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Intermolecular Cyclopropanation versus CH Insertion in Rh^{II}-Catalyzed Carbenoid Reactions

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Abstract—The product ratio of intermolecular insertion and cyclopropanation in transition metal-catalyzed diazo decompositions depends strongly upon the metal, its ligands and upon the substituents of the diazo compound. Ethyl diazoacetate (**2a**) reacts with cyclohexene (**1**) almost exclusively by cyclopropanation. However, diazomalonate (**2d**) and methyl 2-diazophenylacetate (**2e**) in the presence of Rh^{II} catalysts exhibit a marked tendency towards allylic CH insertion. With 1,4-cyclohexadiene (**6**), methyl 2-diazophenylacetate (**2e**) in the presence of chiral Rh^{II} catalysts affords the allylic insertion product **7** in almost quantitative yield and with up to 74% ee.

Introduction

The intermolecular addition of metal carbenoids to olefins or acetylenes affords cyclopropanes or cyclopropenes, respectively, in high yields and with almost perfect enantioselectivity in selected cases.[1] In contrast, until very recently, efficient and enantioselective carbon hydrogen bond-insertions of carbenoids were limited to intramolecular reactions.[2] Intermolecular CH insertions of carbenes and metal carbenoids have the reputation of being unselective, resulting usually in mixtures of products[3] and are, therefore, considered of no synthetic significance.[1,4] In addition to their lack of selectivity, the intermolecular carbenoid insertions suffer from competing secondary reactions, such as formation of formal carbene dimers. Recently, Davies and coworkers[5] have shown that the formation of carbene dimers is characteristic for monosubstituted diazo compounds such as ethyl diazoacetate; it does not occur with carbene precursors carrying two organyl substituents at the carbenic center, such as 2-diazophenylacetates, diazovinylacetates or diazoacetoacetates. Enantioselective intermolecular insertions have been carried out with methyl 2-diazophenylacetate into CH bonds of cycloalkanes and cyclic ethers.[6]

The selectivity of metal carbenoids depends upon the metal, its ligands, and upon the substituents of the carbene, and it may be controlled by an appropriate selection of parameters.[1] In Rh^{II}-catalyzed intramolecular competition reactions between cyclopropanation and aromatic substitution for example, the product ratio is inverted in function of the ligand. With caprolactam as ligand the main pathway is cyclopropanation, but with perfluorobutyrate it is aromatic substitution.[7]

Some time ago, we observed that the cyclopropanation of cyclohexene (**1**) with dimethyl diazomalonate (**2d**) and $PhI{=}C(COOMe)_2$ in the presence of Rh^{II} catalysts afforded mixtures of products derived from intermolecular insertion and cyclopropanation. The product ratio **3d**/**4d** fluctuated from 41:59 to 20:80 according to the reaction conditions.[8] Subsequently, we found that the product ratio varied in function of the structure of the diazo compound, the metal atom of the catalyst, and of its ligands. The present investigation was started with the objective of finding reaction conditions under which intermolecular CH insertion of cyclohexene and cyclohexadiene would be the predominant pathway. Some of our results have been reported in preliminary form since 1998.[9]

Results and Discussion

We have investigated the ratio for intermolecular insertion vs. intermolecular cyclopropanation products upon reaction of cyclohexene (**1**) with diazoacetate esters **2** by varying the parameters which are known to influence carbene selectivity.[7,10] Reactions were carried out in CH_2Cl_2 at 25° using 2% of catalyst and 10 equiv. of cyclohexene (**1**) (Table 1) (Scheme 1).

The Cu^{I}-catalyzed reaction of ethyl diazoacetate (EDA, **2a**) with **1** has been reported in the literature.[11] It results essentially in cyclopropanation and no insertion product **4a** has been detected. With $[Rh_2(OAc)_4]$ as catalyst and EDA (**2a**)

Keywords: diazo decomposition; CH bond insertion; rhodium catalyst; asymmetric induction.

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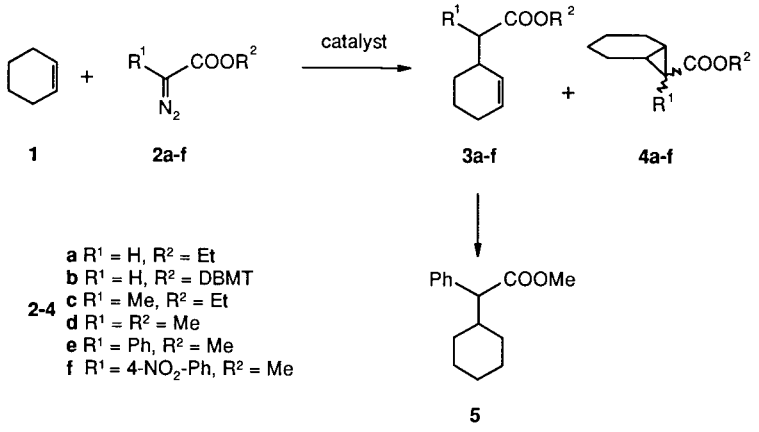
Table 1. Intermolecular insertion and cyclopropanation of cyclohexene (**1**) (conditions: syringe pump addition (12 h) of **2** (1.00 mmol) in CH_2Cl_2 (10.0 mL) to **1** (10.0 equiv.) in CH_2Cl_2 (5.0 mL) and 2% of catalyst at 25°C)

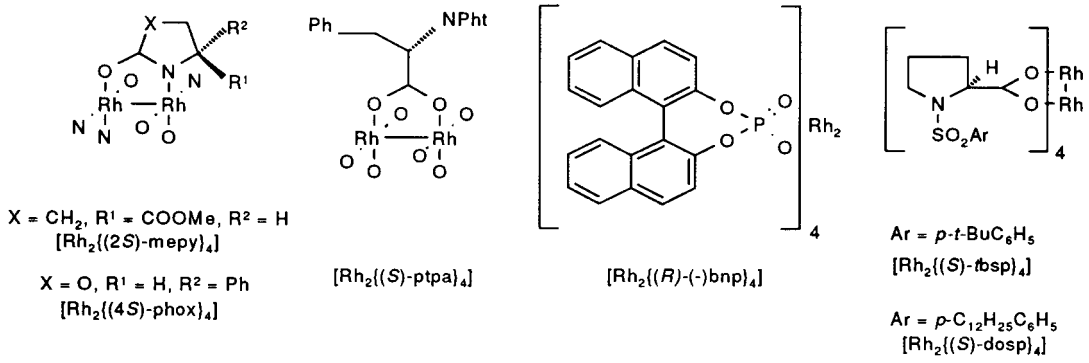
No.	R^1	R^2	Catalyst	Yield **3**+**4**, (%)	Ratio **3**:**4**	ee of **3** (C2), (%)	Comment
2a	H	Et	$[Cu(MeO)_3PI]$[a]	8.5	<5:95	–	Ref. [11]
2a	H	Et	$[Rh_2(OAc)_4]$	80	20:80	–	
2b	H	DBMP[b]	$[Rh_2(OAc)_4]$	54[c]	67:33	–	
2b	H	DBMP[b]	$[Rh_2(pfb)_4]$	70[c]	33:67	–	
2c	Me	Me	$[Rh_2(OAc)_2]$	0	-		
2d	COOMe	Me	$[Cu(MeO)_3PI]$[a]	63	10:90	–	Ref. [11]
2d	COOMe	Me[d]	$[Cu(acac)_2]$	57	9:91	–	Ref. [8]
2d	COOMe	Me	$[Rh_2(OAc)_4]$	96	38:62	–	Ref. [8]
2d	COOMe	Me	$[Rh_2(pfb)_4]$	48	52:48	–	
2d	COOMe	Me	$[Rh_2\{(-)$-(*S*)-ptpa$\}_4]$	86	24:76	–	24% ee at C(3′)
2d	COOMe	Me	$[Rh_2\{(R)$-(−)-bnp$\}_4]$	30	49:51	–	7% ee at C(3′)
2e	Ph	Me	$[Rh_2(OAc)_4]$	50[c]	75:25	–	
2e	Ph	Me	$[Rh_2(pfb)_4]$	36[c]	83:17	–	
2e	Ph	Me	$[Rh_2\{(5S)$-phox$\}_4]$	52[c]	66:34	4	dr 57:43, 4% ee at C(3′)
2e	Ph	Me	$[Rh_2\{(2S)$-mepy$\}_4]$	50[c]	93:7	45 (*S*)	dr 37:63; 10% ee at C(3′)
2e	Ph	Me	$[Rh_2\{(-)$-(*S*)-ptpa$\}_4]$	45[c]	50:50	53 (*S*)	dr 53:47; 5% ee at C(3′)
2e	Ph	Me	$[Rh_2\{(4S)$-dosp$\}_4]$	33[c]	80:20	75 (*R*)	dr 52:48; 5% ee at C(3′)
2f	4-NO_2-Ph	Me	$[Rh_2(OAc)_4]$	47	69:31	–	

[a] In neat cyclohexene (**1**), at reflux.
[b] DBMP=2,6-di-*t*-butyl-4-methylphenyl.
[c] In the presence of (2.0 g) of molecular sieves.
[d] With PhI=C(COOMe)$_2$ as carbene precursor.



Scheme 1.

the ratio of insertion/cyclopropanation is 20:80. Increasing the steric bulk in the alcohol moiety of the diazoester produces a significant increase in allylic substitution. Thus with R=DBMP (2,6-di-*t*-butyl-4-methylphenyl diazoacetate, (**2b**)) allylic insertion becomes predominant with a 67:33 ratio of **3b**/**4b**. A ratio 86:14 for the same reaction and 66:34 for that of **2b** with cyclopentene has been reported by Doyle and coworkers.[12] Upon changing the catalyst from $[Rh_2(OAc)_4]$ to $[Rh_2(pfb)_4]$[13] (pfb=perfluorobutyrate), the ratio changed unexpectedly[10] to 33:67. The reaction of



methyl 2-diazopropionate (**2c**)[14] afforded neither insertion nor cyclopropanation products, presumably owing to competing 1,2-hydrogen migration of the intermediate metallocarbene. Dimethyl diazomalonate (**2d**)[15], in turn, gave a *ca*. 10:90 ratio in favour of cyclopropanation in the presence of Cu(I)-catalysts. The ratio changed to 32:68 with $[Rh_2(OAc)_4]$[8] and 52:48 with $[Rh_2(pfb)_4]$. The chiral Rh^{II}-catalysts, $[Rh_2\{(-)\text{-ptpa}\}_4]$[16] and $[Rh_2\{(-)\text{-bnp}\}_4]$[17] had only a limited effect on the chemoselectivity of the reaction, and the enantioselectivity of the insertion was modest with **2d** (Scheme 1).

The highest chemoselectivity was observed with methyl 2-diazophenylacetate (**2e**)[18] which afforded a ratio of 75:25 with $[Rh_2(OAc)_4]$. The introduction of a *p*-nitro substituent into the phenyl ring (**2f**)[19] had only a minor effect on the product ratio. The insertion product **3e** was isolated as a mixture of 2 diasteromers in a 62:38 ratio. The configuration of the cyclopropane **4e** was assigned on the grounds of the analogy with the general trend observed in olefin cyclopropanations with **2e**. The major cyclopropane isomer has the carboxylate group *trans* with respect to the substituents of the olefin, which, in the case of cyclohexene as substrate, corresponds to the carboxylate having *exo*-configuration.[20] Four chiral Rh^{II} catalysts were examined with respect to chemoselectivity with very variable results. $[Rh_2\{2S\text{-mepy}\}_4]$[21] afforded a very high 93:7 ratio in favour of insertion, but the ratio with the sterically crowded $[Rh_2\{5R\text{-phox}\}_4]$[22] was only 66:34, below that found for $[Rh_2(OAc)_4]$. The proline derived $[Rh_2\{(4S)\text{-dosp}\}_4]$,[23] in turn, produced a ratio of 80:20. The catalyst of Ikegami, $[Rh_2\{(-)\text{-}(S)\text{-ptpa}\}_4]$[16] was less efficient and led to a product ratio of 50:50.

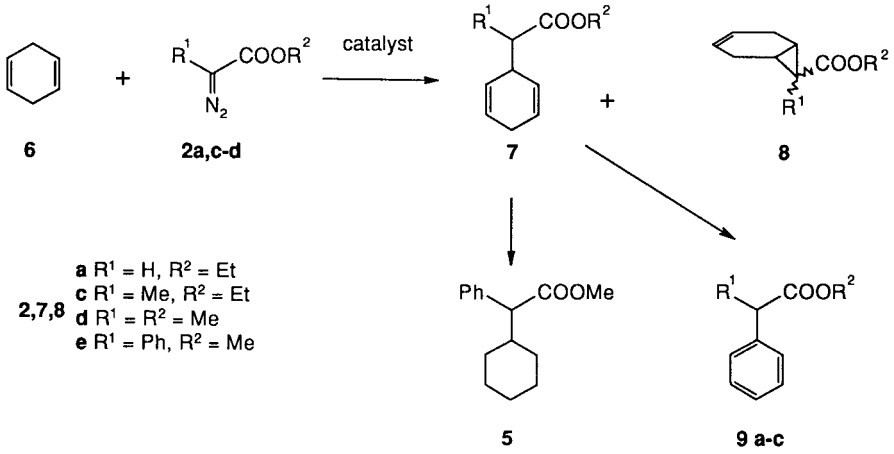
The diastereomer ratio of **4e** (dr) was determined by GC (methylsilicone column). Catalytic hydrogenation of **4e** afforded **5e**, from which the enantiomeric excess at the carbenic center (C(2)) was obtained by GC. By far the highest ee (75%) was observed with $[Rh_2\{(4S)\text{-dosp}\}_4]$. The absolute configuration at C(2) of the major enantiomer of **5e** resulting from reaction with $[Rh_2(4S)\text{-dosp}\}_4]$ was determined to be *R* by comparison of the optical rotation of the product ($[\alpha]_D^{20}=-27$, $c=0.50$, $CHCl_3$ for 75% ee) with that reported in the literature for the *R*-enantiomer ($[\alpha]_D^{25}=-38.8$ ($c=20.0$, $CHCl_3$)).[6,24] The absolute configuration of **5e** resulting from the other reactions was assigned on the grounds of the GC retention times (SUPELCO β-dex 120 column). The asymmetric induction at the allylic position of the cyclohexene, C(3′) in **3e**, was calculated from the enantiomer distribution, the ee at C(2) and the diastereomer ratio. It was in the range of 4–10%. The absolute configuration at the cyclohexene ring of **3e** was not determined.

The observed trends for the competition between intermolecular insertion and cyclopropanation appear to be largely due to a steric effect, as evidenced by the strong preference for insertion observed with **1b**. The disubstituted diazo compounds exhibit a stronger selectivity in favour of insertion than their monosubstituted analogues, and the presence of an electron-donating group (Ph) in the diazoacetate ester is more efficient than an electron acceptor (COOR). This indicates that electronic effects are also important. The trend to a higher amount of insertion upon going from Cu^{I} to Rh^{II} catalysts has been observed frequently in carbenoid reactions.[1,7] Insertion is particularly predominant when the Rh^{II} carries electron-withdrawing ligands,[25] and this is also reproduced in the present investigation, except in the case of **2b**. The preference for insertion observed with some of the chiral Rh^{II} catalysts, in turn, can not be rationalized safely at present, and may be due to a combination of steric and electronic effects.

Cyclohexa-1,4-diene (**6**) is known to react with ethyl diazoacetate (**2a**) or diethyl diazomalonate (**2c**) in the presence of copper powder or [CuCl], respectively, via cyclopropanation.[26] The presence of a second double bond in **6** was expected to enhance the reactivity of the allylic position, and have only a minor effect on the reactivity of the double bonds. However, reaction of **6** with **2a** in the presence of $[Rh_2(OAc)_4]$ at 25° afforded exclusively the cyclopropane **8a**. Ethyl 2-diazopropionate (**2c**), in turn, reacted by insertion at the allylic position to afford **7c** in 82% yield. The insertion product underwent dehydrogenation upon standing, and was characterized as 2-methyl 2-phenylpropionate **9c**, the methyl ester of hydratropic acid. If equimolar ratios of **6** and **2c** were used, no products of cyclopropanation nor insertion were formed, presumably owing to competing 1,2-hydrogen migration of the metal carbenoid, as suggested for the reaction of **2c** with **1**. Effective Rh^{II}-catalyzed intramolecular carbenoid additions of 2-diazopropionates to olefins[27] and intermolecular cyclopropenations of acetylenes[28] have been reported, however. Diazomalonate (**2d**) exhibited partial selectivity and yielded a 66:34 ratio of insertion:cyclopropanation products. As above, the insertion product **3d** was isolated after aromatization to dimethyl 2-phenylmalonate (**9d**). The most striking results were again obtained with methyl 2-diazophenylacetate (**2e**). Its decomposition in the presence of **6** (10 equiv.) and $[Rh_2(OAc)_4]$ afforded the insertion product **7e** in 95% yield. The cyclopropane **8e** could not be detected in the reaction mixture. The yield of **7e** dropped only slightly to 70% when equimolar ratios of **2e** and **6** were used (Scheme 2) (Table 2).

The structure of the insertion products **7** was deduced from their chemical behavior and from the NMR data. Thermal aromatization of cyclohexa-1,4-dienes is a *cis*-stereospecific, symmetry-allowed process, while that of cyclohexa-1,3-dienes occurs step-wise and requires higher temperatures.[29] The olefinic protons of **7c** and **d** resonate in the range of 5.55–5.88 ppm, in good agreement with those of simple substituted cyclohexa-1,4-dienes.[30] In the case of **7e** one of the olefinic protons occurs at slightly higher field (5.19–5.22) and the others between 5.63 and 5.88 ppm. Similar shifts have been reported for insertion products obtained from *p*-substituted phenyl diazoacetates into cyclohexa-1,4-dienes.[31] In contrast, the resonance lines of the olefinic protons of substituted conjugated cyclohexa-1,3-dienes are found in the range of 5.68–5.77 and 5.90–6.00 ppm.[31]

The asymmetric induction was investigated with Rh^{II}-carboxamidate and carboxylate catalysts. The enantiomer composition of the insertion product **7e** of methyl 2-diazophenylacetate **2e** with **6** could not be determined directly,



Scheme 2.

Table 2. Intermolecular CH insertion of diazoesters **2** with cyclohexa-1,4-diene (**6**) (conditions as for Table 1)

2	R^1	R^2	Catalyst	Yield (%)	7:8	ee of 7 (%)	Comment
2a	H	Et	Cu	48	<5:95		Ref. [26]
2a	H	Et	$[Rh_2(OAc)_4]$	90	<2:98		
2c	Me	Et	$[Rh_2(OAc)_4]$	82	>98:2		
2c	Me	Et	$[Rh_2(OAc)_4]$	0[a]			
2d	COOMe	Me	$[Rh_2(OAc)_4]$	63	66:34		
2d′	COOEt	Et	CuCl	28	<5:95		Ref. [26]
2e	Ph	Me	$[Rh_2(OAc)_4]$	95	>98:2		
2e	Ph	Me	$[Rh_2(OAc)_4]$	70[a]	>98:2		
2e	Ph	Me	$[Rh_2\{(2S)\text{-mepy}\}_4]$	98	>98:2	4	
2e	Ph	Me	$[Rh_2\{(-)\text{-}(S)\text{-ptpa}\}_4]$	98	>98:2	40 (*S*)	
2e	Ph	Me	$[Rh_2\{(4S)\text{-dosp}\}_4]$	98	>98:2	65 (*R*)	
2e	Ph	Me	$[Rh_2\{(4S)\text{-dosp}\}_4]$	50[b]	>98:2	71 (*R*)	
2e	Ph	Me	$[Rh_2\{(4S)\text{-dosp}\}_4]$	37[c]	>98:2	72 (*R*)	
2e	Ph	Me	$[Rh_2\{(4S)\text{-tbsp}\}_4]$	98	>98:2	74 (*R*)	
2e	Ph	Me	$[Rh_2\{(4S)\text{-tbsp}\}_4]$	86[c]	>98:2	33 (*R*)	

[a] 1 equiv. of **6**.
[b] In pentane, 25°C.
[c] In $CF_3C_6H_5$.

owing to its spontaneous aromatization to **9e** upon standing. The compound was therefore subjected to catalytic hydrogenation and afforded the known cyclohexane derivative **5e**[6] from which ee and absolute configuration were obtained. $[Rh_2\{(4S)\text{-dosp}\}_4]$ produced **7e** in practically quantitative yield and with 65% ee in CH_2Cl_2. The ee increased to 71% and 72% in pentane and trifluorotoluene, respectively, but the yields in these latter solvents were significantly lower. The highest ee (74%) resulted from reaction with $[Rh_2\{(4S)\text{-tbsp}\}_4]$. The Rh carboxylate catalyst of Ikegami, and $[Rh_2\{2S)\text{-mepy}\}_4]$ were less satisfactory with respect to enantioselectivity, however. In all cases, the absolute configuration of the insertion product **7e** was identical to that at C(2) of **3** when the same catalyst was used.

The present results show clearly that intermolecular carbenoid insertions into CH bonds may be effected with Rh^{II}-catalysts in acceptable yields. Carbenes carrying two substituents at the carbenic center exhibit marked preference for insertion rather than cyclopropanation with cyclohexene, and react almost exclusively via insertion with 1,4-cyclohexadiene. These carbenes are less prone to undergo dimer formation, and high yields of insertion products may result even when a 1:1 ratio of substrate and diazo compound is used. These results open new perspectives for enantioselective CC-bond formation via intermolecular carbenoid insertions.

The synthetic potential of intermolecular CH insertions of metal carbenoids has been recognized by other researchers. Davies[32]and Winkler[33] reported the intermolecular insertion of methyl 2-diazophenylacetate into *N*-BOC protected cyclic amines as a key step in the asymmetric synthesis of methylphenidate (Ritaline). While this manuscript was in preparation, Davies also published efficient and highly enantioselective CH insertions into the allylic positions of cyclohexa-1,3- and 1,4-dienes and the former reaction was exploited for a formal synthesis of (+)-sertraline.[31] Enantioselective intermolecular CH insertions were also reported between allyl silyl ethers and methyl aryldiazoacetates.[34]

Experimental

General

See Refs. 22 and 35.

Diazoacetates: Ethyl diazoacetate (**2a**), commercially available, was distilled before use. 2,6-Di-*t*-butyl-4-methylphenyl diazoacetate (**2b**) was prepared according to Doyle et al. [12] Methyl 2-diazopropionate (**2c**) was synthesized via diazo transfer[14] and dimethyl 2-diazomalonate (**2d**) was obtained according to the procedure of Regitz et al.[15] Methyl 2-diazophenylacetate (**2e**) was prepared via Bamford–Stevens reaction from methyl α-oxophenylacetate[18] and the *p*-nitro derivative (methyl 2-diazo-(*p*-nitrophenyl)diazoacetate via diazo transfer of methyl *p*-nitrophenylacetate.[19]

Catalysts: $[Rh_2(OAc)_4]$ and $[Cu(acac)_2]$ are commercially available. The other catalysts were synthesized according to published procedures, as follows: $[Rh_2(pfb)_4]$: Ref. 13; $[Rh_2\{(-)\text{-}(S)\text{-ptpa}\}_4]$: Ref. 16; $[Rh_2\{(R)\text{-}(-)\text{-bnp}\}_4]$: Ref. 17; $[Rh_2\{(5S)\text{-phox}\}_4]$: Ref. 22; $[Rh_2\{(2S)\text{-mepy}\}_4]$: Ref. 21; $[Rh_2\{(4S)\text{-dosp}\}_4]$: Ref. 23; $[Rh_2\{(4S)\text{-tbsp}\}_4]$: Ref. 36.

General procedure for catalyzed carbenoid reactions of diazo acetates with olefins

The diazo compound (1.0 mmol) in anhydrous CH_2Cl_2 (10.0 mL) was added with stirring at room temperature by means of a syringe pump and under inert atmosphere, to the olefin (10.0 mmol) in anhydrous CH_2Cl_2 and the appropriate catalyst (0.02 mmol) over a period of 12–16 h. After the addition, stirring was continued until all of the diazo compound had been consumed. The solvent and excess olefin were removed in vacuo, and the residue was filtered on a column of silica gel to remove the catalyst. The crude product was purified by column chromatography, and the product composition determined by capillary GC. For yields and product composition: see Tables 1 and 2. Enantiomer separation with SUPELCO Betadex 120 column. In the case of **2b** the reaction was carried out with 0.1 mmol.

Product characterisation

Most of the insertion and cyclopropanation products resulting from the reactions are known in the literature, or are derivatives of commercially available compounds. Therefore only the most important characteristic data are reported here.

Ethyl (cyclohexen-3-yl)acetate (3a).[37] IR ($CHCl_3$): 1708s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.24–1.28 (m, 2H); 1.41–1.59 (m, 2H); 1.60–1.77 (m, 3H); 1.78–2.10 (m, 4H); 4.13–4.15 (q, *J*=8 Hz, 2H); 4.40–4.53 (m, 1H); 5.65–5.75 (m, 1H); 5.88–5.98 (m, 1H).

2,6-Di-*tert*-butyl-4-methylphenyl (cyclohexen-3-yl)acetate (3b).[12] IR ($CHCl_3$): 1703s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (s, 18H); 1.98–2.02 (m, 6H); 2.32 (s, 3H); 2.61–2.63 (m, 2H); 5.68–5.74 (m, 2H); 7.11 (s, 1H); 7.27 (s, 1H). ^{13}C NMR (100 MHz): 21.0 (t); 21.5 (q); 25.1 (t); 29.2 (d); 31.1 (d); 35.2 (q); 42.0 (t); 127.0 (d); 128.2 (d); 130.4 (d); 134.3 (d); 172.6 (s).

Dimethyl (cyclohexen-3-yl)malonate (3d).[7a,11] IR ($CHCl_3$): 1735s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.19–1.21 (m, 1H); 1.37–1.41 (m, 1H); 1.43–1.53 (m, 2H); 1.63–1.82 (*mi*, 2H); 2.71–2.74 (m, 1H); 3.13 (d, *J*=8 Hz, 1H); 3.57 (s, 6H); 5.34–5.37 (m, 1H); 5.57–5.61 (m, 1H). ^{13}C NMR (100 MHz): 20.5 (t); 24.5 (t); 26.2 (t); 35.0 (d); 51.8 (d); 56.3 (q); 127.0 (d); 129.1 (d); 168.28 (s); 168.33 (s). MS: 212 (M^+, 10), 81 (64).

Methyl 2-(cyclohexen-3-yl)-phenylacetate (3e). IR ($CHCl_3$): 1700s. ^{1}H NMR (400 MHz, $CDCl_3$: 0.89–2.02 (m, 6H); 2.79–2.92 (m, 1H); 3.42 (d, *J*=20 Hz, 1H); 3.68 (s, 3H); 5.16 (d, *J*=20 Hz, 1H); 5.61–5.83(m, 1H); 7.22–7.39 (m, 5H). ^{13}C NMR (100 MHz): 20.5 (t); 20.9 (t); 25.5 (d); 34.3 (t); 52.3 (q); 126.9 (d); 128.2 (d); 132.3 (d); 134.8 (d); 175.9 (s). MS: 230 (M^+, 2), 150 (88), 81 (100).

Methyl 2-(cyclohexen-3-yl)-*p*-nitrophenylacetate (3f). IR ($CHCl_3$): 1700s. ^{1}H NMR (400 MHz, $CDCl_3$): 0.84–2.11 (m, 6H); 2.84–2.95 (m, 1H); 3.44–3.51 (m, 1H); 3.69 (s, 3H); 5.08 (m, 1H); 5.58–5.86 (m, 1H); 7.51–7.58 (m, 2H); 8.16–8.22 (m, 2H). ^{13}C NMR (100 MHz): 20.5 (t); 24.9 (t); 26.3 (d); 38.8 (d); 52.3 (d); 57.1 (q); 123.6 (d); 129.7 (d); 144.8 (s); 147.3 (s); 172.7 (s). MS: 275 (M^+, 2), 195 (14), 164 (12), 135 (13).

7-*exo*-Ethoxycarbonylbicyclo[4.1.0]heptane (4a).[37,38] IR ($CHCl_3$): 1708s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.15–1.38 (m, 2H); 1.38 (t, *J*=24 Hz, 3H); 1.55–1.62 (m, 2H); 1.62–1.75 (m, 2H); 1.86–1.96 (m, 2H); 4.07–4.14 (q, *J*=24 Hz, 2H).

(2,6-Di-*tert*-butyl-4-methylphenyl)-*anti*-7-bicyclo[4.1.0]-heptanecarboxylate (4b).[12] IR ($CHCl_3$): 1703s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (s, 18H); 1.56–1.91 (m, 10H); 2.31 (s, 3H); 7.11 (s, 2H). ^{13}C NMR (100 MHz): 15.3 (s); 17.8 (t); 18.7 (t); 20.9 (d); 21.5 (t); 22.6 (q); 31.5 (q); 126.9 (d); 134.1 (d); 142.2 (d); 145.8 (d); 172.3 (s). MS (electrospray): 381 ($M+K^+$).

7,7-Dimethoxycarbonylbicyclo[4.1.0]heptane (4d).[8a,39] IR ($CHCl_3$): 1735s. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99–1.01 (m, 2H); 1.24–1.29 (m, 2H); 1.81–1.99 (m, 6H); 3.68 (s, 3H); 3.78 (s, 3H). ^{13}C NMR (100 MHz): 19.6 (d); 20.6 (d); 24.9 (d); 35.4 (t); 52.2 (s); 52.6 (s); 167.9 (s); 171.7 (s). MS: 212 (M^+, 17), 184 (31), 181 (51), 180 (100), 169 (50), 158 (28), 152 (80).

***r*-7-Methoxycarbonyl-*t*-7-phenyl-*t*-bicyclo[4.1.0]heptane (4e).** IR ($CHCl_3$): 1700s. ^{1}H NMR (400 MHz, $CDCl_3$): 0.52–0.64 (m, 2H); 1.18–1.45 (m, 2H); 1.69–1.79 (m, 2H); 1.91–2.06 (m, 4H); 3.54 (s, 3H); 7.27–7.38 (m, 5H). ^{13}C NMR (100 MHz): 20.5 (t); 20.9 (t); 25.5 (d); 52.3 (q);126.9 (d); 128.2 (d); 132.3 (d); 134.8 (s); 175.9 (s). MS: 230 (M^+, 100), 198 (82), 169 (29), 142 (32), 141 (27), 129 (39), 128 (27), 115 (31). HRMS: 230.1307 ($C_{15}H_{18}O_2^+$; Calc 230.1325).

***r*-7-Methoxycarbonyl-*t*-7-*p*-nitrophenyl-*t*-bicyclo[4.1.0]-heptane (4f).** IR ($CHCl_3$): 1700s. ^{1}H NMR (400 MHz,

$CDCl_3$): 0.52–0.65 (m, 2H); 0.99–1.15 (m, 2H); 1.69–1.81 (m, 2H); 1.86–2.04 (m, 4H); 3.69 (s, 3H); 7.49 (m, 2H); 8.19 (m, 2H).

Methyl 2-cyclohexylphenylacetate (5)[6] **via catalytic hydrogenation of 3e or 7e.** To a stirred solution of olefin (20.0 mg, 0.086 mmol) in MeOH (3.0 mL) was added Pd/C. The mixture was stirred under H_2 at room temperature until completion of the reaction (monitoring by GC). Yield 100%. IR ($CHCl_3$): 1732s. ^{1}H NMR (400 MHz, $CDCl_3$): 0.69–0.81 (m, 2H); 0.99–1.39 (m, 2H); 1.56–1.86 (m, 2H); 1.99–2.09 (m, 1H); 3.22 (d, *J*= 20 Hz, 1H); 3.66 (s, 3H); 7.15–7.31 (m, 5H). ^{13}C NMR (100 MHz): 25.8 (t); 25.9 (t); 26.2 (t); 30.3 (td; 31.9 (t); 51.6 (d); 58.7 (q); 127.1 (d); 128.3 (d); 128.5 (d); 137.8 (s); 174.3 (s).

Ethyl 2-(cyclohexa-1,4-dien-3-yl)propionate (7c). IR ($CHCl_3$): 1708s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.06 (t, *J*=7 Hz, 3H); 1.27 (d, *J*=7 Hz, 3H); 2.60–2.65 (m, 2H); 3.12–3.38 (m, 1H); 4.13 (q, *J*=16 Hz, 2H); 5.55–5.57 (m, 2H); 5.78–5.79 (m, 2H).

Dimethyl 2-(cyclohexa-1,4-dien-3-yl)malonate (7d). IR ($CHCl_3$): 1735s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.51–1.63 (m, 1H); 2.35–2.39 (m, 1H); 2.58–2.69 (m, 2H); 3.69 (s, 6H); 5.58–5.69 (m, 2H); 5.77–5.88 (m, 2H).

Methyl 2-(cyclohexa-1,4-dien-3-yl)phenylacetate (7e). IR ($CHCl_3$): 1725s, 3019s. ^{1}H NMR (400 MHz, $CDCl_3$): 2.61–2.63 (m, 2H); 3.42–3.44 (m, 2H); 3.75 (*s*, 3H); 5.19–5.22 (m, 1H); 5.63–5.88 (m, 3H); 7.25–7.35 (m, 5H). ^{13}C NMR (100 MHz): 26.4 (t); 38.5 (d); 51.9 (d); 58.3 (q); 85.9 (d); 125.8 (d); 126.3 (d); 126.6 (d); 127.4 (d); 128.6 (d); 136.7 (d); 173.4 (s).

Ethoxycarbonylbicyclo[4.1.0]hept-3-ene (8a),[26] **unseparable mixture of *exo*- and *endo* isomers.** IR ($CHCl_3$): 1708s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.21–1.28 (m, 2×3H); 1.39–1.49 (m, 1H); 1.57–1.71 (m, 2H); 2.31–2.42 (m, 4H); 4.05–4.18 (m, 2×2H); 5.31–5.48 (m, 2H); 5.54–5.72 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): 14.1 (q); 14.3 (q); 20.1 (t); 21.4 (d); 22.4 (d); 22.6 (t); 59.9 (t); 60.2 (t); 123.06 (d); 123.13 (d); 172.5 (s); 174.8 (s).

7,7-Dimethoxycarbonylbicyclo[4.1.0]hept-3-ene (8d).[40] IR ($CHCl_3$): 1735s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.93–2.02 (m, 2H); 2.45–2.55 (*m*, 2H); 2.58–2.69 (m, 2H); 3.69 (s, 3H); 3.75 (s, 3H); 5.40–5.44 (m, 2H).

Ethyl 2-phenylpropionate (9a),[41] **via dehydrogenation of 7a.** IR ($CHCl_3$): 1708s. ^{1}H NMR (400 MHz, $CDCl_3$): 1.17 (t, *J*=7 Hz, 3H); 1.46 (d, *J*=7 Hz, 3H); 3.67 (q, *J*=7 Hz, 1H); 4.24 (q, *J*=7 Hz, 2H); 7.22–7.32 (m, 5H).

Dimethyl 2-phenylmalonate (9d),[42] **via dehydrogenation of 7d.** IR ($CHCl_3$): 1735s. ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (s, 6H); 7.39–7.41 (m, 3H); 7.81–7.83 (m, 2H). ^{13}C NMR (100 MHz): 21.5 (d), 52.8 (q); 57.5 (q); 128.6 (d); 129.1 (d); 129.7 (d); 174.8 (s).

Methyl 2,2-diphenylacetate (9e),[43] **via dehydrogenation of 7e.** IR ($CHCl_3$): 1725s. ^{1}H NMR (400 MHz, $CDCl_3$): 3.74 (s, 3H); 5.03 (s, ^{1}H); 7.25–7.32 (m, 10H).

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References

1. (a) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919–7946. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935. (c) Doyle, M. P., McKervey, M. A., Ye, T. *In Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1997.

2. (a) Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W. *J. Am. Chem. Soc.* **1991**, *113*, 8982–8984. (b) Müller, P.; Polleux, P. *Helv. Chim. Acta* **1994**, *77*, 645–654; (c) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Cañas, F.; Pierson, D. A.; van Basten, A.; Müller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507–4508. (d) Doyle, M. P.; Kaliin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837–8846.

3. (a) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc. Chem. Commun.* **1981**, 688–689. (b) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc.Chim. Belge.* **1984**, *93*, 945. (c) Callot, H. J.; Metz, F. *Nouv. J. Chem.* **1985**, *9*, 167–171. (d) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873–876.

4. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

5. Davies, H. L. M.; Hodges, L. M.; Matasi, J. J.; Hansen, T. D.; Stafford, G. *Tetrahedron Lett.* **1998**, *39*, 4417–4420.

6. Davies, H. L. M.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075–9076.

7. (a) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797–1815. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680.

8. (a) Fernandez, D. Ph.D. Thesis, University of Geneva, Thesis No. 2933, 1997. (b) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947–958.

9. (a) Tohill, S.; Maîtrejean, E.; Müller, P. Fall Meeting, New Swiss Chemical Society, 1998; Abstracts: *Chimia* **1998**, *52*, 478. (b) Tohill, S.; Müller, P. Fall Meeting, New Swiss Chemical Society, 1999; Abstracts: *Chimia* **1999**, *53*, 375. (c) Tohill, S.; Müller, P. Second Swiss COST Chemical Symposium, 1999; Abstracts: *Chimia* **1999**, *53*, 399.

10. Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; Sess, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680.

11. Wulfman, D. S.; McGibboney, B. G.; Steffen, E. K.; Thinh, N. V.; McDaniel, R. S.; Peace, B. W. *Tetrahedron* **1976**, *32*, 1257–1265.

12. Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906–1912.

13. Doyle, M. P.; Mahapatro, S. N.; Caughey, A. C.; Chinn, M. S.; Colsman, M. R.; Harn, N. K.; Redwine, A. E. *Inorg. Chem.* **1987**, *26*, 3070–3072.

14. Sohn, M. B.; Jones Jr. M.; Hendrick, M. E.; Rando R. R.; Doering, W. V. E. *Tetrahedron Lett.* **1972**, *1*, 53–56; Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610–3618

15. Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth. Coll. Vol. V* **1973**, 179–183; Ando, W.; Kondo, S.; Migita, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 571–572.
16. Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Tetrahdron Lett.* **1990**, *31*, 5173–5174; Hashimoto, S.-I.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109–5112; Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Synlett*, **1994**, 353–355;. Watanabe, N.; Anada, M.; Hashimoto, S.-I.; Ikegami, S. *Synlett.* **1994**, 1031–1033
17. Pirrung, M. -C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987–5990.
18. Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696–5700; Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299–6302.
19. Regitz, M. *Chem. Ber.* **1965**, *98*, 1210–1224.
20. Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; García, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129–4132; Davies, H. L. M.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133–4136.
21. Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968–9978; Doyle, M. P.; Wincheser, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Synth.* **1995**, *73*, 13–24.
22. Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Müller, P.; Bernardinelli, G.; Ene, D.; Motallebi, S. *Helv. Chim. Acta* **1993**, *76*, 2227–2235.
23. Davies, H. L. M.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907; Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3872–3979.
24. Camps, P.; Gimenez, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1227–1234; Barlow, R. B.; Franks, F. M.; Pearson, J. D. *J. Med. Chem.* **1973**, *16*, 493.
25. Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874–1876.
26. Musso, H.; Biethan, U., *Chem. Ber.* **1964**, *97*, 2282–2289; Clive, D. L. J.; Daigneault, A. *J. Org. Chem.* **1991**, *56*, 5285–5289.
27. Doyle, M. P.; Zhou, Q. -L. *Tetrahedron: Asymmetry* **1995**, *6*, 2157–2160.
28. Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1995**, *78*, 129–144.
29. (a) Fleming, J.; Wildsmith, E. *J. Chem. Soc. Chem. Commun.* **1970**, 223–224. (b) Benson, S. W., Shaw, R. *J. Am. Chem. Soc.* **1967**, *89*, 5351–5354. (c) Ellis, R. J.; Frey, H.; M. *J. Chem. Soc. (A)* **1966**, 553. (d) Müller, P.; Joly, D.; Mermoud, F. *Helv. Chim. Acta* **1984**, *67*, 105–112.
30. Stoos, F.; Rocek, J. *J. Am. Chem. Soc.* **1972**, *94*, 2719–2723.
31. (a) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233–238. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459–2469.
32. Davies, H. L. M.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510.
33. Axten, J. M.; Ivy, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6511–6512.
34. Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383–385.
35. Müller, P.; Baud, C.; Ene, D.; Motallebi, S.; Doyle, M. P.; Brandes, B. D.; Dyatkin, A. B.; See, M. M. *Helv. Chim. Acta* **1995**, *78*, 459–470.
36. Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc. Chem. Commun.* **1990**, 361–362; McKervey, M. A.; Ye, T. *J. Chem. Soc. Chem. Commun.* **1992**, 823–824; Ye, T.; McKervey, M. A.; Brandes, B. D.; Doyle, M. P., *Tetrahedron Lett.* **1994**, *35*, 7269–7272.
37. Demonceau, A.; Noels, A. F.; Huber, A. J. *Tetrahedron* **1990**, *46*, 3889–3896; Patel, S. K.; Paterson, I. *Tetrahedron Lett.*, **1983**, 12, 1315–1318.
38. Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssié, P. *Synthesis* **1976**, 600–602; Doyle, M. P.; van Leusen, D.; Tamblin, W. H. *Synthesis 1981*, 787–789; Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié Ph. *J. Org. Chem.* **1980**, *45*, 695–702
39. Hood, J. N. C.; Lloyd, D.; McDonald, W. A.; Shepherd, T. M. *Tetrahedron* **1982**, *38*, 3355–3358.
40. Peace, B. W.; Carman, F.; Wulfman, D. S. *Synthesis* **1971**, 658–661; Berson, J. A.; Hartter, D. R.; Klinger, H.; Grubb, P. W. *J. Org. Chem.* **1968**, *33*, 1669–1671.
41. Chiao, W.-B.; Saunders, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 2802–2805; Shiner, V. J.; Smith, M. L. *J. Am. Chem. Soc.* **1961**, *83*, 593–598; Loupy, A. *Bull. Soc. Chim. France* **1975**, 2662–2669.
42. Leake, W.; Lewine, R. *J. Am. Chem. Soc.* **1959**, *81*, 1627–1629.
43. Kametami, T.; Taub, W.; Ginsburg, D. *Bull. Chem. Soc. Jpn.* **1958**, 860–861.