ELSEVIER

Journal of Molecular Catalysis A: Chemical 196 (2003) 83–91

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

www.elsevier.com/locate/molcata

Progress towards asymmetric intermolecular and intramolecular cyclopropanations using α-nitro-α-diazo carbonyl substrates

André B. Charette*, Ryan Wurz

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Que., Canada H3C 3J7

Received 28 May 2002; accepted 15 July 2002

Abstract

A variety of Rh(II) catalysts were screened for enantioselectivity in the cyclopropanation of styrene with α-nitro-α-diazo carbonyl compounds and found to give modest to high yields in a wide range of solvents but modest enantioselectivities (up to 41% e.e. for substrate **9c**). Copper catalysts with bis(oxazoline) ligands gave higher enantioselection, with e.e. up to 72% for the major diastereoisomer and yields up to 55%. The use of ethyl diazoacetate as an additive was necessary to obtain improved yields. The first example of intramolecular cyclopropanation involving α-nitro-α-diazo carbonyls is also reported. Rh(II) carboxylate **4b** catalysed the formation of 9-membered nitro cyclopropyl lactones giving up to 66% yield and 61% e.e.

Keywords: Cyclopropanation; α-Nitro-α-diazo carbonyls; Rhodium; Copper; Nitro cyclopropane carboxylates

1. Introduction

There have been many developments in the field of diazo chemistry in the last decade and numerous catalytic asymmetric C–H, C–C, C–X (X = heteroatom) bond forming reactions catalysed by Ni, Co, Cu, Ru, Rh and Fe complexes have been reported [1,2]. Of these transformations, cyclopropanation of alkenes by transition metal catalysts with diazo compounds represents a straightforward approach to cyclopropanes. Our group has focused on cyclopropanes because they appear in a variety of natural products [3–5] and can be used as valuable synthetic intermediates [6,7].

The variety of useful diazo substrates used in transition metal catalysed processes has also expanded rapidly, each possessing different electronic characteristics and reactivity patterns. The recent focus of our research has been on α-nitro-α-diazo carbonyl compounds which have been the subject of fewer reports in the literature [8–11]. We envisioned their application in a rapid method of accessing cyclopropane α-amino acids through reduction of the nitro group following cyclopropanation [12]. This approach would eliminate the necessity for Curtius-type rearrangements commonly employed in other reported syntheses [13,14].

We recently reported an efficient method for the synthesis of α-nitro-α-diazo carbonyl compounds involving a diazo transfer with triflyl azide [15]. With this in hand, we set out to screen a variety of asymmetric catalysts for the enantioselective cyclopropanation of styrene. Asymmetric cyclopropanation using α-nitro-α-diazo carbonyl compounds has been only briefly mentioned by O'Bannon and Dailey [11]

* Corresponding author. Tel.: +1-514-343-6283; fax: +1-514-343-5900.
E-mail address: andre.charette@umontreal.ca (A.B. Charette).

1381-1169/02/$ – see front matter
PII: S1381-1169(02)00636-2

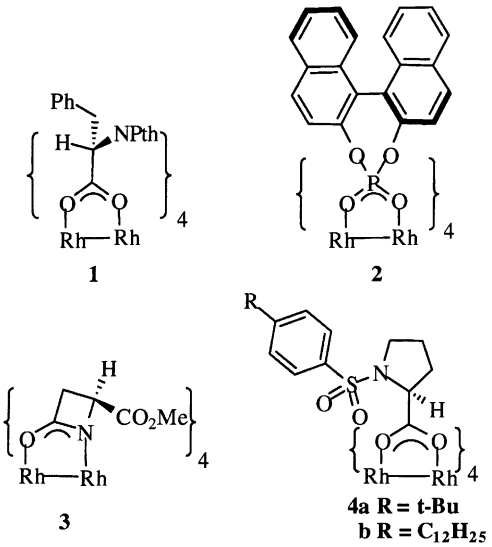


Fig. 1.

involving the $Cu(OAc)_2$-based catalyst reported by Brunner and Miehling [16] and Kunz and Reissig [17]. In their work, they indicate that optical activity was observed, but the optical purity was not determined. This research was not further pursued to the best of our knowledge.

We began catalyst screening with a number of structurally diverse chiral Rh(II) catalysts due to their efficiencies in the cyclopropanation reaction with α-nitro-α-diazo carbonyl substrates. Their structures are illustrated in Fig. 1.

Copper-based catalysts with a number of chiral ligands of general type **5** were also screened as there has been some success in the literature with intermolecular cyclopropanation reactions [18] and related ligands [19,20]. The specific ligands studied are illustrated in Fig. 2.

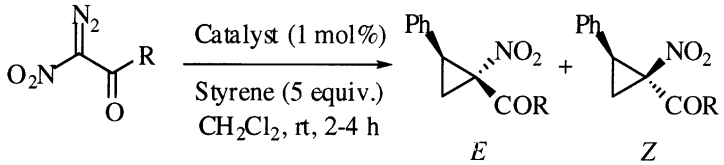
2. Experimental

2.1. General methods and chemicals

Caution: Although we have not experienced any complications in handling α-nitro-α-diazo carbonyl derivatives, extreme care should be taken when manipulating them due to their explosive nature.

Unless otherwise mentioned, all reactions were carried out under argon atmospheres using oven dried glassware. Anhydrous solvents were transferred by oven-dried syringes. All solvents were dried on a GlassContour system (Irvine, CA). High-resolution mass spectra (HRMS) were obtained from the Centre régional de spectrométrie de masse de l'Université de Montréal on a MS50 Kratos mass spectrometer and are reported as *m/e*. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal. Infrared spectra were recorded on a Perkin-Elmer 783 as neat liquids or as solids directly. Only, the most important and relevant IR frequencies are reported. Melting points were determined on a Thomas–Hoover melting point apparatus in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were taken on Bruker AMX 300 or AMX R 400 spectrometers. Chemical shifts of ^1H NMR spectra are reported from an internal standard of residual chloroform (7.27 ppm) and ^{13}C NMR with the central peak of chloroform at 77.23 ppm. Enantiomeric excess was determined on the mixture of *E* and *Z* diastereoisomers using super critical fluid chromatography (SFC) by Berger Instruments on chiral stationary phase.

2.2. Rh(II) catalysed intermolecular cyclopropanation of styrene



9a R = OMe
b R = OEt
c R = O*t*-Bu
d R = Ph

10a R = OMe
b R = OEt
c R = O*t*-Bu
d R = Ph

(1)

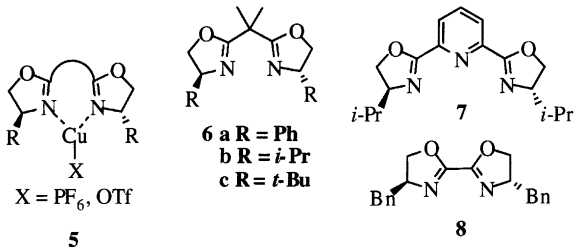


Fig. 2.

Rh(II) complexes **1**–**3** were prepared according to known literature procedures [21–23] while catalysts **4a** and **b** were purchased from the Aldrich Chemical Company. The diazo substrates **9a**–**d** were prepared according to our recently reported protocol [15] except that pyridine addition was done at 0 °C and the solution was allowed to warm slowly overnight.

*2.2.1. Methyl diazo-nitro-acetate (**9a**)*

Yield: 90%. Pale yellow solid, mp: 55–57 °C. R_f 0.33 (hexanes/EtOAc 80:20). IR (cm^{-1}): $\nu(CN_2)$ 2153; ν(C=O) 1727; $\nu(NO_2)$ 1496. ^{1}H NMR ($CDCl_3$): δ = 3.94 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 155.8, 101.8 (CN_2), 53.4. Diazo substrates **9b**–**d** have been previously reported [11,24].

General cyclopropanation procedure: To a stirring solution containing the Rh(II) catalyst (1.0 mol% based on diazo) and freshly distilled, degassed styrene (5 eq.) under argon was added 100 mg of substrate **9** as a 1.0 M solution in anhydrous dichloromethane slowly via syringe over 30 min. The solution was allowed to stir for an additional 2–4 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexanes/EtOAc 96:4) afforded pure cyclopropanes **10**.

*2.2.2. Methyl E-1-nitro-2-phenyl-cyclopropane carboxylate (**10a**)*

Yield: see Table 1. Clear, colourless oil, R_f 0.76 (hexanes/EtOAc 80:20). HRMS (MAB) Found: 221.06937. $C_{11}H_{11}NO_4$ $[M]^+$ Calc.: 221.06881. IR (cm^{-1}): ν(C=O) 1747; $\nu(NO_2)$ 1539. ^{1}H NMR ($CDCl_3$): δ = 7.29–7.34 (m, 3H), 7.20–7.22 (m, 2H), 3.78 (t, J = 9.3 Hz, 1H), 3.51 (s, 3H), 2.46 (dd, J = 9.2, 6.6, Hz, 1H), 2.24 (dd, J = 10.8, 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 162.7, 132.2, 128.7, 128.6, 128.5, 71.9, 53.3, 34.4, 21.1. Methyl *Z*-1-nitro-2-phenyl-cyclopropane carboxylate (**10a**). Pale yellow solid, mp: 35–37 °C, R_f 0.64 (hexanes/EtOAc 80:20). Anal. Found: C, 59.83; H, 5.19; N, 6.33. $C_{11}H_{11}NO_4$. Calc.: C, 59.73; H, 5.01; N, 6.33. IR (cm^{-1}): ν(C=O) 1747; $\nu(NO_2)$ 1536. ^{1}H NMR ($CDCl_3$): δ = 7.30–7.34 (m, 3H), 7.21–7.23 (m, 2H), 3.90 (s, 3H), 3.49 (t, J = 9.3 Hz, 1H), 2.69 (dd, J = 9.2, 7.0 Hz, 1H), 2.05 (dd, J = 9.9, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 166.1, 131.5, 128.93, 128.89, 128.5, 76.9, 54.0, 34.1, 20.3. Enantiomeric excess determined by SFC: Chiracel OJ column, modifier: 1.5% MeOH, flow: 1.5 ml/min.

The cyclopropanation of styrene using a variety of α-nitro-α-diazo carbonyl substrates **9a**–**d** (Eq. (1)) was used to determine the enantiomeric induction of the ensuing cyclopropanation reaction (Table 1).

Table 1
Asymmetric cyclopropanation of styrene with α-nitro-α-diazo carbonyls

Entry	Substrate	Catalyst	Ratio *E*:*Z*[a]	%Yield (**10**)[b]	%e.e. (*E* isomer)[c]	%e.e. (*Z* isomer)
1	**9a**	**1**	86:14	75	28	13
2	**9b**	**1**	83:17	72	30	0
3	**9c**	**1**	68:32	68	41[d]	6
4	**9d**	**1**	39:61	64	31	13
5	**9b**	**2**	75:25	71	13	16
6	**9b**	**3**	86:14	76	33	0
7	**9b**	**4a**	89:11	89	2	17
8	**9b**	**4b**	79:21	74	8	10

[a] *E*:*Z* ratios were determined by ^{1}H NMR of crude reaction mixtures.
[b] Isolated yields after column chromatography.
[c] Enantiomeric excess was determined by super critical fluid chromatography (SFC).
[d] Enantiomeric excess was determined by $LiAlH_4$ reduction to the corresponding nitro cyclopropyl methanol followed by typical SFC determination.

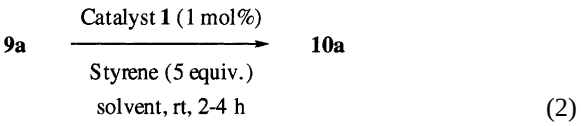
Table 2
Influence of solvent on enantiomeric excess

Entry	Solvent[a]	Ratio *E*:*Z*	%Yield (**10a**)	%e.e. (*E* isomer)	%e.e. (*Z* isomer)
1	CH_2Cl_2	86:14	75	28	13
2	Benzene	90:10	81	27	12
3	DME	89:11	65	25	6
4	Et_2O[b]	89:11	75	28	9
5	THF	94:6	32	25	0
6	Acetone	88:12	81	22	18
7	CH_3CN	80:20	78	24	22

[a] A 1.0 M solution of **9a** in the corresponding solvent was used.
[b] A 0.5 M solution was used due to limited solubility of **9a** in this solvent.

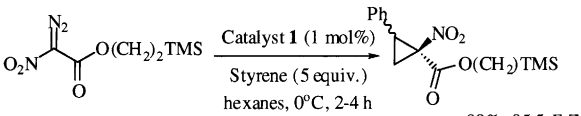
2.3. Influence of solvent on Rh(II) catalysed intermolecular cyclopropanation of styrene

Experimental variables, such as temperature and solvent have been shown to greatly influence the enantioselection in intermolecular cyclopropanation reactions [14,25,26]. The influence of solvent on the intermolecular cyclopropanation was then investigated. Enantiomeric excesses were then determined for the cyclopropanation of styrene using catalyst **1** (Eq. (2)) in a variety of solvents (Table 2).



(2)

Diazo substrate **11** was prepared allowing for a hexanes soluble diazo precursor, see Eq. (3).



(3)

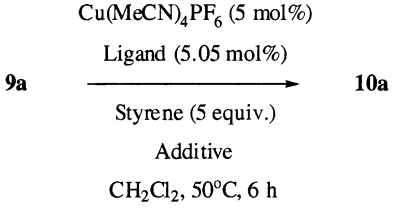
2.3.1. 2-Trimethylsilanyl-ethyl diazo-nitro-acetate (11)

The precursor to substrate **11** was obtained by a DCC coupling of trimethylsilyl ethanol and nitro acetic acid [27] Yield: 74%. Clear, colourless oil, R_f 0.57 (hexanes/EtOAc 80:20). HRMS (MAB) Found: 205.07747. $C_7H_{15}NO_4Si$ $[M]^+$ Calc.: 205.07704. IR (cm^{-1}): ν(C=O) 1747; $\nu(NO_2)$ 1567. ^1H NMR ($CDCl_3$): δ = 5.14 (s, 2H), 4.34–4.38 (m, 2H), 1.04–1.08 (m, 2H), 0.06 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 162.1, 76.7, 66.1, 17.5, −1.39. Substrate **11** was then obtained according to the modified diazo transfer procedure [15]. Yield: 99%. Yellow oil, R_f 0.67 (hexanes/EtOAc 80:20). IR (cm^{-1}): $\nu(CN_2)$ 2144; ν(C=O) 1747; ν(C=O) 1698; $\nu(NO_2)$ 1521. ^1H NMR ($CDCl_3$): δ = 4.41–4.47 (m, 2H), 1.07–1.13 (m, 2H), 0.07 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 155.7, 66.0, 53.5, 17.8, −1.4.

2.3.2. 2-Trimethylsilanyl-ethyl-1-nitro-2-phenyl-cyclopropane carboxylate (12)

The title compound was obtained according to the general cyclopropanation procedure except hexanes was used as solvent and the reaction was cooled in an ice bath at 0 °C. Yield: 89%. White solid, mp: 40–41 °C, 2-trimethylsilanyl-ethyl-*E*-1-nitro-2-phenyl-cyclopropane carboxylate (**12**). R_f 0.71 (hexanes/EtOAc 80:20). HRMS (MAB) Found: 307.123549. $C_{15}H_{21}NO_4Si$ $[M]^+$ Calc.: 307.123987. IR (cm^{-1}): ν(C=O) 1742; $\nu(NO_2)$ 1546; $\nu(NO_2)$ 1352. ^1H NMR ($CDCl_3$): δ = 7.26–7.34 (m, 3H), 7.20–7.23 (m, 2H), 3.95–3.98 (m, 2H), 3.76 (t, J = 9.4 Hz, 1H), 2.44 (dd, J = 9.1, 6.7 Hz, 1H), 2.19 (dd, J = 10.7, 6.6 Hz, 1H), 0.58–0.65 (m, 2H), −0.050 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 162.2, 132.3, 128.7, 128.6, 128.4, 72.0, 65.2, 34.1, 20.8, 17.0, −1.54. 2-Trimethylsilanyl-ethyl-*Z*-1-nitro-2-phenyl-cyclopropane carboxylate (**12**). Clear, colourless oil: R_f 0.70 (hexanes/EtOAc 80:20). ^1H NMR ($CDCl_3$): δ = 7.26–7.34 (m, 3H), 7.20–7.23 (m, 2H), 4.36–4.42 (m, 2H), 3.46 (t, J = 9.6 Hz, 1H), 2.66 (dd, J = 9.2, 6.9 Hz, 1H), 2.01 (dd, J = 9.9, 6.9 Hz, 1H), 1.06–1.12 (m, 2H), 0.069 (m, 9H).

2.4. Copper catalysed intermolecular cyclopropanation of styrene

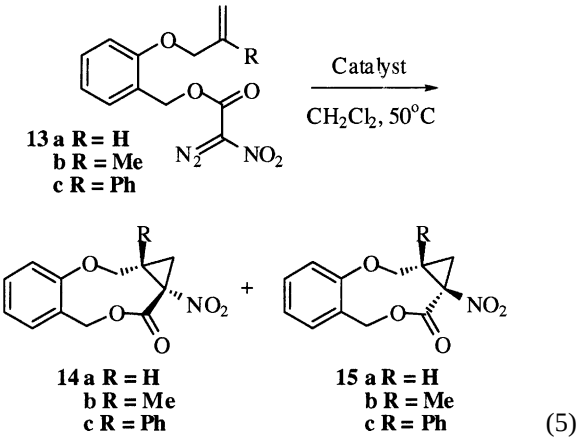


(4)

General copper catalysed cyclopropanation procedure: To the copper source (5.0 mol% based on diazo) was added the desired ligand (5.05 mol% based

on diazo) in the glove-box followed by addition of distilled, degassed dichloromethane to form a 0.1 M solution (Eq. (4)). The solution was stirred 1 h, then was treated with distilled, degassed styrene under argon and heated with a reflux condensor to 50 °C at which point the additives were introduced for catalyst activation. Directly following catalyst activation, **9a** (0.5 M in anhydrous dichloromethane) was added via syringe pump over 2 h. The solution was allowed to stir an additional 6 h at 50 °C before it was filtered through a short silica gel pad and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the pure cyclopropane **10a**.

2.5. Rh(II) catalysed intramolecular cyclopropanation



(5)

2.5.1. 2-Allyloxy-benzyl-diazo-nitro-acetate (**13a**)

Yield: 99%. Yellow oil, R_f 0.52 ($CHCl_3$). HRMS (MAB) Found: 277.069488. $C_{12}H_{11}N_3O_5$ $[M]^+$ Calc.: 277.069871. IR (cm^{-1}): $\nu(CN_2)$ 2143; $\nu(C{=}O)$ 1740; $\nu(C{=}O)$ 1700; $\nu(NO_2)$ 1515. ^1H NMR ($CDCl_3$): δ = 7.32–7.36 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 5.99–6.09 (m, 1H), 5.38–5.44 (m, 3H), 5.28–5.31 (m, 1H), 4.57–4.59 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 157.1, 155.4, 133.1, 130.8, 130.7, 122.9, 120.9, 117.7, 112.0, 69.0, 64.4.

2.5.2. 2-(2-Methyl-allyloxy)-benzyl-diazo-nitro-acetate (**13b**)

Yield: 95%. Pale yellow solid, mp: 50–52 °C, R_f 0.52 (hexanes/EtOAc 80:20). HRMS (MAB) Found: 291.085559. $C_{13}H_{13}N_3O_5$ $[M]^+$ Calc.: 291.085521. IR (cm^{-1}): $\nu(CN_2)$ 2146; $\nu(C{=}O)$ 1748; $\nu(NO_2)$ 1521; $\nu(NO_2)$ 1322. ^1H NMR ($CDCl_3$): δ = 7.29–7.36 (m, 2H), 6.93–6.97 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.42 (s, 2H), 5.09 (s, 1H), 5.00 (s, 1H), 4.46 (s, 2H), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 157.0, 155.2, 140.5, 130.7, 130.5, 122.6, 120.6, 112.6, 111.7, 71.6, 64.1, 19.3.

2.5.3. 2-(2-Phenyl-allyloxy)-benzyl-diazo-nitro-acetate (**13c**)

Yield: 96%. White solid, mp: 89–91 °C, R_f 0.48 (hexanes/EtOAc 80:20). IR (cm^{-1}): $\nu(CN_2)$ 2143; $\nu(C{=}O)$ 1744; $\nu(NO_2)$ 1518; $\nu(NO_2)$ 1495; $\nu(NO_2)$ 1319. ^1H NMR ($CDCl_3$): δ = 7.45–7.48 (m, 2H), 7.31–7.40 (m, 5H), 6.97–7.02 (m, 2H), 5.62 (s, 1H), 5.46 (s, 1H), 5.33 (s, 2H), 4.96 (s, 2H). ^{13}C NMR ($CDCl_3$): δ = 157.0, 155.1, 143.0, 138.2, 131.0, 130.8, 128.6, 128.2, 126.1, 122.9, 121.0, 115.2, 112.0, 69.9, 64.3.

General intramolecular cyclopropanation procedure with Rh(II) catalysts: To a solution of Rh(II) catalyst (1.0 mol% based on diazo) in dichloromethane (2.0 ml) at 50 °C was added 100 mg of **13** (0.5 M in anhydrous dichloromethane) via syringe pump to for the indicated amount of time (see Eq. (5), Table 4). The solution was allowed to stir for an additional 2 h before it was concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the pure cyclopropanes **14** and **15**.

2.5.4. 6-Nitro-2,8-dioxa-tricyclo[8.4.0.0^{4,6}] tetradeca-1(10),11,13-trien-7-one (**14a**)

Yield: 33%. White solid, mp: 110–113 °C. R_f 0.35 (hexanes/EtOAc 80:20). HRMS (MAB) Found: 249.064186. $C_{12}H_{11}NO_5$ $[M]^+$ Calc.: 249.063723. IR (cm^{-1}): $\nu(C{=}O)$ 1751; $\nu(NO_2)$ 1542; $\nu(NO_2)$ 1351; $\nu(NO_2)$ 1331. ^1H NMR ($CDCl_3$): δ = 7.28–7.21 (m, 1H), 7.06–7.12 (m, 2H), 6.97–6.99 (s, 1H), 5.89 (d, J = 14.1 Hz, 1H), 5.30 (d, J = 14.1 Hz, 1H), 4.39–4.43 (m, 1H), 4.27–4.31 (m, 1H), 2.64–2.73 (m, 1H), 2.12–2.21 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 164.1, 158.1, 129.4, 128.1, 126.4, 124.8, 122.4, 70.1, 66.8, 30.4, 20.1. Enantiomeric excess was determined by SFC: Chiracel OJ column, modifier: 1.4% MeOH, flow: 1.4 ml/min. The relative stereochemistry was determined by DPFGSE-NOE.

*2.5.5. 4-Methyl-6-nitro-2,8-dioxa-tricyclo[8.4.0.0^{4,6}] tetradeca-1(10),11,13-trien-7-one (**14b**)*

Yield: 58%. White solid, mp: 95–98 °C. R_f 0.26 (hexanes/EtOAc 90:10). HRMS (MAB) Found: 263.079297. $C_{13}H_{13}NO_5$ $[M]^+$ Calc.: 263.079373. IR (cm^{-1}): ν(C=O) 1750; $\nu(NO_2)$ 1542; $\nu(NO_2)$ 1347. ^{1}H NMR ($CDCl_3$): δ = 7.21–7.24 (m, 1H), 7.09–7.11 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.03 (d, J = 14.3 Hz, 1H), 5.20 (d, J = 14.3 Hz, 1H), 4.24 (d, J = 10.3 Hz, 1H), 4.04 (d, J = 10.3 Hz, 1H), 2.23 (d, J = 6.9 Hz, 1H), 2.16 (d, J = 6.9 Hz, 1H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 164.6, 157.5, 129.2, 127.8, 126.7, 125.2, 123.4, 76.2, 73.4, 66.3, 35.2, 23.2, 15.0. Enantiomeric excess was determined by SFC: Regis Whelk O column, modifier: 1.5% MeOH, flow: 1.5 ml/min. The relative stereochemistry was determined by DPFGSE-NOE.

*2.5.6. 6-Nitro-4-phenyl-2,8-dioxa-tricyclo[8.4.0.0^{4,6}] tetradeca-1(10),11,13-trien-7-one (**15c**)*

Yield: 66%. White crystalline solid, mp: 172 °C. R_f 0.49 (hexanes/EtOAc 80:20). Anal. Found: C, 66.68; H, 4.75; N, 4.31. $C_{18}H_{15}NO_5$ Calc.: C, 66.46; H, 4.65; N, 4.31. IR (cm^{-1}): ν(C=O) 1742; $\nu(NO_2)$ 1538; $\nu(NO_2)$ 1343. ^{1}H NMR ($CDCl_3$): δ = 7.31–7.37 (m, 5H), 7.20–7.27 (m, 1H), 7.13–7.16 (m, 2H), 6.97 (d, J = 7.8 Hz, 1H), 6.32 (d, J = 14.4 Hz, 1H), 5.17 (d, J = 14.4 Hz, 1H), 4.40 (d, J = 10.5 Hz, 1H), 4.25 (d, J = 10.5 Hz, 1H), 2.76 (d, J = 6.9 Hz, 1H), 2.55 (d, J = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 164.1, 157.2, 133.5, 129.3, 129.2, 129.1, 128.8, 127.8, 126.7, 125.4, 123.6, 76.3, 73.0, 66.3, 44.2, 20.8. Enantiomeric excess determined by SFC: Regis Whelk O column, modifier: 6.0% MeOH, flow: 2.0 ml/min. The relative stereochemistry was determined by X-ray crystallography.

3. Results and discussion

3.1. Rh(II) catalysed intermolecular cyclopropanation of styrene

The yields of the cyclopropanation reactions (Eq. (1)) were, generally, modest to high. The diastereoselection favouring the *E*-isomer proved to be the highest for the least sterically demanding esters (Table 1, entries 1 and 2), while the use of α-nitro-α-diazo ketone **9d** proved modestly selective for the *Z*-isomer in the case of catalyst **1** (Table 1, entry 4). However, the enantioselection remained low to modest for all catalysts tested.

Commercially available Rh(II) amide type catalysts, generally, were not sufficiently reactive to promote a cyclopropanation reaction with these diazo substrates even under forcing conditions (refluxing toluene) and either led to decomposition or recovery of unreacted diazo substrate. However, catalyst **3** (Table 1, entry 6) proved to be an exception as Doyle et al. have proposed that the ligand strain on the dirhodium(II) framework results in higher reactivity toward diazo decomposition relative to other Rh(II) amide type catalysts [23]. It also exhibits one of the highest levels of enantioselection among the catalysts tested.

High enantiomeric induction in intermolecular cyclopropanations catalysed by Rh(II) catalysts are not common in the literature and usually involve disubstituted diazo substrates containing one functional group that can potentially act as an electron donating group [14,28,29]. Presumably, the lack of enantioselection in this reaction can be attributed to two factors: the high electrophilicity of the diazo substrate making them highly reactive, thus allowing little time for enantiotopic discrimination, and the difficulty in differentiation of the nitro and ester groups of the substrate by the catalyst since they are similar in terms of steric bulk. The later idea might be supported by the slight improvement in enantioselection with substrate **9c** (Table 1, entry 3) of 41% e.e. for the *E* diastereoisomer versus **9a**, **b** and **d** of 28, 30, 31% e.e., respectively for the *E* diastereoisomers (Table 1, entries 1, 2 and 4).

It is also notable to mention that in these cyclopropanation experiments the rate of addition of the diazo substrate into the catalyst/alkene solution can be done very rapidly (<30 min) and dimers have never been isolated, nor observed in the crude reaction mixtures. In typical cyclopropanation reactions, such as those involving ethyl diazoacetate or diazo malonates, dimerisation can only be avoided if extended addition times are used, and as a result, a syringe pump is commonly employed.

3.2. Influence of solvent on Rh(II) catalysed intermolecular cyclopropanation of styrene

Davies et al. have observed that in non-polar solvents, such as pentane, increased enantioselection

results. They have proposed that these solvents prevent stabilisation of net dipole moments resulting in a potentially more selective D_2 symmetric catalyst rotomer form α, β, α, β [14].

The effect of solvent was tested (Eq. (2)) and surprisingly, the effect on the enantioselectivity was minimal with the enantioselectivities ranging from 22 to 28% e.e. for the major *E* diastereoisomer with slightly more variation for the minor *Z* diastereoisomer (see Table 2). The isolated yields were moderately affected with the change in solvent, except for THF (Table 2, entry 5) where a large decline in the reaction yield was observed, possibly due to reaction of the THF with the carbene intermediate. These results suggest that the discrimination of the nitro and ester groups by the catalyst is difficult in our case as opposed to loss of selectivity due to rotomers of the catalyst proposed by Davies et al. [14].

The influence of solvent polarity on the enantioselectivities of the cyclopropanation reaction was further examined (Eq. (3)) by the preparation of substrate **11** which allowed for solubility in hexanes. A small improvement in enantioselection was observed with 35% e.e. for the major *E* diastereoisomer (Eq. (3)) versus 41% e.e. for the best example in other solvents using catalyst **1** (Table 1, entries 3). For the sake of comparison, the cyclopropanation reaction was also performed in dichloromethane and the enantioselectivity was found to be 29% e.e. for the *E* diastereoisomer and 0% e.e. for the minor *Z* diastereoisomer in a 93:7 *E*:*Z* ratio and 86% isolated yield. Again, using substrate **11**, catalysts **4a** and **b** showed only slight improvements on their enantioselection relative to their results in dichloromethane (Table 1, entries 7 and 8) and were inferior to those obtained with catalyst **1**.

3.3. Copper catalysed intermolecular cyclopropanation of styrene

The low to modest enantioselectivities for the variety of Rh(II) catalysts tested made us turn our focus to copper-based catalysts of type **5** (Eq. (4), Fig. 2). Of particular interest were the ligands reported by Evans et al. with C_2 symmetric bis(oxazolines) [18]. Initially cyclopropanations using these catalysts were also plagued by low yields as reported by O'Bannon and Dailey in their copper catalysed cyclopropanations [11].

The reproducibility in cyclopropanation yields was also problematic and one particularly intriguing observation was the consistently low yields regardless of reaction time, ligand, solvent and reaction temperature. We also observed that reactions catalysed by the same Cu source and ligands with ethyl diazoacetate as a substrate were quite efficient, eliminating the possibility that the Cu source had been improperly handled. It is also important to note that substrate **9a** did not decompose under the reaction conditions and could be recovered along with the converted cyclopropane with greater than 90% mass recovery.

Thus, to improve the cyclopropanation reaction yields we tried activating the catalyst. One report in the literature outlined the use of traces of benzoyl peroxide to increase yields in copper catalysed cyclopropanations involving diazomalonates [30]. With this additive we found only slight improvements (Table 3, entry 1). Provided that the cyclopropanation reaction was efficient with ethyl diazoacetate, we reasoned that it could be acting as an activator to produce a more active form of the catalyst, potentially via simple displacement of co-ordinating solvent and liberation

Table 3
Copper catalysed cylopropanation of styrene

Entry	Ligand	Additive	%Yield (**10a**)	Ratio *E*:*Z*	%e.e. (*E* isomer)	%e.e. (*Z* isomer)
1	**6a**	$(BzO)_2$	27	90:10	nd	nd
2	**6a**	EDA (20%)[a]	55	90:10	72	51
3	**6a**	EDA (10%)[b]	52	90:10	66	49
4	**6a**	$PhNHNH_2$[c]	39	90:10	70	49
5	**6b**	EDA (10%)[a]	16	95:5	68	nd
6	**6c**	EDA (10%)[a]	7	95:5	63	nd

[a] The catalyst was pre-treated with a solution of ethyl diazoacetate in dichloromethane.
[b] The ethyl diazoacetate was mixed with **9a** in dichloromethane.
[c] Cu(II)OTf_2 was used as the copper source.

Table 4
Rh(II) catalysed intramolecular cyclopropanation

Entry	Substrate	Catalyst	Addition time (h)	Yield (**14**)	Ratio (**14**:**15**)	%e.e. (major)
1	**13a**	$[Rh(OPiv)_2]_2$	3	14	>95:5 **14a**	na
2	**13a**	**4b**	3	33	>95:5 **14a**	45
3	**13b**	$[Rh(C_7H_{15}CO_2)_2]_2$	3	31	92:8 **14b**	na
4	**13b**	**4b**	2	58	>95:5 **14b**	50
5	**13c**	$[Rh(C_7H_{15}CO_2)_2]_2$	4	28	>95:5 **15c**	na
6	**13c**	**4b**	2.5	66	>95:5 **15c**	61

of a free site on the catalyst. Thus, pre-treatment of the $Cu(I)(MeCN)_4PF_6$ ligand complex with 20 mol% ethyl diazoacetate solution based on substrate **9a** followed by the addition of a 1.0 M solution of **9a** resulted in a surprising increase in reaction yields. This new protocol also showed improved reproducibility (Table 3, entry 2).

The diastereo- and enantioselectivities were superior to the cases observed under Rh(II) catalysis (Tables 1 and 2), up to 90:10 *E*:*Z* ratio and 72% e.e. for the major *E* diastereoisomer (Table 3, entry 2). 4-Chlorostyrene also gave identical enantioselectivities under these conditions. The mass balance, however, still consisted of **9a** and could be recovered from the reaction mixture. Ethyl diazoacetate when combined with **9a** also gave similar results (Table 3, entry 3). Finally, the use of $Cu(II)OTf_2$ as the copper source followed by pre-activation with phenyl hydrazine (2 eq. based on Cu) also produced a slightly inferior yield of cyclopropane **10a** (Table 3, entry 4).

The ligand effect was also examined and it was found that the reaction was very sensitive to steric hindrance. The yields declined dramatically using ligands **6b** and **c** (Table 3, entries 5 and 6) and surprisingly the enantioselectivities were also diminished with increasing steric hindrance. With this in mind, less sterically demanding ligands **7** [31] and **8** [32] were tested and gave drastic declines in enantioselectivities (12 and 0% e.e., respectively).

3.4. Rh(II) catalysed intramolecular cyclopropanation

Rh(II) catalysts have found widespread applications in intramolecular cyclopropanations where they have been known to give much higher levels of enantioselection [33,34]. Thus, we prepared suitable substrates of type **13** employing 2-hydroxybenzyl alcohol as a scaffold to test this general trend. Substrate **13** can be readily prepared in three high yielding steps involving allylation of the 2-hydroxybenzyl alcohol [35], followed by DCC coupling of the substituted benzene methanol [27], then diazo transfer [15].

We were pleased to find that the enantioselectivities in the intramolecular cyclopropanation (Eq. (5)) using catalyst **4b** were higher than in the intermolecular cyclopropanation. Catalyst **4b** consistently gave higher yields than the corresponding achiral catalysts $[Rh(OPiv)_2]_2$ or $[Rh(C_7H_{15}CO_2)_2]_2$ which were required for racemic material. The yields of the cyclopropanations follow the trends observed with the ease at which various olefins are cyclopropanated [9]. In this fashion, it is not surprising that the cyclopropanations with the allyloxy substrate **13a** (Table 4, entries 1 and 2) are lower yielding. However, in the intramolecular cyclopropanation the diastereoselectivities of substrate **13a** were superior compared to the intermolecular case for similar substrates which afforded ratios of 60:40 favouring the *E* diastereoisomer [36]. The mass balance is presumably polymeric material resulting from intermolecular cyclopropanation.

Substrate **13b** (Table 4, entries 3 and 4) gave modest yields of **14b** with an enantiomeric excess of 50% (Table 4, entry 4) as the substrate is better able to stabilise formation of partial cationic character in the α-position. Substrate **13c**, when submitted to the same conditions, gave an isolated yield of 66% of **15c** (Table 4, entry 6) and higher enantiomeric excess (61%) was observed. This structure was confirmed by X-ray crystallography.

Attempted optimisation of these results using catalysts **1**, **2** and **4a** gave comparable yields, however, the levels of enantioselection were inferior. Catalyst **3** failed to give products resulting from cyclopro-

panation of the allyloxy group rather cyclopropanation of the aryl ring probably occurred (observed by ^{1}H NMR of crude reaction mixture) which decomposed upon attempted isolation. Again, as observed in the Rh(II) catalysed intermolecular cyclopropanations, the solvent had little effect on the enantiomeric excess.

4. Conclusions

Intermolecular cyclopropanations of styrene with α-nitro-α-diazo carbonyl compounds using chiral Rh(II) carboxylates or amide catalysts were found to provide modest to high yields (Table 1) and excellent solvent tolerance (Table 2) although low enantioselectivities. Copper-based catalysts were found to be more highly enantioselective giving enantiomeric excesses up to 72% for the intermolecular cyclopropanation of styrene with lower yields (up to 55%, Table 3). The first intramolecular cyclopropanation of α-nitro-α-diazo carbonyls is also reported affording 9-membered nitro cyclopropyl lactones. Enantioselection up to 61% e.e. and yields up to 66% were possible with extremely high diastereoselectivities (Table 4). The preliminary results are quite encouraging and we are currently pursuing the synthesis of other copper and Rh(II) catalysts and substrates and their results will be published in due course.

Acknowledgements

This work was supported by the E.W.R. Steacie Fund, NSERC, Merck Frosst Canada, Boehringer Ingelheim, and the Université de Montréal. R.W. thanks NSERC for a postgraduate fellowship. The authors also thank Ms. Francine Bélanger-Gariépy for the elucidation of the solid-state structure.

References

[1] M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides, vol. 94, Wiley, Toronto, 1998.
[2] H.M.L. Davies, E.G. Antoulinakis, Organic Reactions, vol. 57, Wiley, Toronto, 2001, p. 1 (Chapter 1).
[3] L.F. Burroughs, Nature 179 (1957) 360.
[4] R. Faust, Angew. Chem. Int. Ed. Engl. 40 (2001) 2251.
[5] K. Burgess, K.-K. Ho, D. Moye-Sherman, Synlett 1 (1994) 575.
[6] D. Seebach, R. Häner, T. Vettiger, Helv. Chim. Acta 70 (1987) 1507.
[7] T. Vettiger, D. Seebach, Liebigs Ann. Chem. 1990 (1990) 195.
[8] U. Schöllkopf, P. Toone, Ann. Chem. 753 (1971) 135.
[9] P.E. O'Bannon, W.P. Dailey, Tetrahedron Lett. 30 (1989) 4197.
[10] P.E. O'Bannon, W.P. Dailey, J. Org. Chem. 54 (1989) 3096.
[11] P.E. O'Bannon, W.P. Dailey, Tetrahedron 46 (1990) 7341.
[12] R. Häner, D. Seebach, Chimia 39 (1985) 356.
[13] A.B. Charette, B. Côté, J. Am. Chem. Soc. 117 (1995) 12721.
[14] H.M.L. Davies, P.R. Bruzinski, D.H. Lake, N. Kong, M.J. Fall, J. Am. Chem. Soc. 118 (1996) 6897.
[15] A.B. Charette, R.P. Wurz, T. Ollevier, J. Org. Chem. 65 (2000) 9252.
[16] H. Brunner, W. Miehling, Monatsh. Chem. 115 (1984) 1237.
[17] T. Kunz, H.-U. Reissig, Tetrahedron Lett. 30 (1989) 2079.
[18] D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, J. Am. Chem. Soc. 113 (1991) 726.
[19] R.E. Lowenthal, A. Abiko, S. Masamune, Tetrahedron Lett. 31 (1990) 6005.
[20] D. Müller, G. Umbricht, B. Weber, A. Pfaltz, Helv. Chim. Acta 74 (1991) 232.
[21] H.J. Callot, F. Metz, Tetrahedron 41 (1985) 4495.
[22] M.C. Pirrung, J. Zhang, Tetrahedron Lett. 33 (1992) 5987.
[23] M.P. Doyle, S.B. Davies, W. Hu, Org. Lett. 2 (2000) 1145.
[24] H. Balli, R. Löw, Tetrahedron Lett. 7 (1966) 5821.
[25] L. Cai, H. Mahmoud, Y. Han, Tetrahedron: Asymmetry 10 (1999) 411.
[26] D.C. Wynne, M.M. Olmstead, P.G. Jessop, J. Am. Chem. Soc. 122 (2000) 7638.
[27] C. Sylvain, A. Wagner, C. Mioskowski, Tetrahedron Lett. 40 (1999) 875.
[28] H.M.L. Davies, T. Nagashima, J.L. Klino III, Org. Lett. 2 (2000) 823.
[29] H.M.L. Davies, Eur. J. Org. Chem. 1999 (1999) 2459.
[30] B.W. Peace, F. Carman, D.S. Wulfman, Synthesis 3 (1971) 658.
[31] M.J. Totleben, J.S. Prasad, J.H. Simpson, S.H. Chan, D.J. Vanyo, D.E. Kuehner, R. Deshpande, G.A. Kodersha, J. Org. Chem. 66 (2001) 1057.
[32] S.E. Denmark, R.A. Stavenger, A.M. Faucher, J.P. Edwards, J. Org. Chem. 62 (1997) 3375.
[33] M.P. Doyle, W. Hu, B. Chapman, A.B. Marnett, C.S. Peterson, J.P. Vitale, S.A. Stanley, J. Am. Chem. Soc. 122 (2000) 5718.
[34] M.P. Doyle, W. Hu, J. Org. Chem. 65 (2000) 8839.
[35] A. Lachapelle, M. St.-Jacques, Tetrahedron 44 (1988) 5033.
[36] A.B. Charette, R.P. Wurz, unpublished results.