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Tetrahedron Letters 45 (2004) 4031–4034
Tetrahedron Letters

Regioselective synthesis of fluoroalkyl pyridine derivatives from 3-fluoroalkyl substituted 2-aza-1,3-butadienes

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Received 11 March 2004; revised 24 March 2004; accepted 26 March 2004

Abstract—A method for the preparation of 3-fluoroalkyl substituted 2-aza-butadienes by aza-Wittig reaction of *N*-vinylic phosphazenes and aldehydes is reported. [4+2] Cycloaddition reaction with enamines affords fluoralkyl substituted pyridine derivatives in a regioselective fashion.

Functionalized 2-azabutadiene systems have proved to be efficient key intermediates in organic synthesis for the preparation of heterocycles,[1,2] although the great majority of 2-azadienes studied are substituted with electron-donating groups and they are excellent reagents in *normal* Diels–Alder reactions with electron-poor dienophiles.[1–3]

In the field of bioactive molecules, fluoroorganic compounds have received a great deal of attention. Therefore, the development of efficient and mild methods for organofluorine compound synthesis represents a broad area in organic chemistry since the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical and biological properties.[4] Among them, special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks since they are used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[5] Direct fluorination is the most simple way to prepare fluorinated heterocyclic compounds,[6] but usually the use of fluorinated precursors has been of more interest due to the easy formation of the products and the regioselectivity of the fluorine substituents on the heterocyclic ring.[7]

Fluoroalkyl substituted 2-aza-1,3-butadienes, despite their potential interest as synthons in organic synthesis for the construction of more complex fluoro-containing acyclic and cyclic compounds have not received much attention, probably owing to the lack of general methods of synthesis of these compounds. As far as we know, only examples of synthesis of 4-alkoxy-1,4-disilyloxy-1-trifluoromethyl-,[8a] 1,2-bis-(trifluoromethyl)-,[8b] 4,4-difluoro- and 3-trifluoromethyl-2-aza-1,3-butadienes[8c] have been reported and only reactions of 4-alkoxy-1,4-disilyloxy-1-trifluoromethyl-2-aza-1,3-butadienes with carbonyl compounds[9a] and 1,2-bis-(trifluoromethyl-2-aza-1,3-butadiene) with bromide, amines, mercaptans,[9b] diazomethane[9c] and phosphines[9d] have been described.

In this context, we have described the synthesis of electron-poor 2-aza-1,3-butadienes derived from aminophosphorus derivatives,[10] β-amino esters[11] and of neutral azadienes[12] as well as their use in the preparation of nitrogen heterocyclic compounds.[10–12] As a continuation of our work in the design of new building blocks and owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology and industrial applications,[4,5] we report herein an easy and versatile method for the synthesis of fluoroalkyl substituted 2-azadienes **6** involving aza-Wittig reaction[13] of *N*-vinylic phosphazenes **4** and **9** with aldehydes **5** and the use of these substrates as starting materials for construction of fluoroalkyl functionalized heterocycles. (Scheme 1).

Required fluoroalkyl substituted *N*-vinylic phosphazenes **4** were prepared by reaction of phosphorus ylides and perfluoroalkyl nitriles. Gaseous nitrile (CF_3CN)[14]

Keywords: Aza-Wittig reaction; 2-Aza-1,3-butadienes; Fluoroalkyl derivatives; Heterocycles.
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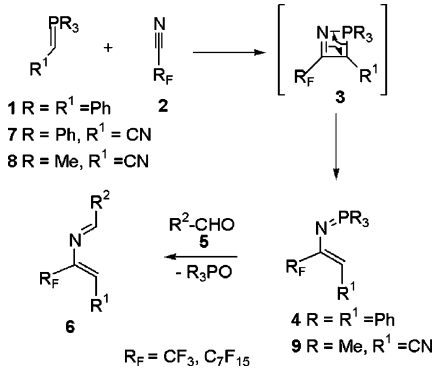
doi:10.1016/j.tetlet.2004.03.174



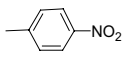
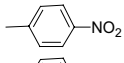
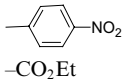
Scheme 1.

was freshly generated and bubbled to the solution of phosphorus ylide **1** ($R = R^1 = Ph$), generated in situ from the corresponding benzyltriphenyl phosphonium salt and methyl lithium to give conjugated phosphazene **4a** ($R_F = CF_3$, $R^1 = Ph$). In a similar way, $C_7F_{15}CN$ was added to a solution of phosphorus ylide **1** for the synthesis of phosphazene **4b** ($R_F = C_7F_{15}$, $R^1 = Ph$), (Scheme 1, Table 1, entries 1 and 2). Phosphazenes **4** derived from triphenylphosphine ($R = R^1 = Ph$) were isolated as *E* isomers and were characterized on the basis of their spectroscopic data.[15] Formation of conjugated phosphazenes **4** can be explained through [2+2] cycloaddition of phosphorus ylide **1** and nitrile **2** followed by ring opening of the unstable four-membered cyclic compound **3**.[12b,16]

The aza-Wittig reaction of fluoroalkyl *N*-vinylic phosphazenes **4a**,**b** with ethyl glyoxalate **5** ($R^2 = CO_2Et$) in $CHCl_3$ gave fluoroalkyl 2-azadienes **6a**,**b** (Scheme 1). The reaction conditions and the yields of the products are summarized in Table 1 (entries 4 and 5). 2-Azadienes **6a** and **6b** were unstable to distillation or chromatography and therefore were not isolated and used in situ for the following reactions, but the presence of the nonisolable compounds was established on the basis of the spectroscopic data of their crude reaction mixtures, which indicated that only the *E*,*E*-isomers were obtained.[17]

In order to extend this strategy to the preparation of functionalized fluoroalkyl 2-azadienes, the synthesis of 2-azadiene **6c** containing a cyano group in position 4 ($R^1 = CN$) was explored. In a similar way conjugated phosphazene **4c** containing a cyan group in position 4 ($R^1 = CN$) can be obtained as a 70/30 mixture of *E*/*Z* isomers by the reaction of phosphorus ylide **7** ($R = Ph$, $R^1 = CN$) and trifluoroacetonitrile **2** ($R_F = CF_3$) (Scheme 1, Table 1, entry 3). However, aza-Wittig reaction of this conjugated phosphazene **4c** derived from triphenylphosphine ($R = Ph$, $R^1 = CN$) with ethyl glyoxalate **5** ($R^2 = CO_2Et$) and *p*-nitrobenzaldehyde ($R^2 = p\text{-}NO_2\text{–}C_6H_4$) at room temperature did not give azadienes **6** and starting material were recovered. The electron-withdrawing effect of the cyan group seems to decrease the reactivity of the conjugated phosphazenes through the P=N linkage. For this reason, we try to prepare more reactive phosphazenes towards the aza-Wittig reaction such as *N*-vinylic phosphazene **9** ($R = Me$, $R^1 = CN$) derived from trimethylphosphine, given that it is known that the substitution in the phosphorus atom of phosphazenes of aryl by alkyl substituents increases the reactivity of the phosphazene[11b] in a similar way to that observed in the isosteric phosphorus ylides.[18] Conjugated phosphazene **9** was prepared by reaction of trifluoroacetonitrile[14] and phosphorus ylide **8** ($R = Me$, $R^1 = CN$)[19] (Scheme 1, Table 1, entry 7). Aza-Wittig reaction of phosphazene **9** derived from trimethylphosphine and *p*-nitrobenzaldehyde ($R^2 = p\text{-}NO_2\text{–}C_6H_4$) in refluxing $CHCl_3$ gave azadiene **6c** ($R_F = CF_3$, $R^1 = CN$, $R^2 = p\text{-}NO_2\text{–}C_6H_4$) (Scheme 1, Table 1, entry 6).

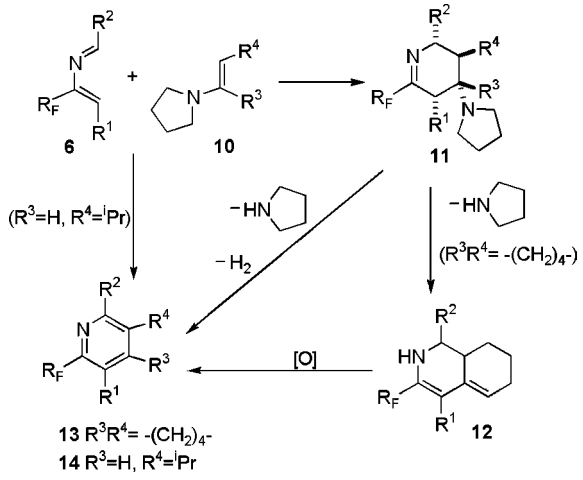
Table 1. Obtained compounds

Entry	Compound	R_F	R	R^1	R^2	R^3	R^4	Reaction conditions			Yield (%)	Mp (°C)
								T (°C)	Time (h)	Solvent		
1	**4a**	CF_3	Ph	Ph	—	—	—	20	12	Et_2O	90[a]	134–135
2	**4b**	C_7F_{15}	Ph	Ph	—	—	—	20	12	Toluene	83[a]	Oil
3	**4c**	CF_3	Ph	CN	—	—	—	20	48	Et_2O	83[b]	Oil
4	**6a**	CF_3	—	Ph	CO_2Et	—	—	20	1	$CHCl_3$	—[c]	—
5	**6b**	C_7F_{15}	—	Ph	CO_2Et	—	—	20	0.5	$CHCl_3$	—[c]	—
6	**6c**	CF_3	—	CN		—	—	75	72	$CHCl_3$	35[a]	Oil
7	**9**	CF_3	Me	CN	—	—	—	20	12	THF	86[a]	133–134
8	**11**	CF_3	—	Ph	–CO_2Et	–$(CH_2)_4$–		20	15	$CHCl_3$	80[a]	Oil
9	**12**	CF_3	—	CN		–$(CH_2)_4$–		20	2	$CHCl_3$	60[d]	156–157
10	**13**	CF_3	—	CN		–$(CH_2)_4$–		100[e]	48[e]	Dioxane	90[e]	Oil
11	**14a**	CF_3	—	Ph	–CO_2Et	H	^{i}Pr	20	24	$CHCl_3$	54[a]	Oil
12	**14b**	C_7F_{15}	—	Ph	–CO_2Et	H	^{i}Pr	20	24	$CHCl_3$	60[a]	Oil

[a] Yield of isolated compounds.
[b] Obtained as a mixture 70:30 of *E*:*Z* isomers.
[c] Not isolated, used in situ for next reaction.
[d] Proportion **12**/**13**: 50/50 obtained from azadiene **6c**.
[e] Obtained by oxidation of compound **12** with quinone.

Pyridine ring is widespread in the alkaloid family and constitute an important class of compounds in pharmaceuticals, agrochemicals and dyestuffs.[20,21] For this reason, in order to test the synthetic usefulness of the new fluoroalkyl substituted azadienes **6** as key intermediates in organic synthesis and especially in the preparation of new fluoroalkyl pyridine derivatives, the [4+2] cycloaddition reaction of fluoroalkyl substituted 2-azadienes **6** with enamines **10** was studied. Alkylfluorinated 2-azadiene **6a** ($R_F = CF_3$, $R^1 = Ph$, $R^2 = CO_2Et$), underwent efficient regio- and stereoselective cycloaddition with *N*-cyclohex-1-enyl pyrrolidine **10a** ($R^3R^4 = (CH_2)_4$) in $CHCl_3$ at room temperature affording the *endo*-cycloadduct **11** in good yield (Scheme 2, Table 1, entry 8) in a regio- and stereoselective fashion.[22]

The structure of compound **11** (Fig. 1) was assigned on the basis of the 1D and 2D spectroscopy, including COSY, NOE, HMQC and HMBC experiments and mass spectral data. Mass spectrometry of **11** showed the molecular ion peak (*m*/*z* 422, 2). The ^{1}H NMR spectrum of compound **11** showed a singlet for a 4-H signal at 3.84 ppm, and a doublet for a 1-H signal at 4.79 ppm with a coupling constant of $^3J_{HH} = 9.8$ Hz, which has a cross-peak connection in the homonuclear COSY spectrum with the 8a-H signal at 2.53–2.56 ppm, confirming the *trans* vicinal coupling relationship. The ^{13}C NMR spectrum of **11** showed a quadruplet at 161.4 ppm with a coupling constant of $^2J_{FC} = 32.0$ Hz, which indicated that C-3 is the imine carbon.



Scheme 2.

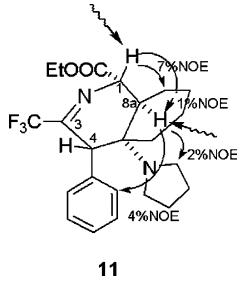


Figure 1.

However, the reaction of heterodiene **6c** ($R_F = CF_3$, $R^1 = CN$, $R^2 = p\text{-}NO_2\text{–}C_6H_4$) with enamine **10a** ($R^3R^4 = (CH_2)_4$) afforded a mixture 50:50 of compounds **12** and **13** (Scheme 2, Table 1, entries 9 and 10). Both compounds were isolated and characterized on the basis of their spectroscopic data. Oxidation of compound **12** with *p*-benzoquinone (dioxane, 100 °C) gave tetrahydroisoquinoline **13** in excellent yield. In further experiments, the cycloaddition reaction of 2-azadienes **6a** ($R_F = CF_3$) and **6b** ($R_F = C_7F_{15}$) with *N*-(3-methyl)-but-1-enyl pyrrolidine **10b** ($R^3 = H$, $R^4 = {}^i\text{Pr}$) was studied. Thus, 2-azadienes **6a**,**b** reacted with *N*-(3-methyl)-but-1-enyl pyrrolidine **10b** to give, after column chromatography, the corresponding aromatized adducts **14a**,**b** in good yield (Scheme 2, Table 1, entries 11 and 12) and in a regioselective fashion. The formation of pyridine derivatives **13** and **14** can be explained through an *inverse demand* aza-Diels–Alder reaction of heterodienes **6** with enamine by formation of cycloadducts **11**, subsequent loss of pyrrolidine and oxidation (Scheme 2). Although several fluoroalkyl substituted pyridines have been synthesized[23] as potential biologically active derivatives by the reaction of fluoroalkylated α,β-unsaturated ketones and enamines, as far as we know, fluoroalkyl substituted tetrahydropyridines **11** and isoquinoline derivatives **12** and **13** has not been described before, and formation of cycloadduct **11** and pyridine derivatives **12**–**14** represent the first example of [4+2] cycloaddition reaction of 2-aza-1,3-butadienes containing fluoroalkyl substituents.

In summary, fluoroalkyl *N*-vinylic phosphazenes can be prepared readily from fluoroalkyl nitriles and phosphorus ylides. They react cleanly and in good yields with aldehydes, by means of an aza-Wittig reaction, to afford fluoroalkyl functionalized 2-azadienes, which have shown to be excellent building blocks for the preparation of fluorinated heterocycles. Fluoroalkylated pyridine derivatives **11**–**14** can be prepared through a Diels–Alder strategy involving heterodienes **6** with electron-rich dienophiles such as enamines. These fluoroalkylated 2-aza-1,3-butadienes may be important synthons in organic synthesis and in the preparation of fluoroalkyl substituted acyclic and heterocyclic derivatives.[1–5] Detailed studies of the mechanism of these processes and an examination of new types of substrates are currently under investigation.

Acknowledgements

The authors thank the *Ministerio de Ciencia y Tecnología* (MCYT, Madrid DGI, BQU2000-0217) and the *Universidad del País Vasco* (UPV-GC/2002) for supporting this work. C.A. thanks the *Departamento de Educación, Universidades e Investigación* of *Gobierno Vasco* for a Postdoctoral Fellowship and M.V. thanks the *Universidad del País Vasco* for a Predoctoral Fellowship.

References and notes

1. For reviews, see: (a) Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1669; (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379; (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
2. For recent contributions, see: (a) Alves, M. J.; Duraes, M. M.; Gil, A. *Tetrahedron Lett.* **2003**, *44*, 5079; (b) Nicolau, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941; (c) Moody, C. J.; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760; (d) Ntirampebura, D.; Ghosez, L. *Synthesis* **2002**, 2043.
3. (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617; (b) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735; (c) Ntirampebura, D.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 7079; (d) Bongini, A.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1997**, *62*, 8911; (e) Ghosez, L. *Pure Appl. Chem.* **1996**, *68*, 15.
4. (a) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: Berlin, 2000; (b) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, 1991.
5. (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, 1999; (b) *Fluorine-Containing Amino Acids: Synthesis and Applications*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: New York, 1995.
6. (a) Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8773; (b) Hou, Y.; Higashiya, S.; Fuchigami, T. *Synlett* **1997**, 655.
7. (a) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455; (b) Shen, Y.; Zhang, Y.; Sun, J. *J. Fluorine Chem.* **2002**, *116*, 157; (c) Peng, W.; Zhu, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3204.
8. (a) Oesterle, T.; Simchen, G. *Synthesis* **1985**, 403; (b) Burger, K.; Dirsteiner, G.; Fehn, J. *Liebigs Ann. Chem.* **1971**, *747*, 45; (c) Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563.
9. (a) Simchen, G.; Pürkner, E. *Synthesis* **1990**, 525; (b) Burger, K.; George, G.; Fehn, J. *Liebigs Ann. Chem.* **1972**, *757*, 1; (c) Burger, K.; Fehn, J. *Liebigs Ann. Chem.* **1972**, *757*, 14; (d) Burger, K.; Meffert, A. *Liebigs Ann. Chem.* **1975**, 316.
10. (a) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; Rodríguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617; (b) Palacios, F.; Gil, M. J.; Martínez de Marigorta, E.; Rodríguez, M. *Tetrahedron Lett.* **1999**, *40*, 2411.
11. (a) Palacios, F.; Herrán, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002**, *67*, 2131; (b) Palacios, F.; Herrán, E.; Rubiales, G. *J. Org. Chem.* **1999**, *64*, 6239.
12. (a) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941; (b) Palacios, F.; Alonso, C.; Rubiales, G. *J. Org. Chem.* **1997**, *62*, 1146.
13. Aza-Wittig reaction affords an excellent strategy for the construction of the C=N double bonds. For reviews, see: (a) Wamhoff, H.; Richard, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159; (b) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1.
14. $C_7F_{15}CN$ was purchased from Lancaster, however CF_3CN was freshly prepared by dehydration of the corresponding amide (CF_3CONH_2) Reisner, D. B.; Horning, E. C. *Org. Synth. Coll. Vol. IV* **1963**, 144.
15. *General procedure for preparation of phosphazenes* **4**. A solution 1.6 M solution of methyllithium in ether (3.125 mL, 5 mmol) was added dropwise to a solution of 2.40 g (5 mmol) of benzyltriphenylphosphonium iodide in ether (20 mL) cooled to 0 °C under N_2. The clear red solution was heated to reflux for 1 h. Fluoroalkylated nitrile was added dropwise or bubbled to the ylide solution at 0 °C and the mixture was stirred at room temperature overnight. Selected data: compound **4a**: IR (KBr) ν 1600, 1341/cm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, $J = 3.2$ Hz, 1H), 6.98–7.85 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.8 (dd, $^3J_{CP} = 11.3$ Hz, $^3J_{CF} = 1.7$ Hz, CH=), 122.8 (dq, $^1J_{CF} = 278.0$ Hz, $^3J_{CP} = 24.5$ Hz, CF_3) 125.5–133.7 (m), 137.0 (q, $^2J_{CF} = 21.4$ Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 7.95; ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1; MS (EI) m/z 447 (M+, 100). Anal. Calcd for: $C_{27}H_{21}F_3NP$ (447): C, 72.48; H, 4.73; N, 3.13. Found: C, 72.02; H, 4.68; N, 3.10.
16. (a) Barluenga, J.; Ferrero, M.; Ortiz, F.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 615; (b) Ciganek, E. *J. Org. Chem.* **1970**, *35*, 3631.
17. In the ^{1}H NMR spectrum of crude reaction of compound **6a** the olefinic hydrogen appeared as a singlet at δ 6.90 ppm and the iminic hydrogen as a quadruplet at δ 7.82 ppm with coupling constant of $^5J_{FH} = 1.2$ Hz.
18. *Ylides and imines of phosphorus*; Johnson, A. W., Kaska, W. S., Starzewski, K. A. O., Dixon, D. A., Eds.; Wiley: New York, 1993.
19. For preparation of ylide **8**, see: Tsunoda, T.; Nagino, C.; Oguri, M.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2459.
20. (a) Coffey, D. S.; Kolis, S. P.; May, S. A. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Amsterdam, 2002; Vol. 14, Chapter 6.1; (b) Bentley, K. W. *The isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; (c) Ciufolini, M. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: London, 1996; Vol. 3; (d) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2. Chapter 2.09.
21. (a) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042; (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.
22. *General procedure for [4+2] cycloaddition reactions*. Enamine **10** (1.5 mmol) was added to a 0–10 °C solution of azadiene **6** (1.5 mmol) in $CHCl_3$ or toluene under N_2, and the mixture was stirred at adequate temperature, until TLC indicated the disappearance of azadiene.
23. (a) Cooke, J. W. B.; Coleman, M. J.; Caine, D. M.; Jenkins, K. P. *Tetrahedron Lett.* **1998**, *39*, 7965; (b) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, 1321.