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Stereoselective Rh_2(*S*-IBAZ)$_4$-Catalyzed Cyclopropanation of Alkenes, Alkynes, and Allenes: Asymmetric Synthesis of Diacceptor Cyclopropylphosphonates and Alkylidenecyclopropanes

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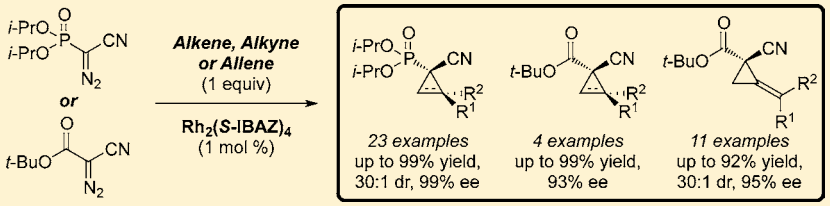
Supporting Information



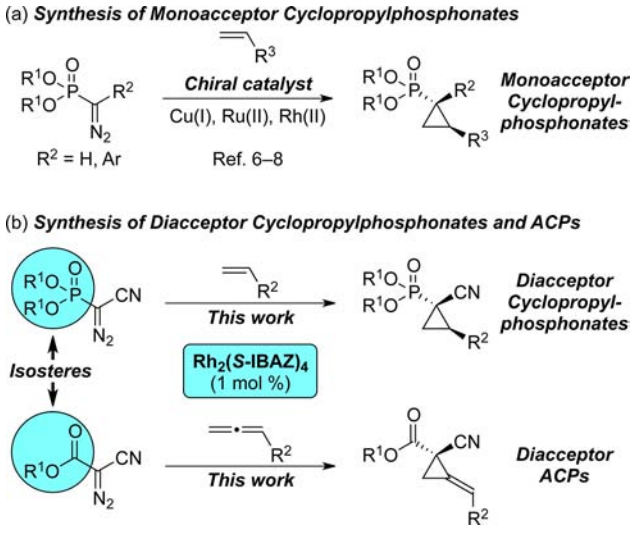
ABSTRACT: A mild and highly stereoselective rhodium(II)-catalyzed cyclopropanation of alkenes, alkynes, and allenes with diacceptor diazo compounds is reported. Using the phosphonate moiety as an efficient trans-directing group, the first catalytic asymmetric route to diacceptor cycloprop(en)ylphosphonates was developed by employing an α-cyano diazophosphonate and Rh_2(*S*-IBAZ)$_4$ as chiral catalyst. The isosteric character of phosphonic and carboxylic acid derivatives allowed the alternative use of an α-cyano diazo ester in the process, leading to α-cyano cycloprop(en)ylcarboxylates in high yields and stereoselectivities. Taking advantage of the particular reactivity of the cyanocarbene intermediates involved in this system, the scope of compatible substrates could be extended to substituted allenes, leading to the development of the first catalytic enantioselective method for the synthesis of diacceptor alkylidenecyclopropanes.

INTRODUCTION

The cyclopropylphosphonate unit is found in numerous natural or synthetic compounds of pharmaceutical interest.[1] Because of their increased resistance to enzymatic hydrolysis, phosphonates and other phosphonic acid derivatives are often employed in medicinal chemistry as isosteres of carboxylates[2] and phosphates.[3] The ubiquity of the cyclopropylcarboxylate unit in biologically relevant compounds has thus motivated several research groups to study cyclopropylphosphonates as active analogues, affording improved pharmaceutical properties in certain cases.[4]

In analogy to cyclopropylcarboxylates,[5] the most efficient catalytic asymmetric methods for their formation involves the reaction of a monoacceptor diazophosphonate species with an alkene using chiral copper(I),[6] ruthenium(II),[6,7] or rhodium(II)[8] catalysts (Scheme 1a).[9] However, the enantioselective synthesis of the corresponding *diacceptor* cyclopropylphosphonates using such a strategy remains unexplored.[10,11] Because of the high potential of diacceptor cyclopropanes in asymmetric synthesis, either as precursors of ACC derivatives,[12] or as substrates in stereospecific substitution[12d,13] and formal cycloaddition reactions,[14] we envisioned that access to their phosphonate-substituted analogues in enantioenriched form would be of considerable value. Herein, we describe the first catalytic asymmetric synthesis of diacceptor cycloprop(en)-ylphosphonate derivatives, using an α-cyano diazophosphonate reagent and Rh_2(*S*-IBAZ)$_4$ as chiral catalyst, under mild reaction conditions (Scheme 1b). The isosteric character of carboxylates and phosphonates permitted the extension of the

Scheme 1. Enantioselective Synthesis of Cyclopropylphosphonates and ACPs via the Metal-Catalyzed Decomposition of Diazo Compounds



Received: October 9, 2012
Published: January 4, 2013

   dx.doi.org/10.1021/ja3099728 | *J. Am. Chem. Soc.* 2013, 135, 1463−1470

scope of enantioenriched products to α-cyano cyclopropylcarboxylates under similar reaction conditions. Importantly, these findings enabled the development of the first catalytic asymmetric cyclopropanation of allenes using diacceptor diazo compounds, leading to a variety of highly enantioenriched alkylidenecyclopropanes (ACPs). Considering the importance of diacceptor cyclopropanes and ACPs as synthetic intermediates in a vast array of transformations, these methods are of broad applicability for the stereoselective synthesis of complex molecules.

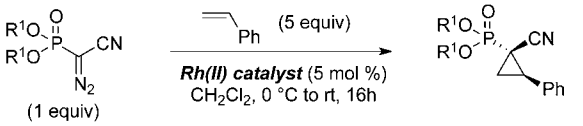
RESULTS AND DISCUSSION

Stereoselective Cyclopropanation of Diacceptor Diazophosphonates. Recently, our group has been interested in the use of diacceptor diazo compounds in stereoselective metal-catalyzed cyclopropanation reactions.[12,15] In such processes, both electron-withdrawing substituents of the substrate compete for their trans-directing abilities, which depend upon steric and electronic factors.[12d,15a] Thus, to obtain a reasonable diastereoselectivity ratio in those reactions, the steric and/or basicity difference of the two groups in play has to be significant. Moreover, the resulting combination of EWGs must lead to an electrophilic, yet sterically accessible, reactive metal–carbene species. Due to the inherent steric congestion of the phosphonate moiety as trans-directing group, the small and strongly electron-withdrawing cyano group was rapidly identified as ideal in such cyclopropanation using diacceptor diazophosphonates.[16] Moreover, the established versatility of diacceptor cyanocyclopropanes ensures considerable synthetic divergence of the resulting enantioenriched α-cyano cyclopropylphosphonates.[12d,16b,17]

To maximize the yield and diastereoselectivity of the reaction, the nature of the phosphonate and the achiral catalyst used was first investigated in the reaction with styrene (Table 1, entries 1–9, and Figure 1). Although substrates **2** and **3** afforded similar results in the reaction with $Rh_2(OAc)_4$ as catalyst, the increased accessibility of **3** in addition to the usefulness of dialkylphosphonates such as **6** convinced us to continue our investigation with this substrate.[17,18] While all achiral Rh(II)-tetracarboxylate catalysts evaluated provided complete consumption of the starting diazo compound, $Rh_2(tfa)_4$ and $Rh_2(tpa)_4$ afforded only poor yields of **6** due to undesired side reactions affording a complex mixture of products (entries 4 and 5). The use of $Rh_2(Adc)_4$[19] proved to be optimal in those conditions with 84% yield and 89:11 dr, and adding a slight excess of the diazo compound **3** with styrene as limiting reagent was found to be crucial, resulting in a 99% isolated yield of **6** when 1,2-DCE was used as solvent (entries 8 and 9).

With these conditions in hand, various chiral catalysts were evaluated in view of an enantioselective version of the reaction (Table 1, entries 10–16). While the more traditional chiral Rh(II)-tetracarboxylate catalysts afforded only poor stereocontrol (entries 10–12), the use of carboxamidate ligands, more particularly azetidinates first developed by Doyle,[20] permitted isolation of **6** in excellent enantioselectivity, although with a lower yield (entries 13–15). Using styrene as limiting reagent in a degassed solvent permitted to drastically improve the yield of the reaction, affording optimal stereocontrol in PhH at room temperature (entry 16). Under these conditions, cyclopropane **6** was reproducibly obtained in 99% isolated yield, 97:3 dr and 99% ee, using only 1 mol % of $Rh_2(S\text{-IBAZ})_4$ as catalyst. It is noteworthy that unlike most metal-catalyzed

Table 1. Optimization of the Nature of the Catalyst and the Diazophosphonate Substrate



entry	R^1	Rh(II) catalyst	yield (%)	dr (t:c)[a]	ee (%)[b]
1	Et (**4**)	$Rh_2(OAc)_4$	58[a]	83:17	–
2	Ph (**5**)	$Rh_2(OAc)_4$	65[a]	87:13	–
3	*i*-Pr (**6**)	$Rh_2(OAc)_4$	72[a]	90:10	–
4	*i*-Pr (**6**)	$Rh_2(tpa)_4$	24[a]	75:25	–
5	*i*-Pr (**6**)	$Rh_2(tfa)_4$	44[a]	73:27	–
6	*i*-Pr (**6**)	$Rh_2(esp)_2$	81[a]	88:12	–
7	*i*-Pr (**6**)	$Rh_2(OPiv)_4$	84[a]	87:13	–
8	*i*-Pr (**6**)	$Rh_2(Adc)_4$	84[a]	89:11	–
9[c–e]	*i*-Pr (**6**)	$Rh_2(Adc)_4$	99[f]	89:11	–
10[e]	*i*-Pr (**6**)	$Rh_2(S\text{-NTTL})_4$	73[f]	84:16	<5
11[e]	*i*-Pr (**6**)	$Rh_2(S\text{-PTTL})_4$	79[f]	76:24	33
12[e]	*i*-Pr (**6**)	$Rh_2(S\text{-TCPTTL})_4$	76[f]	78:22	<5
13	*i*-Pr (**6**)	$Rh_2(S\text{-MEAZ})_4$	47[f]	92:8	82
14	*i*-Pr (**6**)	$Rh_2(S\text{-BNAZ})_4$	36[f]	94:6	86
15	*i*-Pr (**6**)	$Rh_2(S\text{-IBAZ})_4$	52[f]	93:7	90
16[d,e,g]	*i*-Pr (**6**)	$Rh_2(S\text{-IBAZ})_4$	99[f]	97:3	99

[a]Determined by ^{1}H NMR analysis of the crude mixture. [b]Determined by SFC analysis on chiral stationary phase (ee of trans product). [c]Using 1,2-DCE as solvent. [d]Using 1.5 equiv of **3** and 1 equiv of styrene. [e]1 mol % catalyst used. [f]Isolated yield of combined diastereomers. [g]Using degassed PhH as solvent at room temperature.

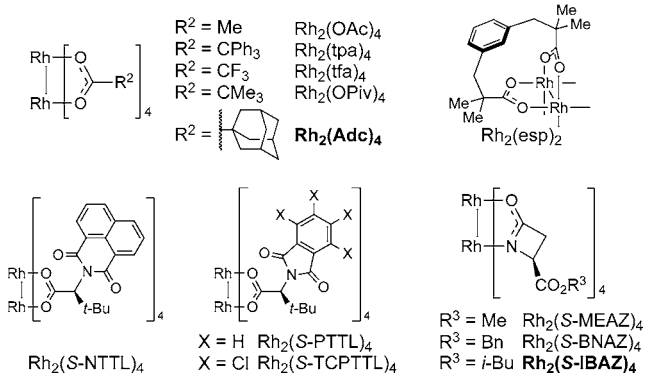


Figure 1. Structure of Rh(II) catalysts investigated.

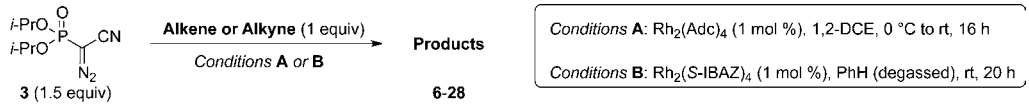
cyclopropanation reactions using diazo compounds,[5] both our protocols do not require syringe-pump techniques or a large excess of one of the reagents. Indeed, α-cyano diazophosphonate **3** (1.5 equiv) is added within 5–10 min via syringe to the mixture containing the alkene (1 equiv) and the catalyst (1 mol %) in solution.

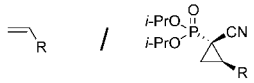
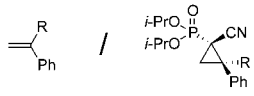
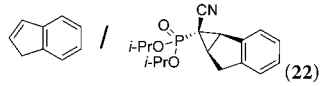
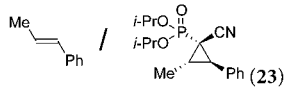
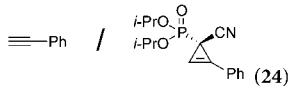
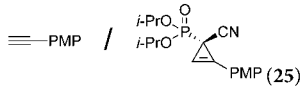
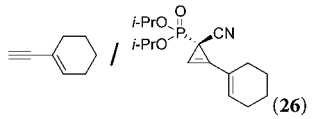
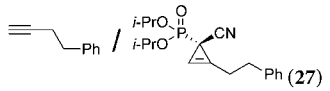
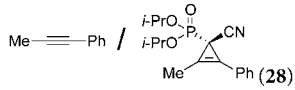
Using the optimized conditions, a wide variety of terminal alkenes were evaluated as substrates in our reaction, leading to an unexpected generality for this type of process (Table 2, entries 1–14).

Indeed, both electron-rich and -poor styrene derivatives, substituted either at the ortho, meta, or para positions, all provided excellent yields and stereoselectivities for the synthesis of the corresponding racemic (conditions A) and enantioenriched (conditions B) diacceptor cyclopropylphosphonates (entries 1–8). Moreover, heterocyclic derivative *N*-tosyl-3-vinylindole was found to be compatible in the process, in

dx.doi.org/10.1021/ja3099728 | J. Am. Chem. Soc. 2013, 135, 1463–1470

Table 2. Scope of the Stereoselective Cyclopropanation Using α-Cyano Diazophosphonate 3



entry	alkene or alkyne / product	yield A (%)[a]	dr A (*t*:*c*)[b]	yield B (%)[a]	dr B (*t*:*c*)[b]	ee B (%)[c]
						
1	R= Ph (**6**)	99	89:11	99	97:3	99
2	R= 4-F_3C-C_6H_4 (**7**)	97	95:5	96	95:5	99
3	R= 4-Cl-C_6H_4 (**8**)	99	90:10	96	97:3	99
4	R= 4-Me-C_6H_4 (**9**)	98	83:17	97	97:3	98
5	R= 4-AcO-C_6H_4 (**10**)	92	87:13	90	97:3	98
6	R = 3-MeO-C_6H_4 (**11**)	98	87:13	94	97:3	98
7	R = 3-O_2N-C_6H_4 (**12**)	99	94:6	96	97:3	98
8	R = 2-Br-C_6H_4 (**13**)	98	97:3	98	96:4	99
9	R = 3-*N*-Ts-indolyl (**14**)	96	65:35	93	95:5	92
10	R = CH=C(Ph)$_2$ (**15**)	96	69:31	87	91:9	96
11	R = CH_2CH_2Ph (**16**)	97	95:5	79	>98:2	99
12	R = CO_2Me (**17**)	81[d]	88:12[d]	17	>95:5	n.d.
13	R = OBz (**18**)	99	95:5	97[d]	97:3[d]	99[d]
14	R = *N*-phthaloyl (**19**)	97	78:22	89[d]	83:17[d]	93[d]
						
15	R = Me (**20**)	98	62:38	96	40:60	95
16	R = Ph (**21**)	99	-	25[d]	-	88[d]
17	 (**22**)	93	97:3	65	57:43	91
18	 (**23**)	82[d]	>95:5[d]	4	>90:10	n.d.
19	 (**24**)	92	-	85	-	98
20	 (**25**)	91	-	86[d]	-	91[d]
21	 (**26**)	73	-	73	-	95
22	 (**27**)	90	-	95	-	93
23	 (**28**)	32[d]	-	<5	-	n.d.

[a]Isolated yield of combined diastereomers. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by SFC analysis on chiral stationary phase (ee of trans product). [d]Using 3 equiv of substrate **3** and 2 mol % of the catalyst (reaction time: 60 h).

addition to a diene and an aliphatic olefin, in excellent enantioselectivity (entries 9−11). The use of electron-poor methylacrylate afforded a good yield under conditions A, whereas only 17% of product **17** was obtained when Rh_2(*S*-

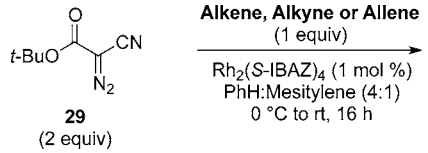
dx.doi.org/10.1021/ja3099728 | J. Am. Chem. Soc. 2013, 135, 1463−1470

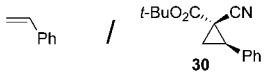
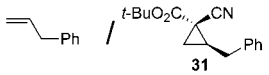
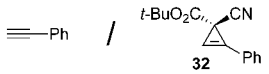
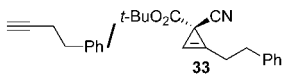
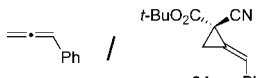
IBAZ)$_4$ was used, presumably due to a lower electrophilicity of the carbene intermediate with such rhodium(II) tetracarboxamidate catalyst (conditions B, entry 12).[5a] The use of Michael acceptors as substrates is unprecedented in Rh(II)-catalyzed cyclopropanation reactions, as only Co(II) carbenoids were previously found to allow electron-poor alkenes to react with the electrophilic metal−carbene intermediate.[16b,21] Additionally, the use of vinylbenzoate and *N*-vinylphthalimide as substrates lead, respectively, to the formation of protected cyclopropanol **18** and cyclopropylamine **19** in high yields and stereoselectivities (entries 13 and 14). 1,1-Disubstituted alkenes were also found to be compatible under our reaction conditions, although only poor diastereoselectivity was observed in the case of α-methylstyrene (Table 2, entries 15 and 16). Nevertheless, it should be noted that almost all mixtures of diastereomers presented in Table 2 were separable by flash chromatography. Conditions A provided high yields and stereoselectivity with both cis and trans 1,2-disubstituted alkenes, while the use of Rh$_2$(*S*-IBAZ)$_4$ under conditions B, a more electron-rich catalyst, led to an important decrease in yield of the corresponding diacceptor 1,1,2,3-tetrasubstituted cyclopropanes **22** and **23** (entries 17 and 18).

Importantly, both conditions developed were successfully applied to various terminal alkynes, leading to the corresponding diacceptor cyclopropenylphosphonates **24**−**27** in good yields and excellent stereoselectivity (Table 2, entries 19−22). Cyclopropenes substituted by either an aromatic or an aliphatic group are obtained with similar efficiency (**24**, **25**, and **27**), and chemoselectivity for an alkyne over an alkene can be achieved when using an enyne possessing an endocyclic double bond (see **26**, entry 21). It is noteworthy that the enantioselective formation of diacceptor cyclopropenes through a metal-catalyzed process is extremely rare in the literature.[22,23] As typically seen in Rh(II) catalysis,[23k−n,24] 1,2-disubstituted alkynes were found to be incompatible in our system because of the inherent paddlewheel structure of these complexes, forbidding the approach of such substrates on the metal−carbene intermediate (entry 23).

Application to the Synthesis of Enantioenriched Diacceptor Cyclopropylcarboxylate Derivatives. Cognizant of the isosteric character of phosphonic and carboxylic acid derivatives,[2,3] we envisioned that α-cyano diazophosphonate **3** could be replaced by an α-cyano diazo ester such as **29** in our system (Table 3). Indeed, the analogous steric profiles of both metal−carbenes should lead to similar enantioinduction mechanisms when using Rh$_2$(*S*-IBAZ)$_4$ as catalyst. In such a situation, the hindered *tert*-butyl ester moiety acts as an efficient trans-directing group, leading to the formation of the corresponding *trans*-α-cyano cyclopropylcarboxylate product in high yield and stereoselectivity, either with an aromatic or an aliphatic olefin (entries 1 and 2). It is noteworthy that the optimal conditions had to be slightly modified with **29**, where mesitylene was added in the solvent mixture to allow a homogeneous reaction at the optimal temperature of 0 °C. Moreover, the high reactivity of our system permitted the extension of the scope of accessible enantioenriched products to cyclopropenes **32** and **33** by reaction with phenylacetylene and phenethylacetylene, respectively (entries 3 and 4). Despite the low propensity of allenes to undergo cyclopropanation reactions, we were delighted to observe the formation of *E*-alkylidenecyclopropane **34** in excellent yield and enantioselectivity (Table 3, entry 5, and Figure 2).[25] While a vast array of catalytic methods exist for the enantioselective synthesis of

Table 3. Rh$_2$(*S*-IBAZ)$_4$-Catalyzed Cyclopropanations with α-Cyano Diazo Ester 29



entry	alkene, alkyne or allene / product	yield (%)[a]	dr (*t*:*c*)[b]	ee (%)[c]
1	 **30**	90[d]	>90:10	86
2	 **31**	82	94:6	>90
3	 **32**	99	-	93
4	 **33**	88	-	83
5	 **34**	92	-	95

[a]Isolated yield of combined diastereomers. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by SFC analysis on chiral stationary phase (ee of trans product). [d]Yield of pure trans diastereomer.

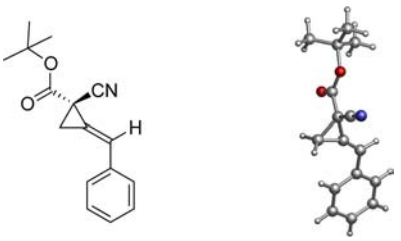


Figure 2. X-ray structure of alkylidenecyclopropane **34**.

cyclopropanes and cyclopropenes from diazo compounds,[5] the corresponding alkylidenecyclopropanation reactions remain underexploited. In fact, this constitutes the first example of a catalytic enantioselective alkylidenecyclopropanation reaction using a diacceptor diazo compound.

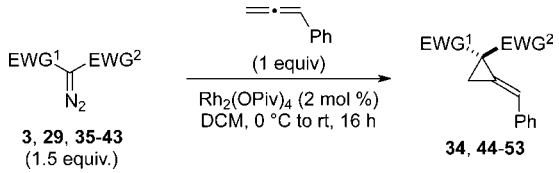
Stereoselective Alkylidenecyclopropanation Reactions. Because of the high potential of alkylidenecyclopropanes (ACPs) as synthetic intermediates,[26] we decided to further investigate on this type of cyclopropanation involving allenes as substrates. ACPs bearing electron-withdrawing groups are known to exhibit an enhanced reactivity in multiple ionic ring-opening processes, due to their increased ability to stabilize a negatively charged open intermediate. Consequently, the versatility of this type of substrate has been explored in various reactions such as cycloisomerizations,[27] ring-opening rearrangements,[28] cycloadditions,[29] and iodolactonizations.[30] Reported syntheses of racemic diacceptor ACPs rely on cyclopropanation of allenes,[31] tandem addition-cyclization onto bromoallenes,[32] intramolecular palladium-catalyzed cyclopropropanative arylation,[29c] and olefin migration.[33] While Gregg reported an elegant

dx.doi.org/10.1021/ja3099728 | *J. Am. Chem. Soc.* 2013, 135, 1463−1470

asymmetric rhodium-mediated cyclopropanation of allenes with aryldiazoacetate,[34] no catalytic enantioselective method has been described for the synthesis of diacceptor ACPs, which has prohibited their use as chiral precursors for stereospecific reactions.

In light of this, we investigated the scope of accessible racemic products using phenylallene as substrate with a variety of diacceptor diazo reagents (Table 4). Presumably due to the

Table 4. Alkylidenecyclopropanation of Phenylallene with Various Diacceptor Diazo Reagents



entry	EWG^1	EWG^2	product	yield (%)[a,b]
1	CO_2t-Bu	CN	**34**	93
2	CO_2Et	CN	**44**	82
3	CO_2Ad	CN	**45**	85
4	C(O)PMP	CN	**46**	42
5	C(O)N(C_4H_8)	CN	**47**	49
6	P(O)(O*i*-Pr)$_2$	CN	**48**	0
7	CO_2Et	NO_2	**49**	0
8	C(O)PMP	NO_2	**50**	0
9	C(O)PMP	CO_2Me	**51**	<5
10	C(O)N(C_4H_8)	CO_2Me	**52**	0
11	CO_2Me	CO_2Me	**53**	0

[a]Isolated yield. [b]Only one diastereoisomer was observed in all cases.

low nucleophilicity of allenes, only the most reactive cyano-substituted carbenes provided useful amounts of the corresponding alkylidenecyclopropane products, with α-cyano diazo ester **29** affording the highest isolated yield (entries 1−5). Indeed, although other diazo compounds substituted by either NO_2 or CO_2Me groups were previously found to be competent carbene precursors with styrene derivatives,[12,15] no desired product was observed with these reagents when phenylallene was used (entries 7−11).

This increased reactivity of cyano-substituted carbenes can be attributed to the inability of the sp-hybridized nitrile moiety to adopt an *out-of-plane* conformation (Figure 3). The *in-plane* conformation is believed to be highly energetic due to a conjugation of the electrophilic metal carbene to an electron-withdrawing group, and the out-of-plane conformation represents the ground state of this reactive species. While NO_2 or C(O)R substituted metal−carbene intermediates are thought to react in such arrangement where the Rh=C bond is not conjugated to the CO or the NO bond (Figure 3a, out-of-plane conformation),[12d,15a,35] α-cyanocarbenes such as the ones formed in our system are forced to stay in-plane, thus leading to a more electrodeficient reactive carbene (Figure 3b). Sterically, the small and in-plane nitrile functionality leads to a less encumbered metal−carbene compared with other electron-withdrawing groups. These properties of diacceptor cyanocarbenes suggest that such intermediates possess a particular electrophilicity, permitting less nucleophilic π systems such as allenes to react. It is noteworthy that such an increase in reactivity for systems forced to stay in-plane was recently reported with the use of cyclic α-diazocarbonyl compounds.[36] Moreover, from all diacceptor diazo reagents evaluated to date

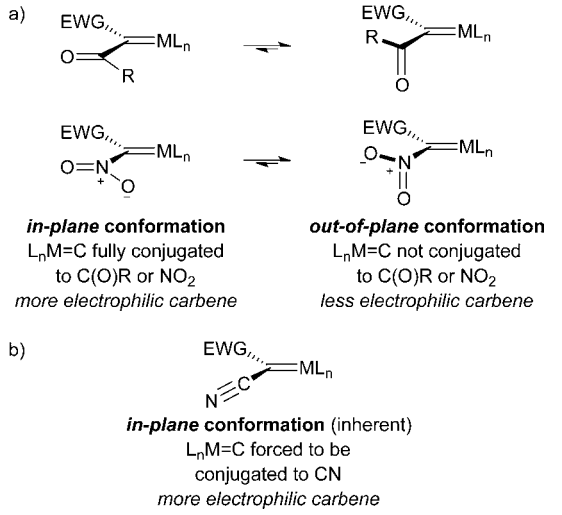


Figure 3. Possible conformations of (a) NO_2- or C(O)R-substituted metal−carbenes and (b) CN-substituted metal−carbenes.

with Rh(II) catalysts, only diazoacetonitrile derivatives are compatible with less nucleophilic aliphatic alkenes as substrates, also suggesting that the corresponding metal−carbene intermediate is more electrophilic when substituted with a cyano group.[12d,15b]

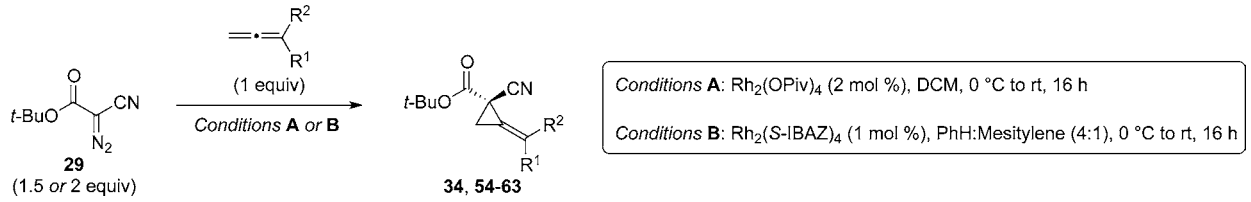
These studies thus permitted us to identify α-cyano diazo ester **29** as an ideal substrate for the stereoselective Rh(II)-catalyzed alkylidenecyclopropanation of phenylallene. To explore the scope of accessible diacceptor ACPs in our system, various allenes were evaluated as substrates, using either Rh_2(OPiv)$_4$ (conditions A) or Rh_2(*S*-IBAZ)$_4$ (conditions B) as catalysts, providing access to both racemic and enantioenriched products, respectively (Table 5). Modification of the aromatic group's electronic properties through the use of differently substituted phenylallenes did not significantly affect the stereoselectivity, as 95−97% ee was observed in all cases (entries 1−5). Gratifyingly, various aliphatic allenes were also well-tolerated, affording good yields and stereoselectivities for the corresponding ACPs **58** and **59** with both methods (entries 6 and 7). Additionally, the presence of an *N*-phthaloyl group directly on the allene moiety was found to be compatible, though a lower isolated yield was observed under conditions B (entry 8). Although a reasonable amount of the product was isolated when ethyl allenoate was used, the electron-withdrawing nature of the ester moiety, affording a less nucleophilic allene, led to a significant decrease in the observed yield (entry 9). Importantly, the more sterically hindered 1,1-disubstituted allenes were also reactive in both processes, and the presence of a trimethylsilyl group considerably improved the reaction yield, presumably via a β-silicon effect enhancing the allene's nucleophilicity (entries 10 and 11).[31b,34] For all aromatic allenes evaluated, only the *E* alkene of the product was observed, while some of the *Z* diastereomer of **58**, **60**, and **61** was detected by ^{1}H NMR of the crude mixtures. Moreover, as previously observed with α-cyano diazophosphonate **3**, the Rh_2(*S*-IBAZ)$_4$-catalyzed reaction generally proved to be slightly less efficient in terms of yield, presumably because of a lower reactivity of the corresponding metal−carbene.

CONCLUSION

In summary, we have developed a highly stereoselective Rh(II)-catalyzed cyclopropanation of alkenes, alkynes, and allenes with

dx.doi.org/10.1021/ja3099728 | J. Am. Chem. Soc. 2013, 135, 1463−1470

Table 5. Scope of the Stereoselective Alkylidenecyclopropanation Using α-Cyano Diazo Ester 29



entry	R^1	R^2	product	yield for cond A (%)[a]	dr for cond A (*E*:*Z*)[b]	yield for cond B (%)[a]	dr for cond B (*E*:*Z*)[b]	ee for cond B (%)[c]
1	Ph	H	**34**	93	>97:3	92	>97:3	95
2	4-Me-C_6H_4	H	**54**	90	>97:3	82	>97:3	95
3	4-Cl-C_6H_4	H	**55**	97	>97:3	76	>97:3	96
4	4-MeO-C_6H_4	H	**56**	68	>97:3	74	>97:3	96
5	2−Br-C_6H_4	H	**57**	99	>97:3	44	>97:3	97
6	CH_2Ph	H	**58**	81	>97:3	86	93:7	>90
7	CH_2-*N*Phth	H	**59**	96	>97:3	80	>97:3	82
8	*N*-phthaloyl	H	**60**	95	>97:3	48	93:7	90
9	CO_2Et	H	**61**	51[d]	82:18	29[d]	80:20	n.d.
10	Ph	Me	**62**	57	>97:3	43	>97:3	96
11	$SiMe_3$	Me	**63**	87	>97:3	83	>97:3	90

[a]Isolated yield of combined diastereomers. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by SFC or GC analysis on chiral stationary phase (ee of *E* product). [d]Yield of pure *E* diastereomer.

diacceptor diazo compounds. By employing the phosphonate moiety as an effective trans-directing group, the first catalytic asymmetric method for the synthesis of diacceptor cyclopropylphosphonates is reported through the use of α-cyano diazophosphonate **3** and catalyst Rh_2(*S*-IBAZ)$_4$, under mild reaction conditions. The reaction was shown to be also efficient using an isosteric substrate, α-cyano diazophosphonate **29**, leading to the formation of the corresponding cyclopropanes and cyclopropenes in high yields and stereoselectivities. Moreover, the particular electrophilicity of cyanocarbene intermediates permitted the use of allenes as substrates, leading to the development of the first catalytic asymmetric alkylidenecyclopropanation reaction using diacceptor diazo compounds. All the methods reported here employ practical procedures, avoiding syringe-pump techniques and using minimal amounts of reagents and catalysts, at 0 °C or room temperature. Cognizant of the array of existing synthetic applications of diacceptor cyclopropanes,[12−14] cyclopropylphosphonates,[2−4] or ACPs,[26−30] this work contributes to access a variety of new and useful enantioenriched cyclopropane-based building blocks for the stereoselective synthesis of complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the Natural Science and Engineering Research Council of Canada (NSERC), the Canada Research Chair Program, the Canada Foundation for Innovation, the Centre in Green Chemistry and Catalysis (CGCC), and the Université de Montréal. We also thank Francine Bélanger-Gariépy and CYLView for X-ray analysis, as well as Christophe Camy and Alexandra Furtos for SFC analysis. The authors are grateful to Dr. James J. Mousseau for useful discussions on the manuscript. V.N.G.L. is grateful to NSERC (PGS D) and Université de Montréal for postgraduate fellowships. D.F. is grateful to NSERC (PGS M) and Université de Montréal for postgraduate fellowships. S.A. is grateful to NSERC (PGS D) for a postgraduate fellowship.

■ REFERENCES

(1) (a) Duquenne, C.; Goumain, S.; Jubault, P.; Feasson, C.; Quirion, J.-C. *Org. Lett.* **2000**, *2*, 453. (b) Erion, M. D.; Walsh, C. T. *Biochemistry* **1987**, *26*, 3417. (c) Hanessian, S.; Cantin, L.-D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103. (d) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264. (e) Clercq, E. D.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464. (f) Hendlin, D.; Stapley, E. O.; Jackson, M.; Wallick, H.; Miller, A. K.; Wolf, F. J.; Miller, T. W.; Chaiet, L.; Kahan, F. M.; Foltz, E. L.; Woodruff, H. B.; Mata, J. M.; Hernandez, S.; Mochales, S. *Science* **1969**, *166*, 122.

(2) (a) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072. (b) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (c) Shie, J.-J.; Fang, J.-M.; Lai, P.-T.; Wen, W.-H.; Wang, S.-Y.; Cheng, Y.-S. E.; Tsai, K.-C.; Yang, A.-S.; Wong, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 17959. (d) White, C. L.; Janakiraman, M. N.; Laver, G. W.; Philippon, C.; Vasella, A.; Air, G. M.; Luo, M. *J. Mol. Biol.* **1995**, *245*, 623. (e) Streicher, H.; Meisch, J.; Bohner, C. *Tetrahedron* **2001**, *57*, 8851. (f) Streicher, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 361. (g) Streicher, H.; Busse, H. *Bioorg. Med. Chem.* **2006**, *14*, 1047. (h) Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271. (i) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654.

(3) (a) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625. (b) Votruba, I.; Bernaerts, R.; Sakuma, T.; De Clercq, E.; Merta, A.; Rosenberg, I.; Holý, A. *Mol. Pharmacol.* **1987**, *32*, 524. (c) Elliott, T. S.; Slowey, A.; Ye, Y.; Conway, S. J. *Med. Chem. Commun.* **2012**, *3*, 735.

(4) (a) Pyun, H.-J.; Chaudhary, K.; Somoza, J. R.; Sheng, X. C.; Kim, C. U. *Tetrahedron Lett.* **2009**, *50*, 3833. (b) Sheng, X. C.; Pyun, H.-J.; Chaudhary, K.; Wang, J.; Doerffler, E.; Fleury, M.; McMurtrie, D.; Chen, X.; Delaney, I. W. E.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3453. (c) Clarke, M. O.; Chen, X.; Cho, A.; Delaney, I. W. E.; Doerffler, E.; Fardis, M.; Ji, M.; Mertzman, M.; Pakdaman, R.; Pyun, H.-J.; Rowe, T.; Yang, C. Y.; Sheng, X. C.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3568. (d) Pyun, H.-J.; Clarke, M. O.; Cho, A.; Casarez, A.; Ji, M.; Fardis, M.; Pastor, R.; Sheng, X. C.; Kim, C. U. *Tetrahedron Lett.* **2012**, *53*, 2360. (e) Sheng, X. C.; Casarez, A.; Cai, R.; Clarke, M. O.; Chen, X.; Cho, A.; Delaney, I. W. E.; Doerffler, E.; Ji, M.; Mertzman, M.; Pakdaman, R.; Pyun, H.-J.; Rowe, T.; Wu, Q.; Xu, J.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1394.

(5) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Davies, H. M. L. *Org. React. (Hoboken, NJ, U. S.)* **2001**, *57*, 1. (d) Roy, M.-N.; Lindsay, V. N. G.; Charette, A. B. In *Stereoselective Synthesis 1: Stereoselective Reactions of Carbon-Carbon Double Bonds*; Georg Thieme-Verlag: New York, 2011; chapt. 1.14.

(6) Charette, A. B.; Bouchard, J.-E. *Can. J. Chem.* **2005**, *83*, 533.

(7) (a) Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* **2004**, *6*, 3211. (b) Le Maux, P.; Abrunhosa, I.; Berchel, M.; Simonneaux, G.; Gulea, M.; Masson, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2569.

(8) (a) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117. (b) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437.

(9) For an elegant enantioselective synthesis of cyclopropylphosphonates using a chiral auxiliary, see ref 1c.

(10) For a synthesis of racemic α-nitro cyclopropylphosphonates, see: (a) Chemagin, A. V.; Yashin, N. V.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirov, N. S. *Synthesis* **2010**, 259. (b) Chemagin, A. V.; Yashin, N. V.; Grishin, Y. K.; Kuznetsova, T. S.; Zefirov, N. S. *Synthesis* **2010**, 3379.

(11) For diastereoselective Rh-catalyzed intramolecular cyclopropanations using diacceptor diazophosphonates, see: (a) Moore, J. D.; Sprott, K. T.; Wrobleski, A. D.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 2357. (b) Moore, J. D.; Hanson, P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 873.

(12) ACC: 1-Aminocyclopropanecarboxylic acid. (a) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (b) Moreau, B.; Alberico, D.; Lindsay, V. N. G.; Charette, A. B. *Tetrahedron* **2012**, *68*, 3487 and references therein. (c) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383. (d) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972. (e) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(13) (a) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (b) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838. (c) Cérat, P.; Gritsch, P. J.; Goudreau, S. R.; Charette, A. B. *Org. Lett.* **2010**, *12*, 564. (d) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373.

(14) For reviews and recent examples of formal cycloaddition using enantioenriched diacceptor cyclopropanes, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (d) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (e) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057. (f) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996. (g) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (h) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370. (i) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem Commun* **2009**, 5135. (j) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830. (k) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (l) Kang, Y.-B.; Tang, Y.; Sun, X.-L. *Org. Biomol. Chem.* **2006**, *4*, 299. (m) Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777. (n) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; de Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504. (o) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (p) Leduc, A. B.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 7945. (q) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. (r) Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y. *Chem.—Eur. J.* **2012**, *18*, 2196. (s) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (t) Wu, L.; Shi, D. M. *Chem.—Eur. J.* **2010**, *16*, 1149. (u) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465. (v) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (w) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560. (x) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (y) Yu, X.; Qiu, G.; Liu, J.; Wu, J. *Synthesis* **2011**, 2268. (z) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573.

(15) (a) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155. (b) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970. (c) Lin, W.; Charette, A. B. *Adv. Synth. Catal.* **2005**, *347*, 1547.

(16) For other examples of enantioselective cyclopropanation using diazoacetonitrile derivatives, see refs 12d, 15b, 15c, and (a) Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238. (b) Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796. (c) Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292.

(17) Nasser, J.; About-jaudet, E.; Collignon, N. *Phosphorus, Sulfur, Silicon* **1991**, *55*, 137.

(18) (a) Gauvry, N.; Mortier, J. *Synthesis* **2001**, 553. (b) Salomon, C. J.; Breuer, E. *Tetrahedron Lett.* **1995**, *36*, 6759. (c) Gulyukina, N.; Makukhin, N.; Beletskaya, I. *Russ. J. Org. Chem.* **2011**, *47*, 633.

(19) $Rh_2(Adc)_4$ was prepared in one step from commercially available materials: (a) Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, R. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 1877. (b) Wurz, R. P. Rhodium Tetrakis[tricyclo[3.3.1.13,7]decane-1-carboxylate]. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: New York, 2001.

(20) (a) Doyle, M. P.; Zhou, Q.-L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697. (b) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.

(21) (a) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (b) Zhu, S.; Ruppel, J. V.; Lu, H.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2008**, *130*, 5042. (c) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074. (d) Ruppel, J. V.; Gauthier, T. J.; Snyder, N. L.; Perman, J. A.; Zhang, X. P. *Org. Lett.* **2009**, *11*, 2273.

(22) (a) Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3304. (b) Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *133*, 170.

(23) For enantioselective cyclopropenation using monoacceptor or donor−acceptor carbenoids, see: (a) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (b) Protopopova, M. N.; Doyle, M. P.; Mueller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755. (c) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (d) Doyle, M. P.; Protopopova, M.; Muller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (e) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419. (f) Doyle, M. P.; Ene, D. G.; Peterson, C. S.; Lynch, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 700. (g) P. Doyle, M.; G. Ene, D.; C. Forbes, D.; H. Pillow, T. *Chem. Commun.* **1999**, 1691. (h) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916. (i) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223. (j) Weatherhead-Kloster, R. A.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171. (k) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233. (l) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211. (m) Briones, J. F.; Davies, H. M. L.

Tetrahedron **2011**, *67*, 4313. (n) Briones, J. F.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 11916. (o) Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6803.
(24) Briones, J. F.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 3984.
(25) Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* **1981**, *14*, 227.
(26) (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (c) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575. (d) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (e) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (g) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (h) Pellissier, H. *Tetrahedron* **2010**, *66*, 8341. (i) Shi, M.; Lu, J.-M.; Wei, Y.; Shao, L.-X. *Acc. Chem. Res.* **2011**, *45*, 641. (j) Yu, L.; Guo, R. *Org. Prep. Proced. Int.* **2011**, *43*, 209. (k) Lu, B.-L.; Dai, L.; Shi, M. *Chem. Soc. Rev.* **2012**, *41*, 3318.
(27) (a) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183. (b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (c) Yao, T.; Hong, A.; Sarpong, R. *Synthesis* **2006**, *21*, 3605.
(28) (a) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (b) Hu, B.; Xing, S.; Wang, Z. *Org. Lett.* **2008**, *10*, 5481. (c) Hu, B.; Jiang, L.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 1358. (d) Hu, B.; Ren, J.; Wang, Z. *Tetrahedron* **2011**, *67*, 763.
(29) (a) Hu, B.; Zhu, J.; Xing, S.; Fang, J.; Du, D.; Wang, Z. *Chem.—Eur. J.* **2009**, *15*, 324. (b) Tran, T. Q.; Diev, V. V.; Molchanov, A. P. *Tetrahedron* **2011**, *67*, 2391. (c) Fujino, D.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2011**, *133*, 9682. (d) Tran, T. Q.; Diev, V. V.; Starova, G. L.; Gurzhiy, V. V.; Molchanov, A. P. *Eur. J. Org. Chem.* **2012**, *10*, 2054.
(30) (a) Ma, S.; Lu, L. *J. Org. Chem.* **2005**, *70*, 7629. (b) Chen, J.; Lu, L.; Ma, S. *Tetrahedron* **2008**, *64*, 8899.
(31) For 1,1-diester ACPs: (a) Jones, M.; Ando, W.; Hendrick, M. E.; Kulczycki, A.; Howley, P. M.; Hummel, K. F.; Malament, D. S. *J. Am. Chem. Soc.* **1972**, *94*, 7469. (b) Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020. (c) See ref 30a. For keto-ACPs: (d) See refs 27b, c.
(32) Xu, L.; Huang, X.; Zhong, F. *Org. Lett.* **2006**, *8*, 5061.
(33) (a) Ullman, E. F. *J. Am. Chem. Soc.* **1959**, *81*, 5386. (b) Zhou, S.; Breitenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2003**, *47*, 566. (c) Boitsov, V. M.; Kostikov, R. R.; Molchanov, A. P.; Stepakov, A. V.; Baird, M. S. *Russ. J. Org. Chem.* **2004**, *40*, 1760.
(34) (a) Gregg, T. M.; Farrugia, M. K.; Frost, J. R. *Org. Lett.* **2009**, *11*, 4434. (b) Gregg, T. M.; Algera, R. F.; Frost, J. R.; Hassan, F.; Stewart, R. J. *Tetrahedron Lett.* **2010**, *51*, 6429.
(35) (a) Nowlan, D. T., III; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902. (b) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.
(36) DeAngelis, A.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 11035.