo, **Qihai Xu**, and **Ohyun Kwon***
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

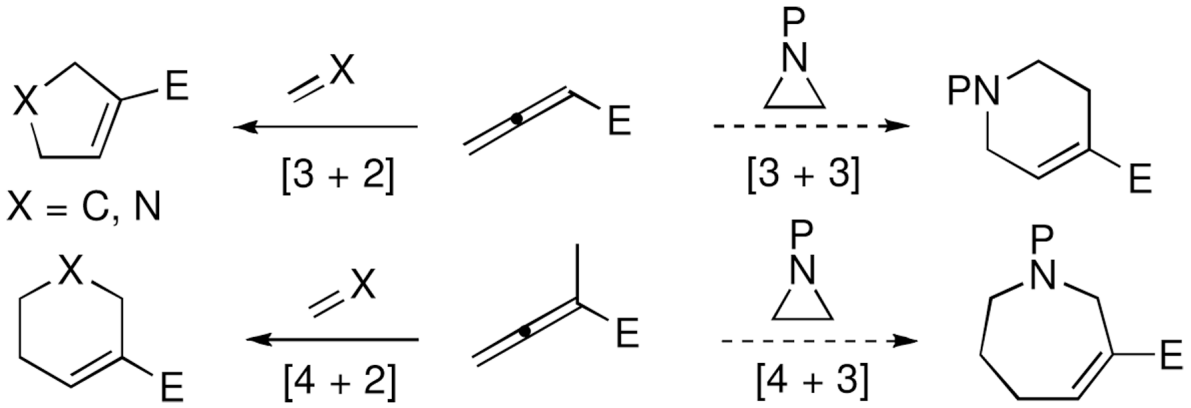
Abstract



The phosphine-mediated [3 + 3] annulations of aziridines and allenes are experimentally simple reactions, run under very mild conditions, for the preparation of highly functionalized tetrahydropyridines in yields of up to 98% and trans/cis ratios of up to 97:3. In addition to steps that are typical of nucleophilic phosphine-catalyzed reactions of allenoates, the mechanism of this new reaction features apparent nucleophilic aromatic substitution and concomitant desulfonylation, hitherto unknown processes during phosphine-promoted cycloaddition reactions. Notably, these reactions are the first reported examples of aziridines as reaction partners in nucleophilic phosphine-catalyzed transformations.

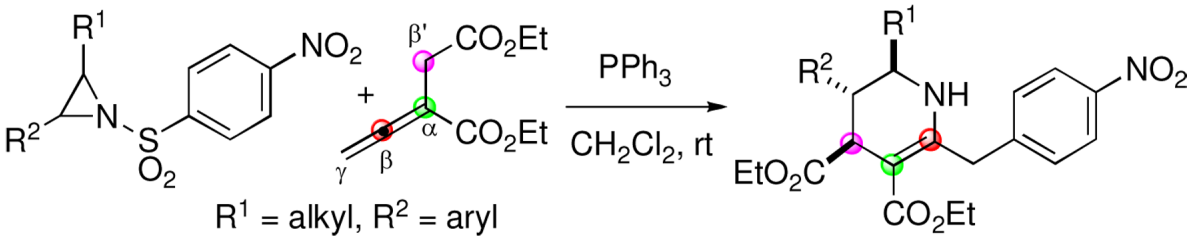
Intermolecular cycloadditions are powerful reactions for synthesizing carbo- and heterocycles from simpler starting materials.[1] The development of many transition metal- and organomolecule-promoted cycloadditions has expanded the scope of starting materials that can be engaged in such transformations.[2] Nucleophilic phosphine catalysis is now established as a reliable platform for cycloadditions employing activated allenes as one of the reaction partners.[3] In phosphine-promoted processes, allenes typically react as three- and four-carbon synthons in [3 + 2] and [4 + 2] additions, respectively, with alkenes or imines.[4] Based on this behavior, we pondered the possibility of employing aziridines as a three-atom components in [4 + 3] and [3 + 3] annulations with allenoates (Eq 1).

E-Mail:ohyun@chem.ucla.edu.



(1)

While [4 + 2] and [3 + 2] cycloadditions are used widely in organic synthesis, only a limited number of [3 + 3] additions have been reported to date.[5] Aziridines contain one of the most valuable three-membered ring systems in modern synthetic chemistry; they are extremely versatile synthetic building blocks.[6] Although formal [3 + 3] cycloadditions of aziridines with Pdtrimethylenemethane (TMM) species have been used to furnish piperidines,[5b] the phosphonium enolate zwitterionic intermediate[7] has not been employed previously for coupling with aziridines. Herein, we describe the development of a new phosphine-promoted [3 + 3] annulation of aziridines with allenoates to afford highly functionalized tetrahydropyridines under simple and mild conditions (Eq 2).



(2)

Initially, we examined the reaction of *N*-nosylaziridine **1a** and diethyl 2-vinylidenesuccinate (**2**) with PBu_3 (20 mol%) at room temperature (Table 1, entry 1).[8] Although the aziridine was consumed completely within 24 h, we obtained no product from its coupling with the allenoate. Given that the aziridine ring can be opened directly through nucleophilic attack,[9] we employed the weaker nucleophile PPh_3 to take advantage of its more discerning reactivity.[10] To our delight, we isolated the [3 + 3] adduct **3a** in modest yield and excellent diastereoselectivity (trans/cis, 10:1; entry 2).[11] Surprisingly, the three carbon atoms constituting the tetrahydropyridine **3a** were the α, β, and β´ carbon atoms of the starting allenoate rather than the α, β, and γ carbon atoms encountered in well-established phosphine-mediated [3 + 2] annulations.[4] Moreover, the *p*-nitrobenzene ring was attached to the γ carbon atom of the starting allenoate, with an apparent loss of SO_2 (vide infra). The reaction yield improved significantly, without erosion of the diastereoselectivity, after increasing the amount of PPh_3 (entry 3). Although NMR spectroscopy revealed that some free phosphine remained after the reaction, we added 1 equiv of phosphine to expedite the reaction (entry 4); more than 1 equiv

of PPh_3 did not improve the reaction efficiency (entry 5). The reaction was best run in CH_2Cl_2 (entry 6) and at room temperature; the product decomposed at elevated temperatures (entry 7). Other tertiary phosphines did not facilitate the reaction as well as PPh_3 did (entries 8–11).

We examined a range of aziridine derivatives for their [3 + 3] annulations under the optimized reaction conditions (Table 2). Aryl-substituted aziridines underwent the reaction in good to excellent yield with good 1,2-trans-diastereoselectivity; phenyl groups featuring electron-withdrawing or -donating substituents at the ortho, meta, and para positions worked well (entries 1–11), as did a naphthyl group (entry 12). Interestingly, the alkyl-substituted aziridine **1n** provided a different regioisomeric tetrahydropyridine with diminished diastereoselectivity, favoring the formation of the 1,3-cis-product **3n** (entry 13).[11] Whereas aryl-substituted C–N bonds of aziridines are polarized for nucleophilic fission, alkyl-substituted carbon atoms block direct nucleophilic attack. The unsubstituted aziridine substrate provided a poorer yield (entry 14), presumably because it is more susceptible to phosphine-mediated direct ring opening, leading to undesired side products.[9]

To better understand the mechanisms of these intriguing processes, we subjected the deuterium-labeled allenoate **2D** (92% D) to [3 + 3] annulations with the aziridines **1a** and **1b** (Scheme 1). We obtained the tetrahydropyridines **3p** and **3q** in yields comparable with those of the non-deuterated allenoate **2**, but with 19 and 25% deuterium at the γ carbon atoms of **3p** and **3q**, respectively, and 27% deuterium at their β′ carbon atoms. The loss of deuterium content at the γ carbon atom and its incorporation at the β′ carbon atom suggests the formation of intermediates featuring carbanions located at both carbon atom centers. The decrease in the overall deuterium content was due to the presence of adventitious water, which facilitated the intermolecular proton transfer processes.[12]

Based on these observations, Scheme 2 presents our suggested reaction mechanism. Addition of PPh_3 to the allenoate forms the intermediate **4**, which undergoes proton transfer to give the vinylogous ylide **5**.[4k] Aziridine ring opening occurs at the β′ carbon atom to furnish the intermediate **6**.[13] Sulfonamide/dienolate equilibrium[4i] provides the intermediate **7**, which undergoes intramolecular[14] nucleophilic aromatic substitution and concomitant desulfonylation.[15] Subsequent conjugate addition and β-elimination of PPh_3 generates the tetrahydropyridine product **3**.[16]

In summary, we have developed a phosphine-mediated [3 + 3] cycloaddition annulation manifold for allenes, incorporating, for the first time, aziridine derivatives as reaction partners. The reaction is operationally simple and produces highly functionalized tetrahydropyridines in good to excellent yield with high levels of diastereoselectivity. The allenoate provides its α, β, and β′ carbon atoms in the [3 + 3] cycloaddition—a new mode of reactivity for this versatile class of molecules. The mechanism includes apparent intramolecular nucleophilic aromatic substitution and extrusion of SO_2; this unprecedented behavior expands the reaction repertoire of nucleophilic phosphine catalysis. We are currently exploring the further applications of azidirines in nucleophilic phosphine catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

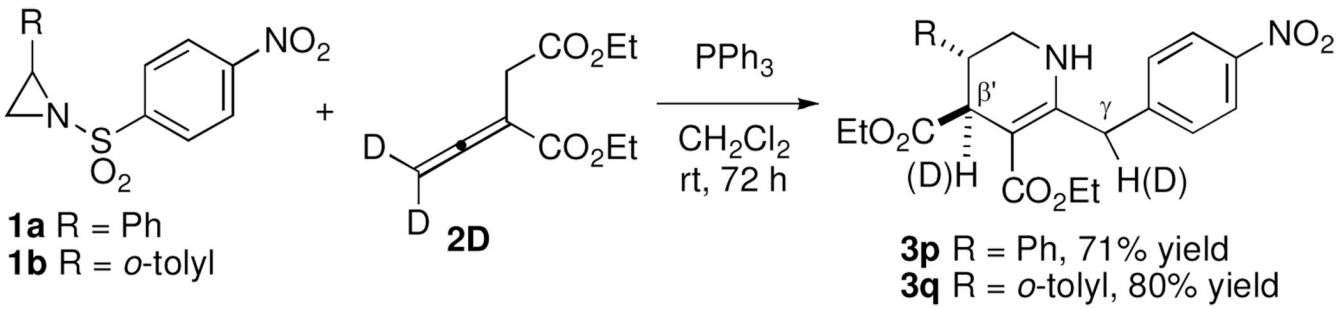
Acknowledgment

This study was funded by the NIH (R01GM071779 and P41GM081282). We thank Dr. Saeed Khan for performing the crystallographic analyses.

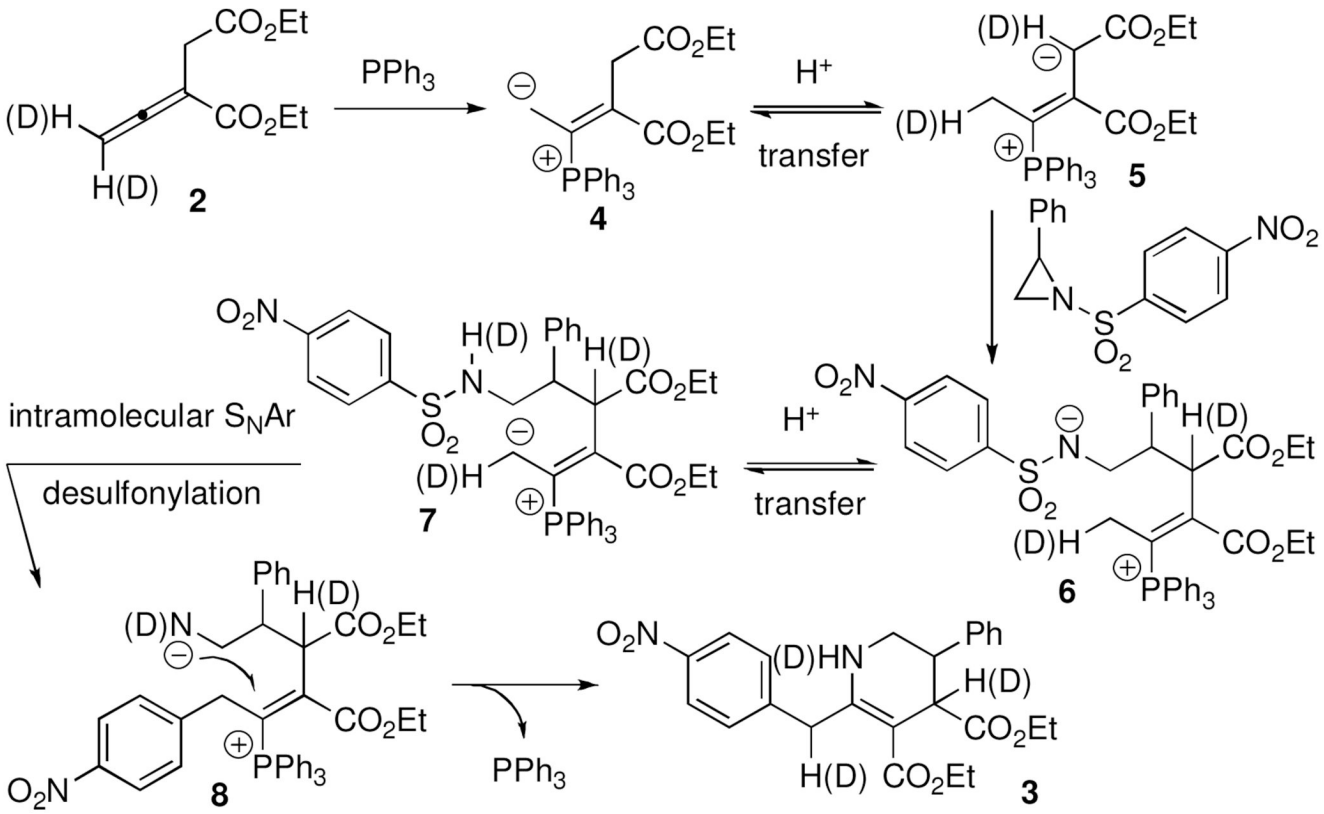
References

1. The Chemical Abstracts Service (CAS) database lists 16 books and 1918 reviews on cycloaddition. For a classical review, see: Padwa A. Trost BM, Fleming I. Comprehensive Organic Synthesis 1991;Vol. 4New YorkPergamon:1069.
2. Li, JJ.; Gribble, GW. Palladium in Heterocyclic Chemistry. New York: Pergamon; 2000. (b) Barluenga J, Santamaria J, Tomas M. Chem. Rev 2004;104:2259. [PubMed: 15137791] (c) Nakamura I, Yamamoto Y. Chem. Rev 2004;104:2127. [PubMed: 15137788]
3. Reviews: (a)Lu X, Zhang C, Xu Z. Acc. Chem. Res 2001;34:535. [PubMed: 11456471] (b)Valentine DH, Hillhouse JH. Synthesis 2003:317. (c)Methot JL, Roush WR. Adv. Synth. Catal 2004;346:1035. (d)Lu X, Du Y, Lu C. Pure Appl. Chem 2005;77:1985. (e)Nair V, Menon RS, Sreekanth AR, Abhilash N, Biji AT. Acc. Chem. Res 2006;39:520. [PubMed: 16906748] (f)Denmark SE, Beutner GL. Angew. Chem., Int. Ed 2008;47:1560. (g)Ye L-W, Zhou J, Tang Y. Chem. Soc. Rev 2008;37:1140. [PubMed: 18497927]
4. For representative examples of [3 + 2] cycloadditions, see: (a)Zhang C, Lu X. J. Org. Chem 1995;60:2906. (b)Zhu G, Chen Z, Jiang Q, Xiao D, Cao P, Zhang X. J. Am. Chem. Soc 1997;119:3836. (c)Wang J-C, Krische MJ. Angew. Chem., Int. Ed 2003;42:5855. (d)Zhu X-F, Henry CE, Kwon O. Tetrahedron 2005;61:6276. (e)Wilson JE, Fu GC. Angew. Chem., Int. Ed 2006;45:1426. (f)Cowen BJ, Miller SJ. J. Am. Chem. Soc 2007;129:10988. [PubMed: 17711278] (g)Fang Y-Q, Jacobsen EN. J. Am. Chem. Soc 2008;130:5660. [PubMed: 18393504] (h)Voituriez A, Panossian A, Fleury-Bregeot N, Retailleau P, Marinetti A. J. Am. Chem. Soc 2008;130:14030. [PubMed: 18834118] For representative examples of [4 + 2] cycloadditions, see: (i)Zhu X-F, Lan J, Kwon O. J. Am. Chem. Soc 2003;125:4716. [PubMed: 12696883] (j)Wurz RP, Fu GC. J. Am. Chem. Soc 2005;127:12234. [PubMed: 16131196] (k)Tran YS, Kwon O. J. Am. Chem. Soc 2007;129:12632. [PubMed: 17914823]
5. The CAS database contains 39,204 references relating to cycloadditions, but only 93 of them relate to [3 + 3] cycloadditions. For reviews on formal [3 + 3] cycloadditions, see: (a)Hsung RP, Kurdyumov AV, Sydorenko N. Eur. J. Org. Chem 2005:23. and references therein. (b)Harrity JPA, Provoost O. Org. Biomol. Chem 2005;3:1349. [PubMed: 15827625] For recent examples, see: (c)Young IS, Kerr MA. Angew. Chem., Int. Ed 2003;42:3023. (d)Sibi MP, Ma Z, Jasperse CP. J. Am. Chem. Soc 2005;127:5764. [PubMed: 15839655] (e)Movassaghi M, Chen B. Angew. Chem., Int. Ed 2007;46:565. (f)Chan A, Scheidt KA. J. Am. Chem. Soc 2007;129:5334. [PubMed: 17407298] (g)Shintani R, Park S, Duan W-L, Hayashi T. Angew. Chem., Int. Ed 2007;46:5901.
6. For recent leading reviews on the synthesis and application of aziridines, see: (a)Müller P, Fruit C. Chem. Rev 2003;103:2905. [PubMed: 12914485] (b)Hu XE. Tetrahedron 2004;60:2701. (c)Tang Y, Ye S, Sun X-L. Synlett 2005:2720. (d)Watson IDG, Yu L, Yudin AK. Acc. Chem. Res 2006;39:194. [PubMed: 16548508] (e)Singh GS, D'hooghe M, De Kimpe N. Chem. Rev 2007;107:2080. [PubMed: 17488062]
7. Zhu X-F, Henry CE, Kwon O. J. Am. Chem. Soc 2007;129:6722. [PubMed: 17488018]
8. *N*-Tosylaziridine was unreactive under the reaction conditions; *N*-(*o*nosyl) aziridine led to a complex mixture of products.
9. Hou XL, Wu J, Fan RH, Ding CH, Luo ZB, Dai LX. Synlett 2006:181.and references therein
10. Henry CE, Kwon O. Org. Lett 2007;9:3069. [PubMed: 17629288]
11. The structures of **3a** and **3n** were established unequivocally through X-ray crystallographic analyses. See the Supporting Information for details.
12. (a) Xia Y, Liang Y, Chen Y, Wang M, Jiao L, Huang F, Liu S, Li Y, Yu Z-X. J. Am. Chem. Soc 2007;129:3470. [PubMed: 17319666] (b) Mercier E, Fonovic B, Henry C, Kwon O, Dudding T. Tetrahedron Lett 2007;48:3617.(c) Ref. 4g
13. When we employed an enantiomerically pure aziridine, we obtained an optically pure tetrahydropyridine product. See the Supporting Information for details.
14. We obtained no crossover product when we reacted the allenaote **2** with a 1:1 mixture of a doubly (deuterium) labeled aziridine and a regular aziridine under the optimized reaction conditions. See the Supporting Information for details.
15. (a) Naito T, Dohmori R, Nagase O. J. Pharm. Soc. Jpn 1954;74:593. (b) Fukuyama T, Jow C-K, Cheung M. Tetrahedron Lett 1995;36:6373. (c) Meng Q, Thibblin A. J. Am. Chem. Soc 1997;119:1224. (d) Wilson MW, Ault-Justus SE, Hodges JC, Rubin JR. Tetrahedron 1999;55:1647.

16. We suspect that the deuterium atom on the enamine nitrogen atom is exchanged to a hydrogen atom in the solvent used for NMR spectroscopy; see the Supporting Information for the results of an enamine H/D exchange experiment. Another possible mechanism explaining the loss of the enamine deuterium atom is enamine/imine tautomerization. The solid state structure of **3a** reveals that the ring $C(sp^2)$–N and C=C bond distances were 1.343 and 1.378 Å, respectively; i.e., they deviate from typical values, indicating a potential enamine/imine mixture. Typical $C(sp^2)$–N, C=N, C=C, and $C(sp^3)$–$C(sp^2)$ bond distances are 1.416, 1.279, 1.322, and 1.507 Å, respectively; see: Lide DR. CRC Handbook of Chemistry and Physics (78th ed.). 199778th ed. Boca Raton, NYCRC Press Section 9.



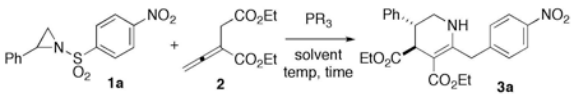
Scheme 1.
Deuterium Labeling Experiments



Scheme 2.
Suggested Mechanism for the Formation of Tetrahydropyridine **3**

Table 1

Phosphine-Mediated [3 + 3] Aziridine/Allene Annulation[a]



entry	PR_3	mol%	yield (%)[b]	dr (trans/cis)[c]
1	PBu_3	20	0	N/A
2	PPh_3	20	15	10:1
3	PPh_3	50	37	9:1
4	PPh_3	100	73	9:1
5	PPh_3	200	61	9:1
6[d]	PPh_3	100	63	9:1
7[e]	PPh_3	100	48	9:1
8	$EtPPh_2$	100	2	–
9	Et_2PPh	100	0	N/A
10	$P(NMe_2)_3$	100	0	N/A
11	$P(OEt)_3$	100	0	N/A

[a] All reactions were performed using 0. 1 mmol of **1a** and 4.8 equiv of **2** in CH_2Cl_2 at rt for 72 h, unless otherwise specified.

[b] Isolated yield after chromatographic purification.

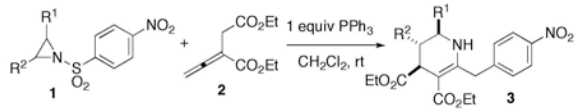
[c] Diastereoisomeric ratio determined through HPLC (internal standard: 2-bromopyridine).

[d] 1,2-Dichloroethane as solvent; other common organic solvents provided isolated product yields of less than 10%.

[e] 40 °C, 48 h.

Table 2

Syntheses of Tetrahydropyridines[a]



entry	R^1	R^2	product	yield (%)[b]	dr (trans/cis)[c]
1	H (**1b**)	2-MeC_6H_4	**3b**	88	90:10
2	H (**1c**)	3-MeC_6H_4	**3c**	82	86:14
3	H (**1d**)	4-MeC_6H_4	**3d**	64	89:11
4	H (**1e**)	2,4-$Me_2C_6H_3$	**3e**	82	81:19
5	H (**1f**)	2,5-$Me_2C_6H_3$	**3f**	98	92:8
6	H (**1g**)	4-FC_6H_4	**3g**	76	88:12
7	H (**1h**)	2-ClC_6H_4	**3h**	46	97:3
8	H (**1i**)	3-ClC_6H_4	**3i**	86	83:17
9	H (**1j**)	4-ClC_6H_4	**3j**	84	90:10
10	H (**1k**)	3-BrC_6H_4	**3k**	58	85:15
11	H (**1l**)	4-BrC_6H_4	**3l**	75	88:12
12	H (**1m**)	2-naphthyl	**3m**	58	85:15
13	Me (**1n**)	H	**3n**	66	41:59
14	H (**1o**)	H	**3o**	37	N/A

[a] All reactions were performed using 0.1 mmol of the aziridine and 4.8 equiv of the allenoate.

[b] Isolated yields.

[c] Diastereoisomeric ratio determined using HPLC (internal standard: 2-bromopyridine).