DOI: 10.1002/adsc.200505187

Rhodium-Catalyzed Asymmetric Intramolecular Cyclopropanation of Substituted Allylic Cyanodiazoacetates

Wei Lin, André B. Charette*

Département de Chimie, Université de Montréal, P. O. Box 6128, Station Downtown, Montréal, QC H3C 3J7, Canada
Phone: (+1)-514-343-2432, Fax: (+1)-514-343-5900, e-mail: andre.charette@umontreal.ca

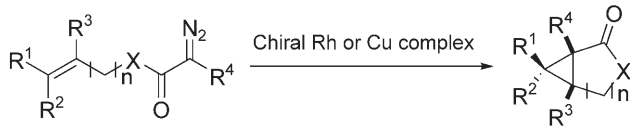
Received: March 5, 2005; Accepted: August 1, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A chiral rhodium catalyst, Rh_2[4*S*-(4′)-FBNAZ]$_4$, was synthesized and was shown to catalyze the intramolecular cyclopropanation of substituted allylic cyanodiazoacetates. Alkenes bearing an electron-deficient substituent including carbonyl and halogens are converted into the corresponding cyclopropanes in high yields with both chiral and achiral rhodium catalysts. The cyclopropane derivatives were generated with an enantioselectivity of up to 91% ee. For the asymmetric intramolecular cyclopropanation, *cis*-halogen-substituted substrates afforded cyclopropanes with higher enantioselectivities than the corresponding *trans* diastereomers. However, only moderate enantioselectivities were observed with alkenes bearing electron-donating groups such as alkyls. The cyclopropanation of 3-substituted 2-propenyl cyanodiazoacetates was strongly influenced by steric and electronic factors arising from substituents on the alkenes. For the first time, we demonstrated that the intramolecular reaction of *gem*-dihaloallylic cyanodiazoacetate afforded highly functionalized *gem*-dihalocyclopropanes. This reaction is an appealing alternative to the addition of dihalocarbenes to alkenes for the formation of *gem*-dihalocyclopropanes.

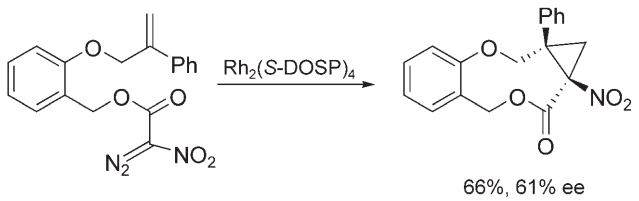
Keywords: chiral catalyst; cyanodiazoacetates; halocyclopropanes; intramolecular cyclopropanation; rhodium

The intramolecular cyclopropanation of alkenes *via* the transition metal-catalyzed decomposition of diazo derivatives is a simple and convenient method to generate synthetically versatile [*n*.1.0]bicycloalkanes.[1] The enantioselective intramolecular cyclopropanation of diazo compounds bearing one electron-withdrawing group (EWG) (Scheme 1, X = C, O or NMe, R^4 = H) is highly efficient both in terms of yields and enantioselectivities.[2] However, the efficient inter- or intramolecular enantioselective [2+1] cycloaddition of diazo derivatives bearing two EWGs (Scheme 1, X = C, O or N, R^4 = COOR, COR, NO_2, CN, SO_2R or CONRR′) is still an unsolved and quite challenging problem in synthesis. To our knowledge, the only report of such an enantioselective cycloaddition (98% ee) is a Cu(I)-catalyzed intramolecular cyclopropanation of α-diazo-β-keto sulfones (Scheme 1).[3] Müller has also reported an enantioselective intramolecular cyclopropanation of a malonate derivative, however, the optimized conditions led to a product having 83% ee in only 24% yield (Scheme 1).[4] The Rh(II)-catalyzed intramolecular cyclopropanation of α-nitro-α-diazo carbonyls as an effective entry into functionalized macrocyclic-fused cyclopropane α-amino acids has been reported by our group, however, the highest enantioselectivity was 61% ee (Scheme 2).[5] Since the cyclopropanation of diazo pre-



$R^1 = R^2 = R^3$ = H, R^4 = H, X = O, n = 1 (95% ee)[2a]
$R^1 = R^2 = R^3$ = H, R^4 = H, X = NMe, n = 1 (93% ee)[2b]
$R^1 = R^2 = R^3$ = H, R^4 = SO_2Mes, X = C, n = 1 (98% ee)[3]
$R^1 = R^2 = R^3$ = H, R^4 = COOBu-*t*, X = O, n = 1 (83% ee)[4]

Scheme 1.



Scheme 2.

cursors with two electron-withdrawing groups (R^4 = EWG) affords generally modest enantioselectivities, we were curious to examine the same reaction in which R^4 is a cyano substituent. The cyano group is not only much smaller than a mesityl sulfone, a *tert*-butyl ester or a nitro group but also stereoelectronically quite different.

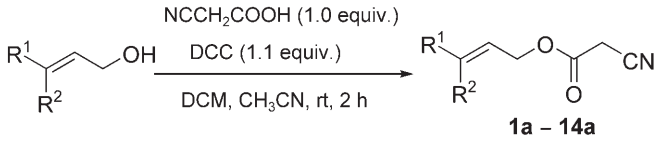
In this communication, we report that the enantioselective intramolecular cyclopropanation of a new class of cyanodiazoacetate is catalyzed by a chiral rhodium catalyst, Rh_2[4*S*-(4′)-FBNAZ]$_4$ that provides oxabicyclo[3.1.0]hexan-2-one-1-carbonitrile derivatives in up to 91% ee. These cyanocyclopropanes are precursors of cyclopropane α- and β-amino acids that are potentially valuable constituents in novel peptides.[6]

Synthesis of racemic 6-substituted-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carbonitrile derivatives: The cyclopropanation reaction involving the transition metal-catalyzed decomposition of diazo ester derivatives is usually most successful with electron-rich alkenes. Therefore, the preparation of allylic α-cyano-α-diazoacetates that were substituted with alkyl or aryl groups at the 3-position was needed for our first attempts. The α-cyano esters **1a**–**14a** were synthesized by the condensation of the substituted allylic alcohols with cyanoacetic acid in 60–96% yields using standard procedures (Scheme 3).[7]

The conversion to their corresponding α-diazo derivatives **1b**–**14b** was smoothly accomplished in excellent yields using a procedure developed by our group that involves treatment of the starting materials with a solution of 1.5 equivs. of triflyl azide and 2 equivs. of pyridine in acetonitrile/hexanes. Good to excellent yields of the diazo compounds were obtained regardless of the substituents on the alkenes (Table 1).[8]

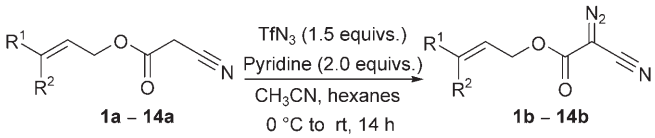
The intramolecular cyclopropanation leading to racemic oxabicyclo[3.1.0] derivatives **1c**–**14c** was typically carried out by slowly adding a solution of the starting diazo species **1b**–**14b** to a rhodium(II) octanoate dimer solution in dichloromethane (Table 2). The alkyl-substituted allylic esters **2b** and **3b** led to the cyclopropane in 53% and 50% yield, respectively (entries 2 and 3), which is lower than the yield observed for the cyclopropanation of the unsubstituted allylic ester **1b** (entry 1).

Furthermore, the ester-substituted allylic ester **5b** (entry 5) provided the corresponding cyclopropane **5c** in 90% yield and after just 2.5 h! Although halocyclopropanes are very useful synthons in organic synthesis,[9] there are only few reports of intramolecular cyclopropanation of allylic diazoacetates bearing halogens.[10] Therefore, a series of 3-halo-substituted allylic cyanodiazoacetates was synthesized and tested in the intramolecular cyclopropanation reaction. Rhodium octanoate dimer efficiently catalyzed the intramolecular cyclopropanation reaction of substrates **6b**–**14b**, albeit in variable yields. As expected, a single diastereomer was



Scheme 3.

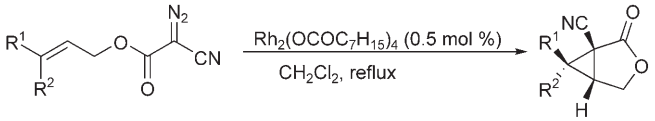
Table 1. Triflyl azide-mediated diazo transfer to allyl α-cyanoacetates.



Entry	R^1	R^2	Product	Yield [%][a]
1	H	H	**1b**	86[b]
2	Me	Me	**2b**	66
3	H	Et	**3b**	84
4	Ph	H	**4b**	84
5	COOEt	H	**5b**	76
6	Cl	H	**6b**	85
7	Br	H	**7b**	85
8	I	H	**8b**	78
9	H	Cl	**9b**	93
10	H	Br	**10b**	86
11	H	I	**11b**	88
12	Br	Br	**12b**	98
13	I	I	**13b**	89
14[c]	F	Br	**14b**	92

[a] Isolated yields after chromatography on silica gel.
[b] See ref.[8]
[c] Ratio (*cis* : *trans*) = 1.3 : 1.

Table 2. Intramolecular cyclopropanation of allyl α-cyano-α-diazoacetate catalyzed by rhodium octanoate dimer.

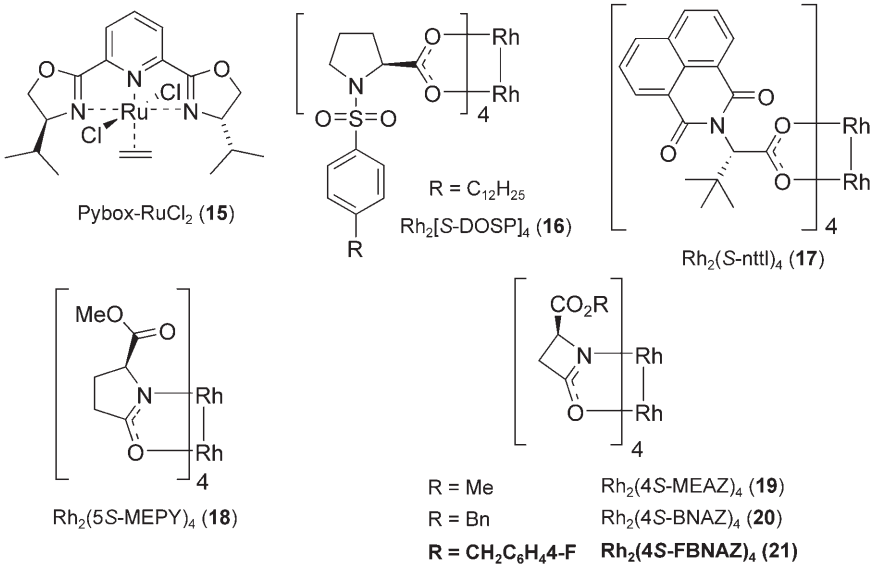


Entry	R^1	R^2	*t* (h)	Product	Yield [%][a]
1	H	H	3.0	**1c**	75
2	Me	Me	2.0	**2c**	53
3	H	Et	5.0	**3c**	50
4	Ph	H	18.5	**4c**	49
5	COOEt	H	2.5	**5c**	90
6	Cl	H	3.5	**6c**	81
7	Br	H	3.5	**7c**	79
8	I	H	8.5	**8c**	33
9	H	Cl	6.0	**9c**	62
10	H	Br	4.0	**10c**	75
11	H	I	3.7	**11c**	63
12	Br	Br	17.0	**12c**	69
13	I	I	19.0	**13c**	55
14[b]	F	Br	21.0	**14c**	38

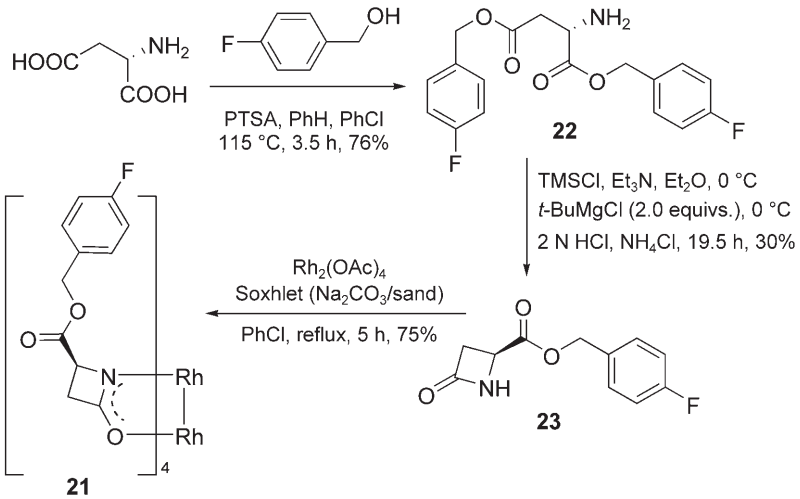
[a] Isolated yields after chromatography on silica gel.
[b] Ratio (*cis*:*trans*) = 1.3 : 1.

formed in all the cases. The efficiency of the intramolecular cyclopropanation for the *E*-haloallylic esters follows the order: Cl > Br > I (entries 6–8) whereas the same reactions run on the *Z*-isomers were generally more efficient regardless of the halide (entries 9–11). Interestingly, the 3,3-dihaloallylic esters underwent smooth cyclopropanation to generate the bicyclic system (entries 12–14). It is clear from the data that the rhodium-catalyzed cyclopropanation of *gem*-dihaloallylic cyanodiazoacetates to form functionalized *gem*-dihalocyclopropanes is a competitive alternative to the only reported synthetic route involving the addition of dihalocarbenes to alkenes in the presence of phase transfer catalysts.

Enantioselective synthesis of 6-substituted 2-oxo-3-oxabicyclo[3.1.0]hexane-1-carbonitriles: Having developed an efficient route to racemic oxabicyclic[3.1.0] systems, we then turned our attention to the elaboration of an enantioselective version of the reaction. We screened five chiral ruthenium and rhodium catalysts that have a proven record in intramolecular cyclopropanation reactions. Unfortunately, Nishiyama's catalyst **15**[11] did not lead to any cyclopropanation (Table 3, entry 1). Since the rhodium carboxylate dimers **16**[12] and **17**[13] led to some desired products but with low enantioselectivities (entries 2 and 3), we turned our attention towards testing the rhodium(II) carboxamide dimers. Even though $Rh_2(5S\text{-MEPY})_4$ (**18**) is known not to be efficient for the cyclopropanation of α-diazomalonate derivatives, the azetidine analogue **19** proved to be more efficient.[14]

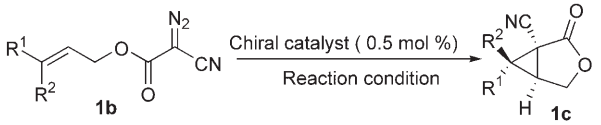


Scheme 4.



Scheme 5.

Table 3. Chiral catalyst screening for the cyclopropanation of α-cyano-α-diazoacetates.



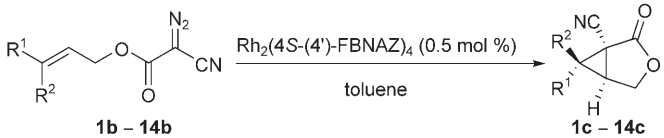
1b 1c

Entry	R^1	R^2	Catalyst	Reaction condition	t [h]	Yield [%][a]	ee [%]
1	H	H	Pybox-$RuCl_2$ (**15**)	reflux, DCM	19	n.r.[b]	---
2	H	H	Rh_2(*S*-DOSP)$_4$ (**16**)	reflux, DCM	4.5	27	<5[c]
3	H	H	Rh_2(*S*-nttl)$_4$ (**17**)	reflux, DCM	8.0	66	<5[c]
4	H	H	Rh_2(4*S*-MEAZ) (**19**)	reflux, DCM	18	44	79[c]
5	H	H	Rh_2(4*S*-BNAZ) (**20**)	reflux, DCM	5.5	70	78[c]
6	H	H	Rh_2(4*S*-(4')-FBNAZ)$_4$ (**21**)	reflux, DCM	4.5	85	85[c]
7	Me	Me	Rh_2(4*S*-BNAZ)$_4$ (**20**)	50 °C, toluene	23	30	45[c]
8	Me	Me	Rh_2(4*S*-(4')-FBNAZ)$_4$ (**21**)	50 °C, toluene	23	37	56[c]
9	H	Br	Rh_2(4*S*-BNAZ)$_4$ (**20**)	–20 °C, toluene	24	52	84[c]
10	H	Br	Rh_2(4*S*-(4')-FBNAZ)$_4$ (**21**)	–20 °C, toluene	24	57	91[c]

[a] Isolated yield.
[b] n.r.: no reaction.
[c] Enantiomeric excess determined by GC.

Dirhodium(II) tetrakis[methyl-2-oxaazetidine-4(*S*)-carboxylate], Rh_2(4*S*-MEAZ)$_4$ (**19**) led to the desired cyclopropane in 44% yield and 79% ee (Table 3, entry 4). The benzyl ester analogue **20**[15] led to a slight improvement in the yield (70%) without any decrease in ee (entry 5). After substantial efforts, we found that the introduction of a 4-fluoro substituent on the benzyl group of the catalyst led to a significant improvement in both the yield and the ee (Table 3, entries 6 and 10). The synthesis of catalyst **21** started from aspartic acid that was converted into the bis(*p*-fluorobenzyl) diester **22**. A subsequent lactamization and conversion to the rhodium(II) carboxamidate was accomplished according to the literature procedure for the preparation of the analogous benzyl ester.

Table 4. Catalytic asymmetric intramolecular cyclopropanation of α-cyano-α-diazo ester derivatives.



1b – 14b 1c – 14c

Starting material	T [°C]	t [h]	Yield [%][a]	ee [%][b]
1b[c]	reflux	5.5	85	85
2b	50	23	37	56
3b[c]	reflux	19	53	N/D
4b[c]	reflux	21	35	29
5b	rt	22.5	32	80
6b	0 – rt	19	11[d]	N/D
7b	–20	24	27	87
8b	rt	24	21	75
9b	–40	24	43	77
10b	–20	24	57	91
11b	–20	24	55	86
12b	rt	17	52	62
13b	rt	24	20	47

[a] Isolated yield after chromatography on silica gel.
[b] Determined by GC or SFC (see Supporting Information).
[c] Reaction run in dichloromethane.
[d] Conversion calculated from the ^{1}H NMR analysis of crude product.

This catalyst was then tested in the intramolecular cyclopropanation of a wide range of 6-substituted allylic ester derivatives (**1b**–**13b**) and the results are illustrated in Table 4. The optimal protocol for this reaction calls for using 0.5 mol % of Rh_2[4*S*-(4′)-FBNAZ]$_4$ in toluene and carrying out the reaction at temperatures ranging from -40 to 50 °C. In all the cases tested, the yields were usually modest to excellent. It appears that the relative activity of the Rh_2[4*S*-(4′)-FBNAZ]$_4$ catalyst was lower than that of rhodium(II) octanoate dimer.

Although the cyclopropanation of halogen- or carbonyl-substituted alkenes proceeded in modest yields, the enantiomeric excesses of the products were above 75% in many instances. However, in the cases of **2b**, **4b** and **13b**, only moderate ees were observed (56% and 29% ee, respectively). It is clear from the data presented in Table 4 that the best substrates for the reaction are the *Z*-haloallylic acetates derivatives that not only produced the highest ees but also the best conversions. For example, 6-bromo-3-oxabicyclo[3.1.0]heptan-2-one-1-carbonitrile (Table 4, **10c**) was obtained in up to 91% ee by the cyclopropanation of *Z*-bromo-substitut-

ed cyanodiazoacetate, whereas the enantiocontrol for the same reaction done on the *E*-isomer was not as high (87% ee) (Table 4, **7b)**. In this process, we found that the enantioselectivity was significantly improved when we decreased the reaction temperature. For instance, in the case of **5b**, the enantioselectivity increased from 67% to 80% ee by lowering the reaction temperature from 50 °C to room temperature. In the case of **10b**, the selectivity was improved up to 91% ee when the reaction was run at −20 °C. With two halogen substituents on the alkenes, the enantioselectivity dropped following the order Br > I (Table 4, **12b** *vs.* **13b**). The absolute configurations of **1c**, **10c** and **11c** were established by single crystal X-ray analysis. The absolute configurations of the other bicyclo adducts were then assumed to be the same.

In summary, we have demonstrated that the rhodium-catalyzed intramolecular cyclopropanation of 3-substituted-2-propenyl cyanodiazoacetates occurred cleanly to form the corresponding cyclopropane derivatives in high yields. In the enantioselective version of this transformation, we found that a chiral rhodium catalyst, Rh_2[4*S*-(4′)-FBNAZ]$_4$, led to the desired cyclopropane in up to 91% ee. However, the level of enantioselection was greatly dependent upon the substitution of the alkene. We have also demonstrated that the cyclopropanation of *gem*-dihaloallylic cyanodiazoacetates produced the *gem*-dihalocyclopropanes very efficiently. We are currently exploring the scope of the rhodium-catalyzed intramolecular cyclopropanation of diazo compounds with alkenes that bear two electron-withdrawing groups and the results will be reported in due course.

Experimental Section

Synthesis of Dirhodium(II) Tetrakis-[4′-fluorobenzyl 2-Oxaazetidine-4(*S*)-carboxylate], Rh_2[4*S*-(4′)-FBNAZ]$_4$

Treatment of dirhodium (II) acetate (0.068 g, 0.15 mmol) with 4′-fluorobenzyl (*S*)-(−)-2-oxaazetidine-4-carboxylate (0.34 g, 1.5 mmol) in chlorobenzene (30 mL) as described in the literature[14d] and subsequent purification by chromatography on silica gel (20% – 100% ethyl acetate in hexane) afforded Rh_2[4*S*-(4′)-FBNAZ]$_4$ as a blue solid; yield: 126 mg (0.12 mmol, 75%); $[\alpha]_D^{20}$: −142° (c 0.108, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30 – 7.39 (m, 8H, ArH), 7.00 – 7.05 (m, 8H, ArH), 5.11 – 5.17 (m, 8H, 4 × CH_2Ar), 3.98 – 4.11 (br, 4H, 4 × CH), 3.16 – 3.37 (m, 8H, 4 × CH_2COO); ^{19}F NMR ($CDCl_3$, 400 MHz): δ = 115.9 (d, *J* = 162.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.6 (CO), 173.3 (CO), 164.1 (d, *J* = 7.1 Hz, CO), 161.6 (d, *J* = 6.6 Hz, CO), 131.4 (d, *J* = 17.4 Hz, Ar), 130.5 (d, *J* = 7.4 Hz, Ar), 115.8 (d, *J* = 11.3 Hz, Ar), 115.6 (d, *J* = 11.3 Hz, Ar), 66.4 (s, CH_2Ar), 52.3 (d, *J* = 19.8 Hz, CHCOO), 43.3 (d, *J* = 114.3 Hz, CH_2COO); IR (film): ν = 2170, 1738 (C=O), 1660 (C=O), 1512, 1225, 1156, 827 cm^{-1}; MS (APCI+): *m/z* = 1095; calcd. for $C_{44}H_{36}F_4N_4O_{12}Rh_2$ [M + 1]$^+$: 1095; anal. calcd. for $C_{44}H_{36}F_4N_4O_{12}Rh_2$: C 48.28, H 3.32, N 5.12; found: C 48.15, H 3.17, N 5.08.

Typical Procedure for the Intramolecular Cyclopropanation (Table 2)

***(1R,5S)-3-Oxabicyclo[3.1.0]hexan-2-one-1-carbonitrile* (1c):** A solution of allyl α-cyano-α-diazoacetate (77 mg, 0.3 mmol) in dichloromethane (2.5 mL) was added via a syringe pump (1.0 mL/h) over 2.5 h to a solution of $Rh_2(C_7H_{15}COO)_4$ (1.2 mg, 0.5 mol %) in 1.5 mL of dichloromethane at reflux. After the completion of the addition, the reaction mixture was stirred at reflux to ensure complete reaction. The mixture was then cooled to room temperature and concentrated under reduced pressure (rotary evaporator). Purification of the crude residue by flash chromatography on silica gel (30% – 45% ethyl acetate/hexane) afforded (1*R*,5*S*)-3-oxabicyclo[3.1.0]hexan-2-one-1-carbonitrile (**1c**) as a white solid; yield: 56 mg (76%).

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-269733 (**1c**), CCDC-269732 (**10c**) and CCDC-269734 (**11c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336 – 033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was supported by NSERC (Canada), Merck Frosst Canada & Co., Boehringer Ingelheim (Canada) Ltd. and the Université de Montréal. We acknowledge Francine Bélanger Gariepy for X-ray technical support.

References and Notes

[1] For selected reviews, see: a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050; b) M. P. Doyle, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; c) G. Maas, *Chem. Soc. Rev.* **2004**, *33*, 183 – 190.

[2] a) M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. L. Zhou, S. F. Martin, *J. Am. Chem. Soc.* **1995**, *117*, 5763 – 5775; b) M. P. Doyle, A. V. Kalinin, *J. Org. Chem.* **1996**, *61*, 2179 – 2184.

[3] a) M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 2860 – 2861; b) M. Honma, M. Nakada, *Tetrahedron Lett.* **2003**, *44*, 9007 – 9011.

[4] a) P. Müller, C. Boléa, *Synlett* **2000**, 826 – 828; b) P. Müller, C. Boléa, *Helv. Chim. Acta* **2001**, *84*, 1093 – 1111.

[5] A. B. Charette, R. P. Wurz, *J. Mol. Catal. A: Chem.* **2003**, *196*, 83–91.
[6] a) F. Gnad, M. Poleschak, O. Reiser, *Tetrahedron Lett.* **2004**, *45*, 4277–4280; b) F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603–1623; c) R. Beumer, O. Reiser, *Tetrahedron* **2001**, *57*, 6497–6503; d) D. Moye-Sherman, S. Jin, S. M. Li, M. B. Welch, J. Reibenspies, K. Burgess, *Eur. J. Chem.* **1999**, *5*, 2730–2739; e) D. Moyesherman, S. Jin, I. Ham, D. Y. Lim, J. M. Scholtz, K. Burgess, *J. Am. Chem. Soc.* **1998**, *120*, 9435–9443.
[7] a) M. Nahmany, A. Melman, *Org. Lett.* **2001**, *3*, 3733–3735; b) Y. Chen, S. M. Sieburth, *Synthesis* **2002**, 2191–2194.
[8] R. P. Wurz, W. Lin, A. B. Charette, *Tetrahedron Lett.* **2003**, *44*, 8845–8848.
[9] For recent reviews, see: a) W. R. Dolbier, M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071–1098; b) M. Fedorynski, *Chem. Rev.* **2003**, *103*, 1099–1132.
[10] In addition to ref.[2a] see: a) A. Wong, C. J. Welch, J. T. Kuethe, E. Vazquez, M. Shaimi, D. Henderson, *Org. Biomol. Chem.* **2004**, *2*, 168–174; b) D. L. Boger, T. J. Jenkins, *J. Am. Chem.* **1996**, *118*, 8860–8870; c) S. F. Martin, M. P. Dwyer, *Tetrahedron Lett.* **1998**, *39*, 1521–1524.
[11] H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223–2224.
[12] H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.
[13] P. Müller, Y. Allenbach, E. Robert, *Tetrahedron: Asymmetry* **2003**, *14*, 779–785.
[14] M. P. Doyle, S. B. Davies, W. H. Hu, *Org. Lett.* **2000**, *2*, 1145–1147.
[15] M. P. Doyle, Q. L. Zhou, S. H. Simonsen, V. Lynch, *Synlett* **1996**, 697.

