Tetrahedron xxx (2015) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective dirhodium(II)-catalyzed cyclopropanations with trimethylsilylethyl and trichloroethyl aryldiazoacetates

Solymar Negretti, Carolyn M. Cohen, Jane J. Chang, David M. Guptill, Huw M.L. Davies *

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322, USA

ARTICLE INFO

Article history:
Received 14 March 2015
Received in revised form 1 May 2015
Accepted 13 May 2015
Available online xxx

This paper is dedicated to the memory of Professor Alan R. Katritzky, an inspirational leader in the field of heterocyclic chemistry

Keywords:
Asymmetric cyclopropanation
Cyclopropanes
Donor/acceptor carbenoids
Dirhodium catalysis

ABSTRACT

Highly functionalized cyclopropanecarboxylates were readily prepared by rhodium-catalyzed cyclopropanation of alkenes with aryldiazoacetates and styryldiazoaceates, in which the ester functionality is either trimethylsilylethyl (TMSE) or trichloroethyl (TCE). By having labile protecting groups on the ester, chiral triarylcyclopropane carboxylate ligands were conveniently prepared. The asymmetric induction during cyclopropanation is dependent on the nature of the ester group and the chiral dirhodium tetracarboxylate catalyst. The prolinate catalyst Rh_2(*S*-DOSP)$_4$ was the optimum catalyst for asymmetric intermolecular cyclopropanation of TMSE diazoesters with styrene, while Rh_2(*R*-BPCP)$_4$ was the optimum catalyst for TCE diazoesters.

1. Introduction

Cyclopropanes are a common motif in natural products and medicinal targets, and are useful building blocks in complex molecule synthesis.[1–4] Therefore, the development of methods for their enantioselective synthesis has been of general interest.[5–11] Cyclopropanation between metal carbenes and alkenes is recognized as a classic reaction for the synthesis of cyclopropanes.[12] We have previously shown that the cyclopropanation reaction of aryldiazoacetates proceeds with high diastereoselectivity even under thermal conditions.[13] When cyclopropanation with donor/acceptor carbenoids is catalyzed by chiral dirhodium(II) tetracarboxylates, the reaction can proceed with high levels of enantioselectivity.[14–18] The reaction is even effective for electron deficient alkanes with the appropriate catalyst.[18] Mechanistic studies have suggested that these rhodium-catalyzed cyclopropanation reactions proceed by means of a concerted-asynchronous process.[19]

In a comparative study of different catalysts, Rh_2(DOSP)$_4$ was found to be the optimal catalyst for a broad range of methyl aryldiazoacetates (Fig. 1).[20] In addition, the two other chiral dirhodium(II) catalysts studied, Rh_2(*S*-PTAD)$_4$ and Rh_2(*R*-BNP)$_4$, were shown to have enantioselectivity profiles complementary to that of Rh_2(DOSP)$_4$. The former provided high levels of enantioinduction when the acceptor of the aryldiazoacetate precursor was varied. Whereas Rh_2(*R*-BNP)$_4$ was well suited for catalyzing highly enantioselective cyclopropanation of alkoxy-substituted methyl aryldiazoacetates. A drawback of Rh_2(DOSP)$_4$, however, is that high levels of enantioselectivity are typically achieved only when the

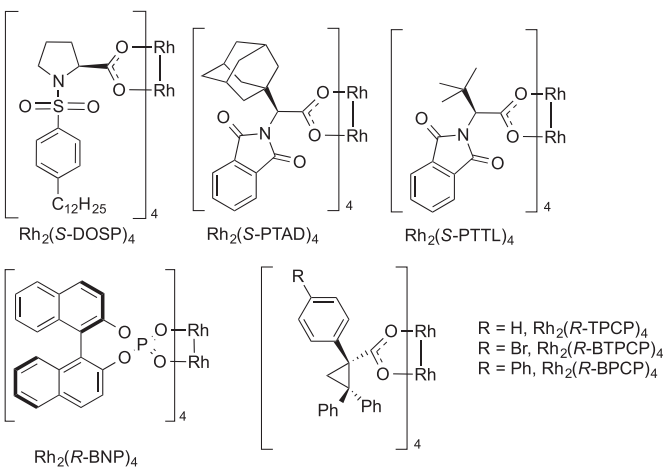


Fig. 1. Dirhodium(II) catalysts.

* Corresponding author. Tel.: +1 404 727 6839; e-mail address: hmdavie@emory.edu (H.M.L. Davies).

http://dx.doi.org/10.1016/j.tet.2015.05.045
0040-4020/

acceptor group is a methyl ester as opposed to larger alkyl esters.[14] Additionally a model was developed to predict the stereochemistry of the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation.[21]

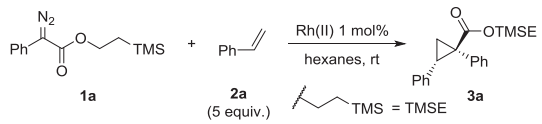
A new generation of chiral D_2-symmetric dirhodium(II) catalysts has emerged from the Davies group that employs chiral triarylcyclopropane carboxylates as ligands.[22] These ligands are derived from Rh_2(*R*-DOSP)$_4$ catalyzed cyclopropanation of 1,1-disubstituted olefins with aryldiazoacetates, followed by ester hydrolysis. The first member of this class was Rh_2(*R*-BTPCP)$_4$, which was found to catalyze classic reactions of donor/acceptor carbenoids such as cyclopropanation, tandem cyclopropanation/Cope rearrangement and combined C–H functionalization/Cope rearrangement/retro-Cope rearrangement. Furthermore, it was employed in the enantioselective synthesis of 2-arylbicyclo[1.1.0]butane carboxylates.[23] These catalysts also show promise in controlling the reactivity of rhodium-stabilized carbenoids derived from vinyldiazoacetates, which traditionally react at the carbene site with the benchmark catalysts, Rh_2(*R*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$. A related analogue, Rh_2(*R*-TPCP)$_4$ was employed for the generation of [3+2] cycloaddition products derived from initial attack at the vinylogous position of the rhodium vinylcarbene.[24] Most recently, the biphenyl derivative Rh_2(*R*-BPCP)$_4$ has shown promise for site selective C–H functionalization. It was applied to the selective functionalization of activated primary C–H bonds, such as allylic and benzylic sites.[25] Furthermore, in combination with the more sterically hindered 2,2,2-trichloroethyl aryldiazoacetates, site selective and enantioselective C–H functionalization of methyl ethers was achieved.[26]

Given the important role that different ester groups play in the reactivity and selectivity of carbenoid C–H functionalization reactions, we undertook a study to uncover the role of 2-(trimethylsilyl)ethyl (TMSE) and 2,2,2-trichloroethyl (TCE) esters in cyclopropanation reactions. Previously, we had shown that the TMSE esters are prone to intramolecular reactions,[27] but we anticipated that this ester functionality would be compatible with intermolecular reactions of reactive alkenes. The TCE group appears to be very robust for rhodium carbene reactions, and so we expected donor/acceptor carbenes bearing TCE ester acceptor group would be very effective in intermolecular cyclopropanations. Both ester groups would be more easily removed than the corresponding methyl ester, which would expand the range of useful carbene transformations for the preparation of novel chiral carboxylate ligands. Herein we report the results of our efforts to develop asymmetric cyclopropanation reactions of TMSE aryldiazoacetates and TCE aryldiazoacetates.

2. Results and discussion

The study began with the reaction of TMSE phenyldiazoacetate **1a** and styrene **2a** to determine the optimal chiral dirhodium(II) catalyst for the formation of cyclopropane **3a** as a single diastereomer with high levels of enantioselectivity. Of the catalysts screened, Rh_2(*S*-DOSP)$_4$ provided the highest yield and level of enantioinduction, producing **3a** in 87% yield and 87% ee (Table 1, entry 1). Rh_2(*S*-BTPCP)$_4$ afforded the desired cyclopropane in moderate yield but low enantioselectivity, 67% yield and 43% ee, respectively (Table 1 entry 2). Both the phthalimido dirhodium(II) catalysts Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-NTTL)$_4$ provided low yields and enantioselectivity in the reaction.

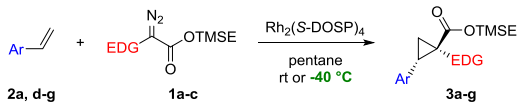
Table 1
Chiral dirhodium(II)-catalyzed cyclopropanation of TMSE phenyldiazoacetate and styrene

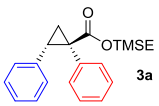
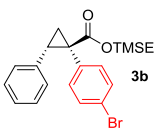
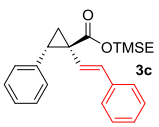
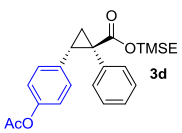
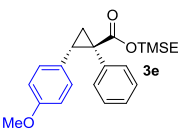
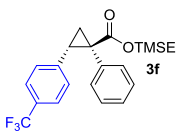
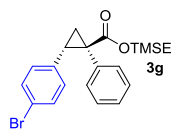


Entry	Catalyst	Yield (%)	ee (%)
1	**Rh_2(*S*-DOSP)$_4$**	**87**	**87**
2	Rh_2(*S*-BTPCP)$_4$	67	43
3	Rh_2(*S*-PTAD)$_4$	46	−35
4	Rh_2(*S*-NTTL)$_4$	35	−51

On the basis of the initial evaluation, Rh_2(*S*-DOSP)$_4$ was used to study the scope of the cyclopropanation with a series of TMSE aryldiazoacetates and styrene derivatives. The results are summarized in Table 2. The enantioselectivity of **3a** was slightly higher in pentane, therefore it was used in the scope study (see Table 1, entry 1 and Table 2, entry 1). The Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of TMSE aryldiazoacetates was fairly general with respect to the donor group on the diazoacetates, as cyclopropanes **3a**–**3c** were formed in high yields and high levels of enantioselectivity when the reactions were conducted at room temperature. Both 4-bromophenyl and styryl substituted TMSE diazoacetates yielded the cyclopropanes **3b** and **3c** with fairly high levels of enantioinduction (88% and 85% ee, respectively, entries 2 and 3). Both electron-withdrawing and electron-donating substituents were well tolerated on the styrene derivative as well (entries 4–7). Both the 4-methoxy and 4-trifluoromethyl substituted styrenes afforded the cyclopropanes in 72% yield. The 4-acetoxy and 4-

Table 2
Substrate scope of the cyclopropanation of TMSE aryldiazoacetates and styrenes

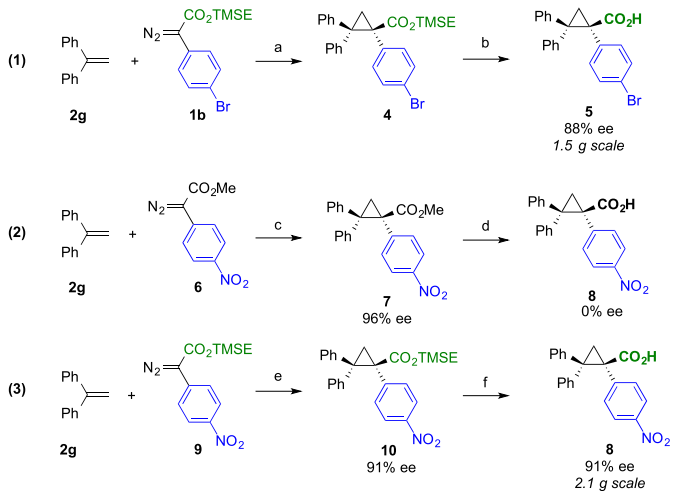


Entry	Product	rt (% yield, % ee)	−40 °C(% yield, % ee)
1		86% yield 88% ee	69% yield 96% ee
2		73% yield 89% ee	63% yield 96% ee
3		64% yield 85% ee	71% yield 87% ee
4		61% yield 88% ee	65% yield 96% ee
5		72% yield 81% ee	76% yield 91% ee
6		72% yield 84% ee	50% yield 96% ee
7		74% yield 86% ee	67% yield 96% ee

Please cite this article in press as: Negretti, S.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.045

bromo substituted styrenes afforded the cyclopropanes **3d** and **3f** in good yields and similar enantioselectivity (88% ee and 86% ee, respectively, entries 4 and 7). Good yields and moderately high levels of enantioselectivity were observed in all cases (81–88% ee). The asymmetric induction could be further improved by lowering the reaction temperature to −40 °C. In nearly all cases, the products were formed with >90% ee. The absolute configuration of the products was assigned based on the previously proposed model.[21] For confirmation, **3a** was hydrolyzed to the acid, and converted the corresponding methyl ester, whose absolute configuration is reported in the literature (see Supplementary data).[22]

The reaction was then applied to the enhanced synthesis of the Rh_2(*S*-BTPCP)$_4$ ligand. The cyclopropanation of **2g** with **1b** afforded cyclopropane **4** in 73% yield and 88% ee (Scheme 1, Eq. 1). The TMSE ester was then cleaved under mild conditions using tetrabutylammonium fluoride (TBAF) in DMF to yield the ligand **5** in 81%



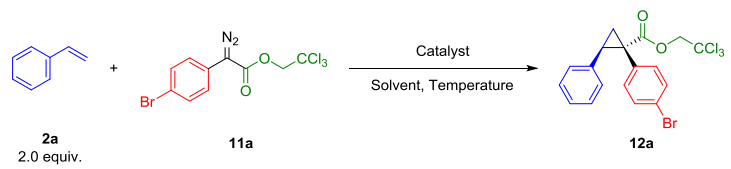
Scheme 1. Synthesis of triarylcyclopropane carboxylate ligands through TMSE aryldiazoacetate cyclopropanation. (a) Rh_2(*S*-DOSP)$_4$, pentane rt (b) TBAF, DMF, 81%, 88% ee (c) Rh_2(*S*-DOSP)$_4$, pentane, $PhCF_3$, 82%, 96% ee (d) KO*t*Bu, DMSO (e) Rh_2(*S*-PTTL)$_4$, pentanes, $PhCF_3$, −78 °C, 87%, 91% ee (f) TBAF, DMF, 77%, 91% ee.

yield. Most importantly the enantioselectivity remained unchanged after the hydrolysis. Additionally, this material was recrystallized from pentane/diethyl ether and enriched to high optical purity (>99.5% ee). An excellent example of the utility of the TMSE esters can be seen from the synthesis of **8** (Scheme 1, Eqs. 2 and 3). Though cyclopropanation of methyl 2-diazo-2-(4-nitrophenyl)acetate **6** and **2g** afforded cyclopropane **7** in 82% yield and 96% ee, the vigorous hydrolysis conditions resulted in complete racemization of the chiral center (Scheme 1, Eq. 2). Synthesis of ligand **8** in an enantiomerically enriched form was successfully achieved employing TMSE diazo compound **9** together with Rh_2(*S*-PTTL)$_4$ as the chiral catalyst in the cyclopropanation to form **10** in 91% ee, which was with TBAF (Scheme 1, Eq. 3) to give **8** without loss of enantioenrichment.

Next, we explored the use of TCE aryldiazoacetates in cyclopropanation reactions. A catalyst screen was performed to find the optimal conditions for this transformation (Table 3). Rh_2(*S*-DOSP)$_4$ afforded the desired cyclopropane **12a** in good yield and moderately high enantioselectivity, 88% yield and −83% ee, while the yield and enantioinduction decreased with Rh_2(*S*-PTAD)$_4$ to 64% yield and 62% ee (entries 1–2). The use of dirhodium(II) triarylcyclopropanecarboxylate catalysts greatly enantioselectivity of the reaction (entries 3–9). In pentane, Rh_2(*S*-BTPCP)$_4$ and Rh_2(*R*-BPCP)$_4$ provided **12a** in −90% ee and 70% ee, respectively. The polarity of the solvent had substantial effects on the enantioselectivity with these catalysts, particularly with Rh_2(*R*-BPCP)$_4$, which in DCM resulted in the formation of **12a** n 69% yield and 96% ee (entry 5). Similar results were observed with DCE as solvent, but the enantioselectivities were slightly lower than in DCM (entries 7–9). The absolute configuration of the product was assigned by hydrolysis of the TCE ester and subsequent conversion into the corresponding methyl ester, which is known in the literature.[28]

The scope of the reaction was examined using the optimized conditions of 0.5 mol % of Rh_2(*R*-BPCP)$_4$ in DCM at room temperature and the results are summarized in Table 4. In the Rh_2(*R*-BPCP)$_4$ catalyzed cyclopropanation of styrene with TCE diazoacetates, both electron-donating groups and electron-withdrawing groups were tolerated (Table 4). The *t*-butyl-substituted cyclopropane **12b** was obtained in good yields and excellent enantioselectivity (74% yield, 98% ee), whereas the electron-withdrawing 4-fluoro TCE diazoacetate yielded the desired cyclopropane **12c** in 58% yield and 93% ee (entries 1–2). Additionally, heterocycles such as pyridines and isoxazoles are tolerated as the aryl group of the TCE diazoacetates. Cyclopropanes **12d** and **12e** were obtained in moderate yields, 61% and 63% respectively, and excellent levels of enantioselectivity, 93% ee and 85% ee respectively (entries 3–4). TCE styryldiazoacetate was also well tolerated and cyclopropane **12f** was formed with high yield and enantioinduction (90% yield and 93% ee, entry 5), whereas with the TMSE stryldiazoacetate **1c** the highest level of enantioselectivity observed was 87% ee. Upon modification of the styrene unit, cyclopropane **12h**, the TCE precursor for the Rh_2(*R*-BTPCP)$_4$ ligand, was obtained in good yields and moderately high enantioselectivity (77%, 86% ee, entry 6). The electronics of the styrene had little effect on the enantioselectivity of the reaction, as both cyclopropanes **12i** and **12j**, with 4-methoxy

Table 3
Chiral dirhodium (II)-catalyzed cyclopropanation of TCE 4-bromophenyldiazoacetate and styrene

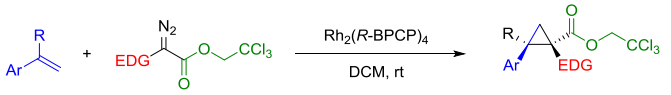


2a 2.0 equiv. **11a** **12a**

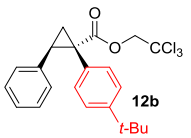
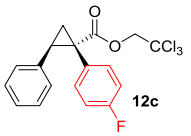
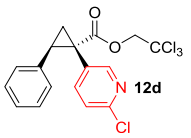
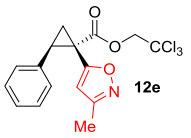
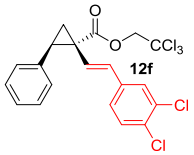
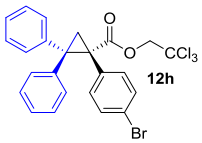
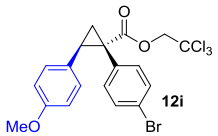
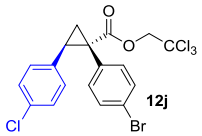
Entry	Catalyst	Catalyst loading (mol %)	Solvent	Temp (°C)	Yield (%)	ee (%)
1	Rh_2(*S*-DOSP)$_4$	1.0	pentane	rt	88	−83
2	Rh_2(*S*-PTAD)$_4$	1.0	pentane	rt	64	62
3	Rh_2(*S*-BTPCP)$_4$	0.5	pentane	rt	81	−90
4	Rh_2(*R*-BPCP)$_4$	0.5	pentane	rt	80	70
5	**Rh_2(*R*-BPCP)$_4$**	**0.5**	**DCM**	**rt**	**69**	**96**
6	Rh_2(*S*-BTPCP)$_4$	0.5	DCM	rt	73	−95
7	Rh_2(*R*-BPCP)$_4$	0.5	DCE	rt	71	92
8	Rh_2(*S*-BTPCP)$_4$	0.5	DCE	rt	68	−90
9	Rh_2(*R*-BPCP)$_4$	0.5	DCE	0	70	95

Please cite this article in press as: Negretti, S.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.045

Table 4
Substrate scope of the cyclopropanation of TCE aryldiazoacetates and styrenes



2.0 equiv. **11b-f** **12**

Entry	Product	Yield (%)	ee (%)
1	 **12b**	74	98
2	 **12c**	58	93
3	 **12d**	61	93
4	 **12e**	63	88
5	 **12f**	90	93
6	 **12h**	77	86
7	 **12i**	90	94
8	 **12j**	64	95

and 4-chloro substituents respectively, were obtained in greater than 94% ee, albeit in a lower yield for **12j** (90% and 64% yield respectively).

These novel TCE and TMSE esters offer several advantages over the methyl ester. The TMSE group provides the advantage of very mild hydrolysis conditions as well as providing high levels of enantioinduction with the benchmark catalyst Rh_2(*S*-DOSP)$_4$ in non-polar solvents. The additional steric bulk provided by TCE and TMSE aryldiazoacetates diminish dimerization of the diazo compound, which is often encountered as a side product, particularly in C–H insertions.[29,30] Additionally the electron-withdrawing nature of the TCE ester group protects against formation of β-lactones from intramolecular C–H insertion.[31–33] The TCE aryldiazoacetates have been reported recently as robust reagents and were successfully applied to the selective asymmetric C–H functionalization of methyl ethers by the Davies group.[26] Furthermore, the TCE group can be used with heteroaryldiazoacetates generating heteroaryl-substituted cyclopropanes, further expanding the scope of the reaction. Like TMSE, the TCE ester can be cleaved under mild conditions with Zn/AcOH (see Supplementary data). Finally, the TCE diazoacetates afford cyclopropanes with high levels of enantioinduction in Rh_2(*R*-BPCP)$_4$ in DCM, a complementary catalyst/solvent system to Rh_2(*S*-DOSP)$_4$ in pentane.

3. Conclusion

This study describes intermolecular asymmetric cyclopropanations of aryldiazoacetates containing different ester groups and styrene derivatives catalyzed by chiral dirhodium (II) complexes Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-BPCP)$_4$. The TMSE aryldiazoacetates afford cyclopropanes in high yields and good enantioselectivity (61–86% yield, 81–88% ee) with Rh_2(*S*-DOSP)$_4$ as the chiral catalyst in pentane. The enantioinduction can be further improved by lowering the reaction temperature to −40 °C (87–96% ee). The reaction was tolerant of different functionality on the styrene as well as in the aryl group of the TMSE diazoacetates. The TCE aryldiazoacetates afford the cyclopropanes in high yields and good enantioselectivity (61–90% yield, 85–98% ee) with Rh_2(*R*-BPCP)$_4$ as the chiral catalyst in DCM, even at room temperature. This study hallmarks the importance and effect of the ester group in chiral dirhodium-(II) catalyzed cyclopropanations of aryldiazoacetates. Finally, this study serves as the cornerstone for our ongoing program to develop triarylcyclopropane carboxylates as ligands for the synthesis of novel chiral dirhodium (II) catalysts.

4. Experimental section

4.1. General

All reactions were conducted under anhydrous conditions in oven-dried glassware under an inert atmosphere of dry argon, unless otherwise stated. Hexanes, pentane, and toluene were dried by a solvent purification system (passed through activated alumina columns). All solvents were degassed by bubbling argon through the solvent for a minimum of 10 min prior to use. All dirhodium(II) catalysts were lyophilized for 48 h from benzene prior to use with a VirTis Benchtop K lyophilizer. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz or 600 MHz. Data presented as follows: chemical shift (in ppm on the δ scale relative to δ_H 7.26 for the residual protons in $CDCl_3$), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 100 MHz and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δ_C 77.00 for $CDCl_3$. Mass spectral determinations were carried out by using APCI or NSI as ionization source. Melting points are uncorrected. Infrared spectral data are reported in units of cm^{-1}. Analytical TLC was performed on silica gel plates using UV light. Flash column chromatography was performed on silica gel 60 Å (230–400 mesh). Optical rotations were measured on Jasco polarimeters. Enantioselectivity was determined using chiral HPLC on a Varian Prostar instrument, with isopropanol/hexanes as the eluent. Chiral HPLC conditions were determined analysis of racemic material, obtained by cyclopropanation with Rh_2(*R*/*S*-DOSP)$_4$ and Rh_2(OOct)$_4$.

Please cite this article in press as: Negretti, S.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.045

4.2. General procedures for the synthesis of diazo compounds

4.2.1. General procedure for the preparation of TMSE aryldiazoacetates. A solution of the corresponding carboxylic acid (1.0 equiv), DMAP (0.1 equiv), and 2-(trimethylsilyl)ethanol (1.2 equiv) in DCM (0.6 M in acid) was cooled to 0 °C. Then a solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.1 equiv) in DCM (2.6 M) was quickly poured into the cold reaction mixture. The solution was stirred overnight, after, which time it had warmed to room temperature. The precipitate was removed by filtration, washing several times with Et_2O. The filtrate was concentrated and the crude material purified by column chromatography (EtOAc in hexanes) to give the TMSE ester intermediate as a colorless oil.

The TMSE arylacetate (1 equiv) and *p*-ABSA (1.3 equiv) were dissolved in acetonitrile and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (DBU, 2.0 equiv) was then added dropwise to the stirring mixture over the course of 1 min. The reaction mixture was allowed to stir for 24 h at while warming to room temperature. The resulting orange solution was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with diethyl ether (3x). The organic layer was then washed with deionized H_2O to remove any residual salts. The combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel.

4.2.2. General procedure for the preparation of TCE aryldiazoacetates. A solution of the corresponding carboxylic acid (1.0 equiv), DMAP (0.1 equiv), and 2,2,2-trichloroethanol (1.2 equiv) in DCM (0.6 M in acid) was cooled to 0 °C. Then a solution of DCC (1.1 equiv) in DCM (2.6 M) was quickly poured into the cold reaction mixture. The solution was stirred overnight, after which time it had warmed to room temperature. The precipitate was removed by filtration, washing several times with Et_2O. The filtrate was concentrated and the crude material purified by column chromatography (EtOAc in hexanes) to give the TCE ester intermediate as a colorless oil.

The TCE arylacetate (1 equiv) and *o*-NBSA (1.3 equiv) were dissolved in acetonitrile and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (DBU, 2.0 equiv) was then added dropwise to the stirring mixture. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for 2 h. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous layer was extracted with diethyl ether (3x). The organic layer was then washed with deionized H_2O to remove any residual salts. The combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc in hexanes).

4.3. General procedures for Rh_2(*S*-DOSP)$_4$ catalyzed cyclopropanation

4.3.1. Room temperature reaction. In a 25-mL round bottom flask equipped with a magnetic stir bar, Rh_2(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and styrene (0.29 mL, 2.5 mmol, 5.0 equiv) were dissolved in pentane (3 mL). To this was added a solution of diazo (0.5 mmol, 1.0 equiv) in pentane (3 mL) dropwise over 1 h via syringe pump. The reaction was allowed to stir at rt for at least 1 h after the addition was complete. The volatiles were removed by rotary evaporation, and the crude residue was purified by silica gel column chromatography (Hexanes:EtOAc or pentane:ether).

4.3.2. −40 °C reaction. In a 25-mL round bottom flask equipped with a magnetic stir bar, Rh_2(*S*-DOSP)$_4$ (9.28 mg, 0.005 mmol, 1 mol %) and styrene (0.29 mL, 2.5 mmol, 5.0 equiv) were dissolved in pentane (3 mL). The flask was cooled down to −40 °C by means of an acetonitrile/dry ice bath. Once cooled, a solution of diazo (0.5 mmol, 1.0 equiv) in pentane (3 mL) was added to the reaction mixture dropwise over 1 h via syringe pump. The reaction was allowed to stir at −40 °C for at least 1 h after the addition was complete. The volatiles were removed by rotary evaporation, and the crude residue was purified by silica gel column chromatography (Hexanes:EtOAc or pentane:ether).

4.4. General procedure for the Rh_2(*R*-BPCP)$_4$ catalyzed cyclopropanation

In a 25-mL round bottom flask equipped with a magnetic stir bar, Rh_2(*R*-BPCP)$_4$ (4.4 mg, 0.5 mol %) and styrene (0.12 mL, 1.0 mmol, 2.0 equiv) were dissolved 2 mL DCM at room temperature. A solution of the diazo (0.5 mmol, 1.0 equiv) in 5 mL DCM was added dropwise to the reaction mixture via syringe pump over 30 min. The reaction was allowed to stir at rt for at least 1 h after the addition was complete. The solvent was removed, and the crude residue was purified by silica gel column chromatography (diethyl ether:pentanes) to give the desired product.

Acknowledgements

Changming Qin is acknowledged for preliminary data on the synthesis of **8** from the methyl ester **7** and the observation that the hydrolysis of the methyl ester in **7** results in racemization of the product. This work was supported by the National Science Foundation under the CCI Center for Selective C−H Functionalization, CHE-1205646, the National Institutes of Health (GM099142) and unrestricted support from Novartis.

Supplementary data

Supplementary data (Detailed experimental for the compounds, HPLC traces for all chiral compounds, ^{1}H NMR and ^{13}C NMR spectra for all new compounds are described in Supplementary data. Supplementary data associated with this article can be found in the online version.) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.045.

References and notes

1. Chen, D. Y. K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.
2. Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051.
3. Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
4. Vendeville, S.; Cummings, M. D. In *Annu. Rep. Med. Chem.*; Desai, M. C., Ed.; 2013; Vol. 48, p 371.
5. Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
6. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons, 1998.
7. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
8. Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979.
9. Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919.
10. Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.
11. Zhu, S.; Cui, X.; Zhang, X. P. *Eur. J. Inorg. Chem.* **2012**, *2012*, 430.
12. Davies, H. M. L.; Antoulinakis, E. G. *Organic React*; John Wiley & Sons,, 2004.
13. Ovalles, S. R.; Hansen, J. H.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 4284.
14. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
15. Davies, H. M. L.; Rusiniak, L. *Tetrahedron Lett.* **1998**, *39*, 8811.
16. Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287.
17. Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.
18. Wang, H.; Guptill, D. M.; Varela-Alvarez, A.; Musaev, D. G.; Davies, H. M. L. *Chem. Sci.* **2013**, *4*, 2844.
19. Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555.
20. Chepiga, K. M.; Qin, C.; Alford, J. S.; Chennamadhavuni, S.; Gregg, T. M.; Olson, J. P.; Davies, H. M. L. *Tetrahedron* **2013**, *69*, 5765.
21. Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902.
22. Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198.

23. Qin, C.; Davies, H. M. L. *Org. Lett.* **2013**, *15*, 310.
24. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 14516.
25. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792.
26. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 17718.
27. Guptill, D. M.; Cohen, C. M.; Davies, H. M. L. *Org. Lett.* **2013**, *15*, 6120.
28. Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403.
29. Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
30. Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.
31. Fu, L.; Wang, H.; Davies, H. M. L. *Org. Lett.* **2014**, *16*, 3036.
32. Doyle, M. P.; May, E. J. *Synlett* **2001**, 967.
33. Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112.

Please cite this article in press as: Negretti, S.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.045