Asymmetric Catalysis

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Highly Enantioselective Cyclopropenation Reaction of 1-Alkynes with α-Alkyl-α-Diazoesters Catalyzed by Dirhodium(II) Carboxylates**

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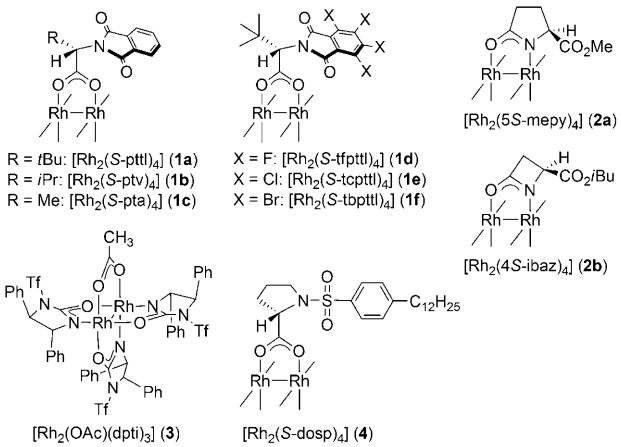
As a result of enormous ring strain, cyclopropene compounds display a range of diverse reactivities in both noncatalytic and transition-metal-catalyzed transformations, thus presenting unique opportunities for organic synthesis.[1,2] To further enhance the synthetic potential of cyclopropenes, the development of expeditious methods for the synthesis of enantioenriched cyclopropenes is highly desirable.[3] In this context, a cyclopropenation reaction of alkynes with diazo compounds that is catalyzed by chiral dirhodium(II) complexes represents one of the most powerful means for the construction of this class of optically active building blocks. Doyle, Müller, and co-workers were the first to demonstrate asymmetric induction (up to ≥98% *ee*) in cyclopropenation reactions of terminal alkynes including propargyl alcohol or propargylamine derivatives with diazoacetates using $[Rh_2(5S\text{-mepy})_4]$ (**2a**; Scheme 1) as a chiral catalyst.[4] Doyle et al. also reported an enantioselective intramolecular cyclopropenation of diazoacetates, in which $[Rh_2(4S\text{-ibaz})_4]$ (**2b**) provided macrocyclic cyclopropenes in up to ≥99% *ee*.[5] Corey and coworkers demonstrated that a new mixed carboxylate/carboxamidate catalyst $[Rh_2(OAc)(dpti)_3]$ (**3**) is highly exceptional for cyclopropenation of a broad range of terminal alkynes with ethyl diazoacetate.[6] The extension of this methodology to include α-substituted α-diazoacetates is particularly attractive because it has the capability to form cyclopropenes with a quaternary stereogenic carbon center.[7–9] Although high levels of enantioselectivity (up to 99% *ee*) in cyclopropenations of terminal alkynes with aryldiazoacetates[7a] or arylvinyldiazoacetates[7b] under catalysis by $[Rh_2(S\text{-dosp})_4]$ (**4**) have been reported by Davies and co-workers, the goal for the reaction with α-alkyl-α-diazoesters remains elusive because of the propensity to form α,β-unsaturated esters through a 1,2-hydride shift.[10] Panne and Fox recently disclosed that dirhodium(II) tetrapivalate exhibits high selectivity for cyclopropenation over alkene formation in the reaction of terminal alkynes with α-alkyl-α-diazoesters.[11,12] However, to the best of our knowledge, an enantioselective version of this reaction has not been reported.



Scheme 1. Chiral dirhodium(II) complexes. pttl = *N*-phthaloyl-*tert*-leucinate, ptv = *N*-phthaloylvalinate, pta = *N*-phthaloylalaninate, tfpttl = *N*-tetrafluorophthaloyl-*tert*-leucinate, tcpttl = *N*-tetrachlorophthaloyl-*tert*-leucinate, tbpttl = *N*-tetrabromophthaloyl-*tert*-leucinate, mepy = 5-methoxycarbonyl-2-oxopyrrolidinonate, ibaz = 4-isobutyloxycarbonyl-2-oxoazetidinonate, dpti = (4*R*,5*R*)-4,5-diphenyl-2-oxo-3-triflylimidazolidinonate, dosp = *N*-[(4-dodecylphenyl)sulfonyl]prolinate.

Our research group has previously demonstrated the first examples of highly enantio-, diastereo-, and chemoselective intramolecular C–H insertion reactions of α-alkyl-α-diazoesters by using dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] ($[Rh_2(S\text{-pttl})_4]$, **1a**) in which high levels of asymmetric induction (up to 95% *ee*) were achieved.[13–15] Herein, we report that $[Rh_2(S\text{-tbpttl})_4]$ (**1f**), a new dirhodium(II) carboxylate complex that incorporates *N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate as chiral bridging ligands, catalyzes the cyclopropenation reaction of terminal alkynes with 2,4-dimethyl-3-pentyl α-alkyl-α-diazoacetates to give 1,2-disubstituted 2-cyclopropenecarboxylates in good to high yields and with up to 99% *ee*.

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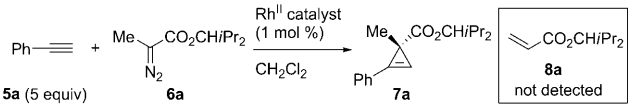
At the outset, we explored the reaction of phenylacetylene (**5a**) with 2,4-dimethyl-3-pentyl α-diazopropionate (**6a**) in dichloromethane at room temperature using dirhodium(II) carboxylate catalysts **1a–c** (1 mol%) that incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands (Table 1,

Table 1: Enantioselective cyclopropenation of phenylacetylene (**5a**) with 2,4-dimethtyl-3-pentyl α-diazopropionate (**6a**) catalyzed by chiral Rh^{II} carboxylates.[a]



5a (5 equiv) **6a** **7a**

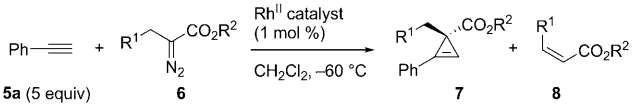
Entry	Rh^{II}	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$[Rh_2(S\text{-pttl})_4]$ (**1a**)	23	0.2	86	46
2	$[Rh_2(S\text{-ptv})_4]$ (**1b**)	23	0.2	78	36
3	$[Rh_2(S\text{-pta})_4]$ (**1c**)	23	0.2	91	38
4	$[Rh_2(S\text{-tfpttl})_4]$ (**1d**)	23	0.2	80	35
5	$[Rh_2(S\text{-tcpttl})_4]$ (**1e**)	23	0.2	89	72
6	$[Rh_2(S\text{-tbpttl})_4]$ (**1f**)	23	0.2	94	85
7	$[Rh_2(S\text{-tbpttl})_4]$ (**1f**)	−40	4	89	94
8	$[Rh_2(S\text{-tbpttl})_4]$ (**1f**)	−60	5	90	95

[a] All reactions were carried out as follows: Rh^{II} catalyst (1 mol%) was added to a solution of **5a** (1.0 mmol, 5 equiv) and **6a** (0.20 mmol) in CH_2Cl_2 (0.1 M). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase using a Daicel Chiralpak IC column.

entries 1–3). Although all of these catalysts provided the corresponding cyclopropene product **7a** in good to high yields with no signs of alkene product **8a**,[16] the highest level of enantioselectivity was only 46% *ee* when $[Rh_2(S\text{-pttl})_4]$ (**1a**) was used (Table 1, entry 1). Notably, syringe-pump techniques for slow addition of the diazo compound **6a** were not necessary to prevent the formation of dimeric products such as carbenes dimers[17] and azines.[12b,c] Focusing on $[Rh_2(S\text{-pttl})_4]$-type catalysts, we then evaluated the performance of $[Rh_2(S\text{-tfpttl})_4]$ (**1d**)[18] and $[Rh_2(S\text{-tcpttl})_4]$ (**1e**),[19,20] which are fluorinated and chlorinated analogues of **1a** and therefore could bring about an electron deficiency on the rhodium(II) center. Although **1d** gave poor enantioselectivity (35% *ee*; Table 1, entry 4), catalysis with **1e** provided cyclopropene derivative **7a** in 89% yield with 72% *ee* (Table 1, entry 5). At this stage, we envisaged that switching to larger halogen atoms could lead to further enhancement of the enantioselectivity. Thus, $[Rh_2(S\text{-tbpttl})_4]$ (**1f**) was prepared from $[Rh_2(OAc)_4]$ by a ligand exchange reaction[21,22] with *N*-tetrabromophthaloyl-(*S*)-*tert*-leucine.[23] Pleasingly, the cyclopropenation under catalysis with **1f** produced **7a** in 94% yield with 85% *ee* (Table 1, entry 6). A survey of solvents with **1f** revealed that dichloromethane was the optimal solvent for this transformation.[24,25] Enantioselectivity was further enhanced up to 95% *ee* using **1f** without compromising product yield when the reaction was conducted at −60 °C (Table 1, entry 8). The preferred absolute configuration of **7a** [$[\alpha]_D^{21} = -125$ ($c = 1.09$, EtOH) for 95% *ee*] was established as *R* by its conversion to the known (1*S*,5*R*)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one [$[\alpha]_D^{24} = -49.6$ ($c = 1.02$, EtOH); Ref. [26], $[\alpha]_D^{26} = -53.3$ ($c = 1.0$, EtOH) for the (1*S*,5*R*)-enantiomer] (see the Supporting Information).

We next turned our attention to the cyclopropenation reaction of **5a** with α-diazobutanoates bearing more reactive C–H bonds at the β position than the methyl C–H bonds of α-diazopropionate (Table 2). The reaction with 2,4-dimethyl-3-pentyl α-diazobutanoate (**6b**) using $[Rh_2(S\text{-tbpttl})_4]$ (**1f**)

Table 2: Enantioselective cyclopropenation of phenylacetylene (**5a**) with α-alkyl-α-diazoesters **6** catalyzed by chiral Rh^{II} carboxylates.



5a (5 equiv) **6** **7** **8**

Entry	**6**	R^1	R^2	Rh^{II}	*t* [h]	**7**/**8**[a]	**7**	Yield [%][b]	*ee* [%][c]
1	**6b**	Me	iPr_2CH	**1f**	11	87:13	**7b**	78	95
2	**6b**	Me	iPr_2CH	**1a**	7	54:46	**7b**	48	53
3	**6b**	Me	iPr_2CH	**1d**	0.3	29:71	**7b**	26	42
4	**6b**	Me	iPr_2CH	**1e**	7	77:23	**7b**	58	85
5	**6c**	Me	*t*Bu	**1f**	6	48:52	**7c**	40	96
6	**6d**	Me	*i*Pr	**1f**	3	31:69	**7d**	25	50
7	**6e**	Me	Et	**1f**	0.5	27:73	**7e**	22	51
8	**6f**	Et	iPr_2CH	**1f**	12	>99:1	**7f**	93	99
9	**6g**	*n*Pr	iPr_2CH	**1f**	22	92:8	**7g**[d]	84	99
10	**6h**	*i*Bu	iPr_2CH	**1f**	22	84:16	**7h**	71	98
11	**6i**	$n\text{-}C_7H_{15}$	iPr_2CH	**1f**	4	94:6	**7i**	85	99
12	**6j**	$Ph(CH_2)_3$	iPr_2CH	**1f**	24	94:6	**7j**	88	98

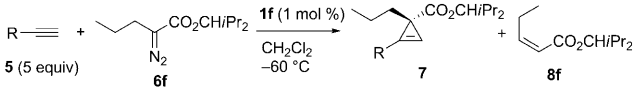
[a] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase using a Daicel Chiralpak IC column. [d] The preferred absolute configuration of **7g** [$[\alpha]_D^{21} = -78.0$ ($c = 1.08$, EtOH) for 99% *ee*] was established as *R* by its conversion to the known (1*R*,2*S*)-ethyl 1-butyl-2-phenylcyclopropane-1-carboxylate [$[\alpha]_D^{23} = -81.8$ ($c = 1.18$, $CHCl_3$); Ref. [14], $[\alpha]_D^{29} = +67$ ($c = 0.93$, $CHCl_3$) for the 1*S*,2*R* enantiomer] (see the Supporting Information).

provided cyclopropene product **7b** in 78% yield with 95% *ee*, along with (*Z*)-alkene **8b** (**7b**/**8b** = 87:13; Table 2, entry 1). In stark contrast, catalysis with $[Rh_2(S\text{-pttl})_4]$ (**1a**), $[Rh_2(S\text{-tfpttl})_4]$ (**1d**), or $[Rh_2(S\text{-tcpttl})_4]$ (**1e**) was accompanied with a significant decrease in enantioselectivity as well as the formation of substantial amounts of (*Z*)-alkene **8b** (Table 2, entries 2–4). The effect of the ester moiety was examined using **1f** as the catalyst. Although the use of *tert*-butyl ester **6c** gave a similar high enantioselectivity (96% *ee*; Table 2, entry 5), reactions with ethyl and isopropyl esters **6d** and **6e** resulted in only modest enantioselection (50–51% *ee*; Table 2, entries 6 and 7). In these reactions, poor product yields (22–40%) were obtained owing to the formation of a large amount of (*Z*)-alkenes **8c–e** (Table 2, entries 5–7). These findings clearly demonstrate that the combined use of $[Rh_2(S\text{-tbpttl})_4]$ (**1f**) and 2,4-dimethyl-3-pentyl ester moiety[27] is crucial for high levels of both enantio- and chemoselectivities. By using this optimal combination, we explored the reaction with a range of α-alkyl-α-diazoesters. Switching the R^1 substituent from a methyl group to ethyl, propyl, or isobutyl groups gave cyclopropenes **7f–h** with good to high chemoselectivities (**7**/**8** from 84:16 to >99:1) and exceptionally high enantioselectivities (98–99% *ee*; Table 2, entries 8–10). Although α-alkyl-α-diazoesters **6i** and **6j** are

potential substrates for intramolecular C–H insertion reactions, cyclopropenation with **5a** proceeded uneventfully and afforded cyclopropenes **7i** and **7j** with excellent enantioselectivities (98–99% *ee*; Table 2, entries 11 and 12).

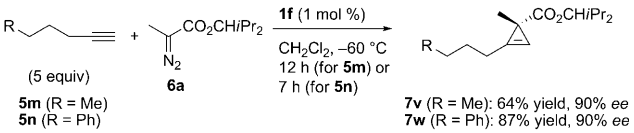
Using 2,4-dimethyl-3-pentyl α-diazopentanoate (**6f**) as a substrate, we then investigated the scope of the reaction with respect to the alkyne component (Table 3). In the case of phenylacetylene derivatives, good to high yields (61–92%) and chemoselectivities (**7**/**8** from 83:17 to >99:1) and excellent enantioselectivities (96–99% *ee*) were consistently observed with either electron-donating or electron-withdrawing groups present at the *para*-, *meta*-, or *ortho*-position on the benzene ring (Table 3, entries 1–8). A slight drop in chemoselectivity (**7**/**8** ratio) was observed by the introduction of electron-withdrawing groups on the benzene ring, probably owing to the decreased reactivity of the alkynes. Aside from phenylacetylene derivatives, good yields and high to excellent enantioselectivities were obtained with 2- or 1-naphthylacetylenes (**5j** and **5k**) and ethynylcyclohexene (**5l**; 65–75% yields, 96–99% *ee*; Table 3, entries 9–11). In addition, it was found that cyclopropenation of 1-hexyne (**5m**) and 5-phenyl-1-pentyne (**5n**) with α-diazopropionate **6a** afforded the corresponding cyclopropene products **7v** and **7w** with 90% *ee* (Scheme 2).

Table 3: Enantioselective cyclopropenation of 1-alkynes **5** with **6f** catalyzed by **1f**.

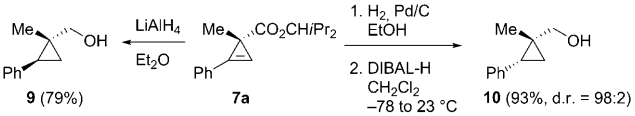


Entry	5	R	t [h]	7/8[a]	7	Yield [%][b]	ee [%][c]
1	**5b**	4-MeOC$_6$H$_4$	11	>99:1	**7k**	92	98
2	**5c**	4-MeC$_6$H$_4$	11	98:2	**7l**	90	99
3	**5d**	4-BrC$_6$H$_4$	12	94:6	**7m**	89	98
4	**5e**	4-CF$_3$C$_6$H$_4$	18	88:12	**7n**	78	96
5	**5f**	3-MeC$_6$H$_4$	12	96:4	**7o**	90	99
6	**5g**	3-ClC$_6$H$_4$	12	90:10	**7p**	75	99
7	**5h**	2-MeC$_6$H$_4$	12	96:4	**7q**	89	99
8	**5i**	2-ClC$_6$H$_4$	20	83:17	**7r**	61	98
9	**5j**	2-naphthyl	12	88:12	**7s**	70	99
10	**5k**	1-naphthyl	38	88:12	**7t**	65	99
11	**5l**	1-cyclohexenyl	12	95:5	**7u**	75	96

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase using a Daicel Chiralpak IC column.



Scheme 2. Enantioselective cyclopropenation of 1-alkynes **5m** and **5n** with **6a** catalyzed by **1f**.



Scheme 3. Transformation of **7a** into **9** or **10**.

The 1,2-disubstituted 2-cyclopropenecarboxylate derivatives **7** are useful for the synthesis of optically active cyclopropane building blocks (Scheme 3).[6a] Treatment of **7a** with $LiAlH_4$ produced *trans*-cyclopropane derivative **9**[28] as the sole product in 79% yield through a sequential reduction of the ester moiety and hydroalumination of the double bond. Alternatively, catalytic hydrogenation of **7a** proceeded from the opposite face to the 2,4-dimethyl-3-pentyl ester moiety and subsequent reduction with DIBAL-H gave *cis*-cyclopropane product **10** in 93% yield with virtually complete diastereoselectivity.

The mechanism of cyclopropenation when dirhodium(II) tetraformate was used as a model catalyst has been studied with density functional theory (DFT) calculations.[7b,11a,14,29] Recently, Davies and co-workers disclosed that the most favored transition state for the cyclopropenation of propyne with methyl styryldiazoacetate involves a tilted end-on approach that also displays a favorable hydrogen-bonding interaction with a carboxylate ligand on the catalyst.[7b] Because the enantioselectivity in the present cyclopropenation reaction was found to be substantially influenced by the ester moiety of α-alkyl-α-diazoesters, DFT calculations at the B3LYP/6-311 + G** (Rh: SDD) level were performed on the reaction between methyl α-diazopropionate and phenylacetylene (**5**) to understand the origin of the selectivity (see the Supporting Information for details). Two viable transition structures, **TSa** and **TSb**, are shown in Figure 1. In both transition structures, the carbonyl carbon atom of the ester group prefers an eclipsed arrangement (the O-Rh-C-CO_2Me dihedral angles: 11–15° in **TSa** and **TSb** and 0° in a model carbene complex), and the ester carbonyl group is almost perpendicular to the Rh–C axis. As shown by Davies,[7b] the terminal alkyne hydrogen atom interacts with an oxygen atom of the formate ligand (the H···O distances: 2.02 Å and 2.01 Å, respectively), and the alkyne is tilted 28–33° from the Rh–C axis to the methyl side. The alkyne approaches the rhodium–carbene species from the ester methoxy side in **TSa** and from the ester carbonyl side in **TSb**. Transition structure **TSb** is 0.88 kcal mol^{-1} higher in energy than **TSa**. This energy difference might be accounted for by the electronic repulsion between the carbonyl group and the alkyne π-electrons.

We next turned our attention to elucidating the chiral environment of [Rh_2(*S*-tbpttl)$_4$] (**1f**). X-ray crystal structural analysis revealed that **1f** adopts a C_4-symmetry-like chiral crown conformation as reported independently by Fox[14] and Charette[20] with [Rh_2(*S*-pttl)$_4$] (**1a**) and other phthalimido-derived catalysts (Figure 2a).[30–32] In this conformation, the four tetrabromophthalimido groups with favorable halogen-bonding interactions[33,34] are protruded in a clockwise twisted arrangement on one face, and the four *tert*-butyl groups are oriented to block the reactivity on the opposite face. Provided that the chiral crown structure of **1f** is available in solution, the stereochemical course of the present cyclopropenation reaction can be rationalized on the basis of the preferred transition structure **TSa**. Two models (**A** and **B**) are presented

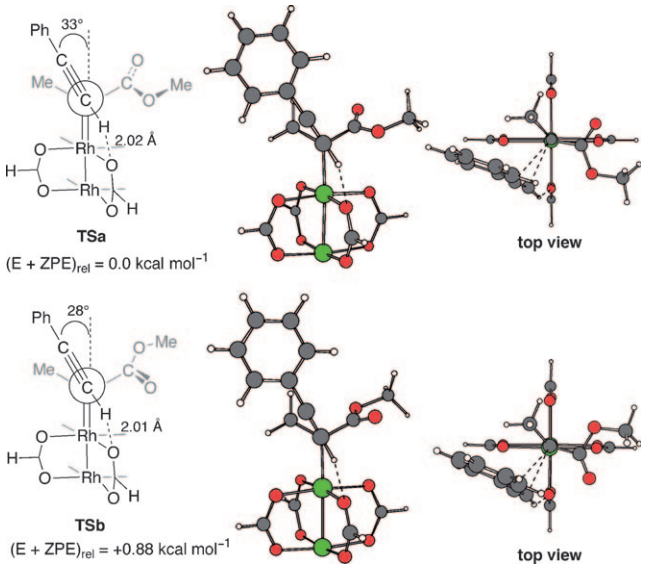


Figure 1. Transition structures **TSa** and **TSb** for cyclopropenation reaction. Green Rh; red O; gray C; white H.

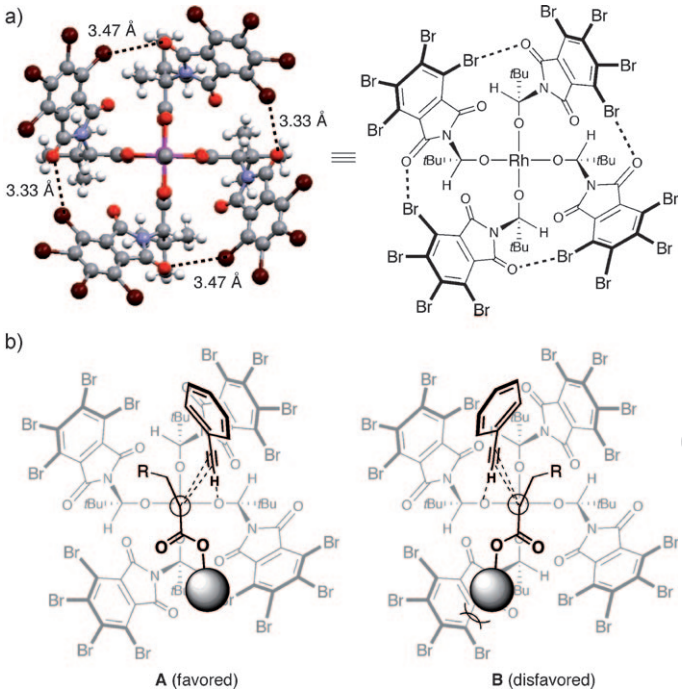


Figure 2. a) Ball-and-stick drawing of **1 f**. Sum of the van der Waals radii of the Br and O atoms is 3.37 Å. Blue N; red O; dark red Br; gray C; white H. b) Plausible stereochemical pathway for enantioselective cyclopropenation using **1 f**.

in Figure 2b. When sterically demanding esters such as 2,4-dimethyl-3-pentyl and *tert*-butyl esters are used, the rhodium–carbene intermediate in model **A** is strongly favored over that in model **B** because of the severe steric repulsion between the ester group and the tetrabromophthalimido group in **B**. The tilted end-on approach of the alkyne from the ester alkoxy side (*Re* face) of the rhodium–carbene in model **A** is consistent with the observed sense of asymmetric induction. The model can also explain a significant decrease in enantioselectivity with sterically less-demanding esters. However, at this stage no explanation for the strong preference for cyclopropenation over alkene formation through a 1,2-hydride shift that was only observed when using the 2,4-dimethyl-3-pentyl ester moiety can be offered.

In conclusion, $[Rh_2(S\text{-tbpttl})_4]$ (**1 f**) has emerged as a catalyst of choice for enantioselective cyclopropenation reactions of 1-alkynes with 2,4-dimethyl-3-pentyl α-alkyl-α-diazoacetates, in which exceptionally high levels of asymmetric induction (up to 99% *ee*) as well as good to high chemoselectivities have been achieved. This reaction occurs in preference to alkene formation through a 1,2-hydride shift. The observed sense of asymmetric induction is rationalized by the proposed model based on a C_4-symmetry-like chiral crown conformation of **1 f** and DFT calculations for a model reaction system. The present catalytic protocol provides attractive and easy access to optically active cyclopropene building blocks containing an all-carbon quaternary stereogenic center.

Experimental Section

Typical procedure (Table 2, entry 8): $[Rh_2(S\text{-tbpttl})_4]\cdot 2H_2O$ (**1 f**) was added in one portion to a solution of **6 f** (45.3 mg, 0.20 mmol) and **5 a** (102 mg, 1.0 mmol, 5 equiv) in CH_2Cl_2 (2 mL) at −60 °C. After stirring for 12 h at this temperature, the mixture was concentrated in vacuo. The ratio of **7 f**/**8 f** was determined to be >99:1 by ^{1}H NMR analysis of the crude product. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 20:1) to provide **7 f** (55.7 mg, 93%) as a colorless oil. The enantiomeric excess of **7 f** was determined to be 99% by HPLC on a chiral stationary phase using a Daicel Chiralpak IC column (eluent: *n*-hexane/2-propanol 100:1; flow: 1.0 mL min^{-1}).

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