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Rhodium-Catalyzed Enantioselective Vinylogous Addition of Enol Ethers to Vinyldiazoacetates

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Abstract

A highly asymmetric vinylogous addition of acyclic silyl enol ethers to siloxyvinyldiazoacetate is described. The reaction features a diastereoselective 1,4-siloxy group migration event. Products are obtained in up to 97% ee. When more sterically crowded silyl enol ethers are employed, an enantioselective formal [3 + 2] cycloaddition becomes the dominant reaction pathway. Control experiments reveal the (Z)-olefin geometry to be critical for high levels of enantiocontrol.

Donor/acceptor carbenoids are valuable intermediates in enantioselective intermolecular C–C bond forming reactions.[1] Vinyldiazoesters have emerged as a synthetically useful class of carbenoid precursors when paired with chiral dirhodium tetracarboxylate catalysts. In addition to C–H insertion and cyclopropanation reactions, the vinyldiazoesters can function in a diverse array of other carbenoid reactions,[2] including the combined C–H functionalization/Cope rearrangement (CHCR) of vinyldiazoacetates and allylic C–H bonds[1b] and the cyclo-propanation/Cope rearrangement of dienes.[3]

Vinylcarbenoids are further distinguished from aryl and alkyl donor/acceptor carbenoids in that they possess electrophilic character at both the carbenoid and vinylogous position. Selective vinylogous reactivity can be achieved through a judicious choice of solvent,[4] catalyst,[4,5] ester substituent,[6] and degree of substitution at the vinyl terminus.[2e,5,7] The effect of this last variable can be quite pronounced. Recently we demonstrated that cyclic silyl enol ethers of type **1** react with methyl-substituted (*Z*)-siloxyvinyldiazoacetate **2** at the carbenoid position *via* a highly enantio- and diasteroselective combined-CHCR in the presence of Rh_2(*S*-PTAD)$_4$ (Scheme 1a).[8] In contrast, reaction of enol ether **1** with the terminally unsubstituted siloxyvinyldiazoacetate **4** favors vinylogous addition. The alkynoate products of type **5** are formed with excellent diastereoselectivity, but only low to moderate enantioselectivity with chiral dirhodium catalysts. (Scheme 1b).[9]

Herein we describe a highly asymmetric vinylogous addition of readily accessible, acyclic (*Z*)-silyl enol ethers (**6**) to siloxyvinyldiazoacetate **4** (Scheme 1c). The reaction provides disiloxyketal products of the opposite diastereomeric series with respect to the cyclic system. The resultant disiloxyketals can be readily deprotected with no erosion in enantiomeric excess, thus providing an operationally simple protocol for the enantioselective α-propargylation of ketones. We have further found that subtle modification of the reaction

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ASSOCIATED CONTENT

Supporting Information. Synthetic details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

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conditions with sterically demanding substrates promotes a formal [3 + 2] cycloaddition to provide highly substituted cyclopentenes, which give rise to enantioenriched cyclopentenone building blocks.

The successful propargylation of cyclic enol ethers prompted us to explore the use of acyclic substrates in this transformation. Specifically, we postulated that the use of (*Z*)-enol ethers might provide a solution to the low to moderate enantioinduction observed in the cyclic series.[10] We therefore initiated our studies with the propiophenone-derived silyl enol ether (*Z*)-**6a**. Our optimization studies are summarized in Table 1. A brief screen of chiral dirhodium catalysts (Figure 1) revealed Rh_2(*S*-PTAD)$_4$ to be optimal for this reaction; disiloxyketal **7a** was isolated in 65% yield and 77% ee (Table 1, entry 1). Cyclopentene **9a** was also isolated as a minor product in 12% yield and 90% ee. The experiment with Rh_2(*S*-DOSP)$_4$ provided only cyclopentene **9a** as a racemic mixture (entry 2), while the reaction with Rh_2(*S*-BTPCP)$_4$[11] produced a roughly 1:1 mixture of **7a:9a** in low yield and poor enantioselectivity (entry 3). Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$ provided **7a** in comparable enantioenrichment to Rh_2(*S*-PTAD)$_4$; however, these reactions were hampered by poor yields and lower overall conversions (entries 4 and 5). The use of nonpolar solvents provided a significant increase in the enantioselectivity of **7a**, albeit with only moderate product ratios (entries 6 and 7). Performing the reaction with 2,2-dimethylbutane (2,2-DMB) as the solvent gave the desired product in slightly higher yield with a substantially improved ratio of **7a**:**9a** (12:1, entry 8).[12] We found the reaction to be equally effective at 1 mol % catalyst loading; under these optimized conditions, alkynoate **7a** was isolated in 85% yield and 95% ee with only 8% yield of cyclopentene **9a** (entry 9).

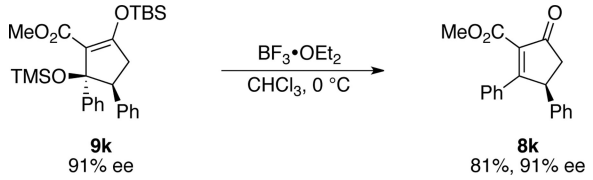
To demonstrate product utility, **7a** was treated with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 to provide the propargylic alcohol **10a** in 84% yield and 95% ee with no observable reduction of the disiloxyketal (Scheme 2). The absolute and relative configuration of **10a** was established by single crystal X-ray analysis and assigned to the remainder of the products by analogy.[13] Disiloxyketal **7a** could also be cleanly deprotected to the corresponding ketone **11a** with no detectable erosion in enantioenrichment in under five minutes by treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in DMF.[14] This method thus provides a two-step route to enantioenriched α-propargyl ketones.

Having established optimized conditions for the formation of **7a**, we proceeded to explore the scope of enol ether substrates. As described in Table 2, a variety of *para* and *meta*-substituted enol ethers provided the desired alkynoate products in high yield with excellent levels of diastereo- and enantioselectivity (70–84% yield, >20:1 dr, 95–97% ee, **7c–e**, Table 2). The reaction of the 2-naphthyl-derived enol ether **6f** led to desired disiloxyketal **7f** in moderate yield and enantioselectivity (48%, 80% ee). The less nucleophilic (*Z*)-silyl enol ethers derived from both hexane 3,4-dione (**6g**) and methyl 2-oxobutanoate (**6h**) also provided the desired products at elevated temperatures in refluxing hexanes. Disiloxyketal **7g** was isolated in 53% yield and 88% ee, while **7h** was isolated in 62% yield and 94% ee. The reaction of the 2-methoxy enol ether **6i** also gave the desired product **7i** in 74% yield and 97% ee.

When the enol ether derived from butyrophenone (**6j**) was employed under the standard reaction conditions, the desired disiloxyketal was furnished in 95% ee; however, the ratio of disiloxyketal to cyclopentene was significantly lower (5:1), and the reaction proceeded with incomplete conversion (Table 3, entry 1). Although performing this experiment at elevated temperatures was effective at promoting complete consumption of the starting enol ether, the product ratio was further eroded (entry 2). This finding, coupled with the high level of enantioenrichment (94% ee) and potential synthetic value of **9j**, led us to explore the

possibility of favoring the minor cyclopentene byproduct in these reactions. Performing the reaction at 70 °C in refluxing hexanes led to even higher yields of **9j** with only a slight drop in enantioselectivity (45% yield, 91% ee, entry 3). Furthermore, we observed that under these reaction conditions, more sterically hindered silyl enol ethers such as **6k** provided only the cyclopentene product; **9k** was obtained in 86% yield and 91% ee (entry 4).[15]

The formal [3 + 2] cycloadducts (**9**) could be directly converted to highly enantioenriched cyclopentenone building blocks under Lewis acidic conditions with no erosion in enantiomeric excess. Upon treatment of enantioenriched cyclopentene **9k** (91% ee) with BF_3•OEt_2 at 0 °C, cyclopentenone **8k** was obtained in 81% yield and 91% ee (eq 1).



(1)

We subsequently found that these enantioenriched cyclopentenones could be synthesized *via* a one-pot operation with minimal reduction in the overall yield (Table 4). Thus, the rhodium-catalyzed formal [3 + 2] cycloaddition was conducted in hexanes at 70 °C; subsequent evaporation of hexanes, addition of $CHCl_3$ and treatment with BF_3•OEt_2 at 0 °C provided cyclopentenones **8j–8o** with only one purification step required. The less hindered substrates **6j** and **6l** provided the desired products in modest yield and high enantioselectivity (**8j–8k**, 29–41% yield, 91–92% ee, Table 4), while the one-pot reaction with silyl enol ether **6k** led to aryl cyclopentenone **8k** in 66% overall yield and 91% ee. As a highlight of this method, sterically and electronically demanding silyl enol ethers **6m-o**, which reacted poorly under the standard conditions at room temperature, provided the desired cyclopentenones **8m-o** in good yield (51–70%) and high enantioselectivity (90–94% ee).

In order to obtain information about the absolute stereochemical configuration at C3 in cyclopentenones **8** we synthesized cyclopentenone **8p** as described in Scheme 3 (59% yield, 78% ee). Subsequent reduction of **8p** to the corresponding diol with DIBAL-H yielded cyclopentene **12p** as a 2.5:1 mixture of diastereomers. From this mixture we were able to obtain a crystal of **12p** suitable for X-ray diffraction analysis. The absolute stereochemistry at C4 of **12p** (C3 of **8p**) was determined to be of (*S*)-configuration and assigned to the remainder of the cyclopentenones by analogy.[16]

In an effort to probe the mechanism of the unusual 1,4-siloxy group transfer observed in Table 2, we performed the following control experiment. A 2.3:1 mixture of (*E*)/(*Z*)-**6a** was subjected to the standard reaction conditions described in Table 2 (eq 2). Disiloxyketal **7a** was isolated in 70% yield as a 2.3:1 mixture of isomers favoring the opposite diastereomer from that observed with (*Z*)-**6a**. The major diastereomer was obtained in 43% ee, while the minor diastereomer was determined to be in 95% ee.

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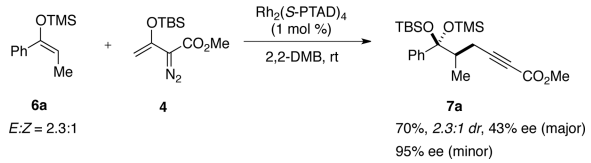

(2)

The observation that (*E*)-**6a**, a substrate that is able to undergo bond rotation after nucleophilic addition, provided the opposite diastereomer from that observed with (*Z*)-**6a** strongly suggests a 1,4-siloxy group transfer that occurs faster than sigma bond rotation. These data indicate that the high diastereoselectivity observed in Table 2 is thus a function of enol ether geometry. In addition, the asymmetric results obtained from the experiment described in eq 2 also reveal a requirement for the (*Z*)-enol ether geometry in order to achieve high enantioselectivity, which is consistent with the low to moderate levels of enantioinduction observed in the cyclic series.[9]

A tentative mechanism that rationalizes the observed enantioselectivity and product divergency is described in Scheme 4. Ample precedent exists for Rh_2(*S*-PTAD)$_4$, in combination with **4**, to direct substrate approach from the *re*-face of the carbenoid in enantioselective cyclopropanation and C–H insertion reactions.[1b,3,8] Based on these results, we propose the silyl enol ether approaches the chiral rhodium carbenoid from the front face as drawn (**13**). The (*Z*)-geometry of the enol ether most likely dictates attack *via* an "end on" mode, in which the bulky OTMS and R^1 groups are pointed away from the phthalimido blocking groups.[17] Vinylogous addition is followed by rapid OTBS group migration/β-elimination from a fleeting intermediate **14** in which the oxocarbenium ion is properly aligned with a participating lone pair on the OTBS group. We postulate that a negative steric interaction between a bulky R^1 group and the catalyst "wall" disfavors a trajectory that promotes siloxy group migration and, instead, favors a still highly facial selective "side on" approach (**15**). Reaction through this approach would provide intermediate **16**, which is aligned to undergo a diastereoselective ring closure to access **9**. The similar but not quite identical levels of enantioinduction for the formation of the two classes of products (Tables 1 and 3) is consistent with two mechanisms that are differentiated by a subtle alteration in the trajectory of approach of the substrate to the rhodium carbenoid. Further studies are being conducted in our laboratory in an attempt to gain a better understanding of the mechanistic nuances that control this striking product divergence.

We have demonstrated a highly enantio- and diastereoselective vinylogous addition/1,4-siloxy group migration of silyl enol ethers and siloxyvinyldiazoacetate catalyzed by Rh_2(*S*-PTAD)$_4$. The isolated disiloxyketal products are easily deprotected to the subsequent carbonyl to provide access to highly enantioenriched α-propargyl ketones. Reactions with sterically demanding substrates allow for the one-pot synthesis of enantioenriched cyclopentenone building blocks. Extending this unusual transformation to other nucleophiles, as well as exploring the migratory aptitude of other leaving groups on the diazo precursor comprises our future interests.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgments

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10. Doyle reports a significant dependence on reaction partner geometry for high enantioselectivity in the formal [3+3] cycloaddition of nitrones with **4**. See ref 2e.
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12. 2,2-DMB has previously been demonstrated to be an optimal solvent for enantioselective C?????????H functionalization, especially of unreactive substrates. For example, see Ref 1a and references cited therein.
13. The crystal structures of **10a** and **12p** have been deposited at the Cambridge Crystallographic Data Centre and the deposition numbers CCDC 899871 and 899870, were allocated, respectively. For X-ray crystallographic data of **10a**, see the Supporting Information.
14. The use of TBAF resulted in lower yields for the deprotection of **7a**.
15. For alternative methods to all-carbon 5-membered rings using silyl enol ethers, see: Singleton DA, Church KM, Lucero MJ. Tetrahedron Lett. 1990; 39:5551–5554. Fang J, Ren J, Wang Z. Tetrahedron Lett. 2008; 47:6659–6662. Komatsu M, Suehiro I, Horiguchi Y, Kuwajima I. Synlett. 1991; 11:771–773. Qu J-P, Deng C, Zhou J, Sun X-L, Tang Y. J. Org. Chem. 2009; 74:7684–7689. [PubMed: 19761235] de Nanteuil F, Waser J. Angew. Chem. Int. Ed. 2011; 50:12075–12079.
16. For X-ray crystallographic data of a single isomer of **12p**, see the Supporting Information.
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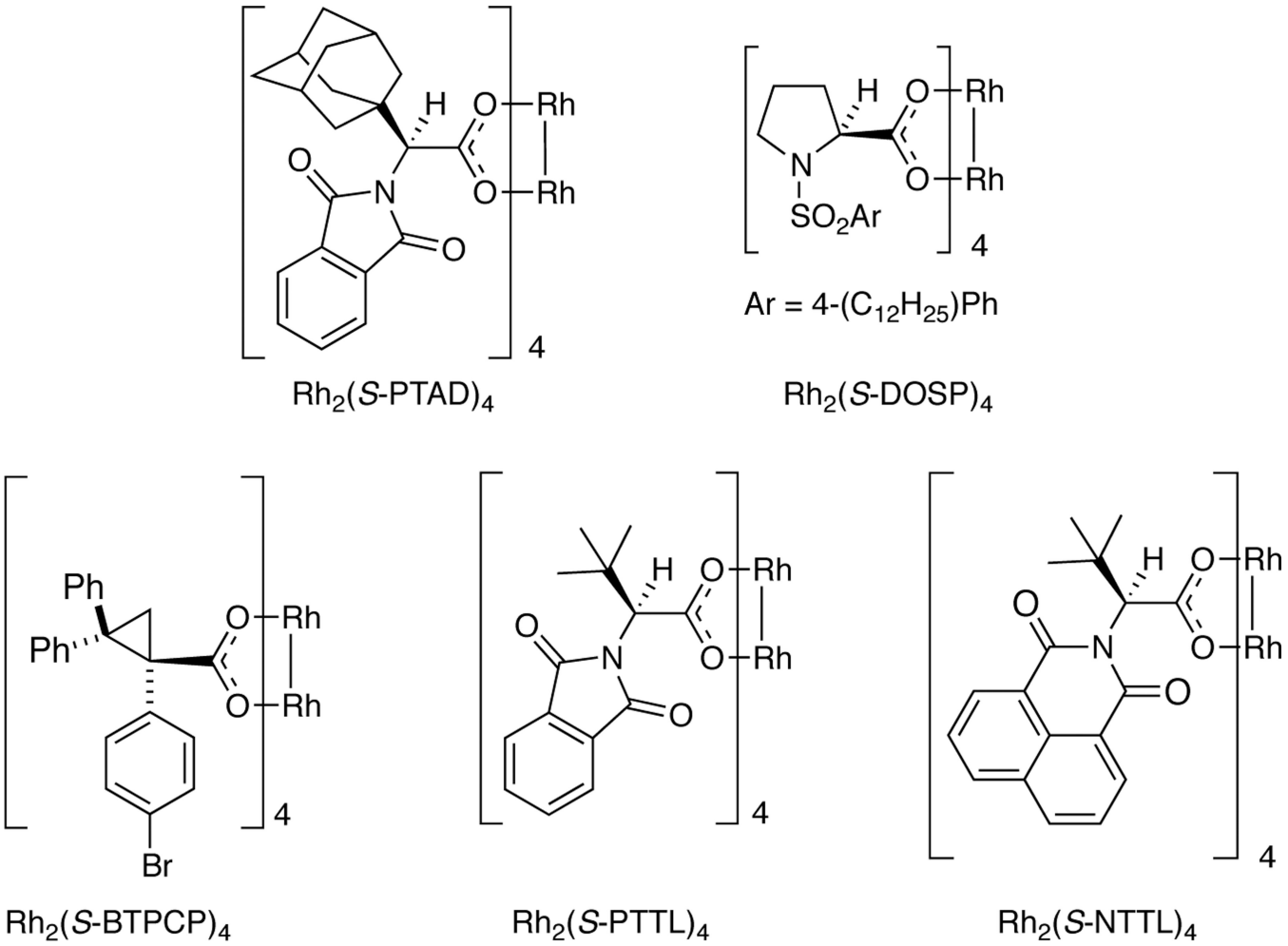

Figure 1.
Structures of chiral dirhodium catalysts used in this study.

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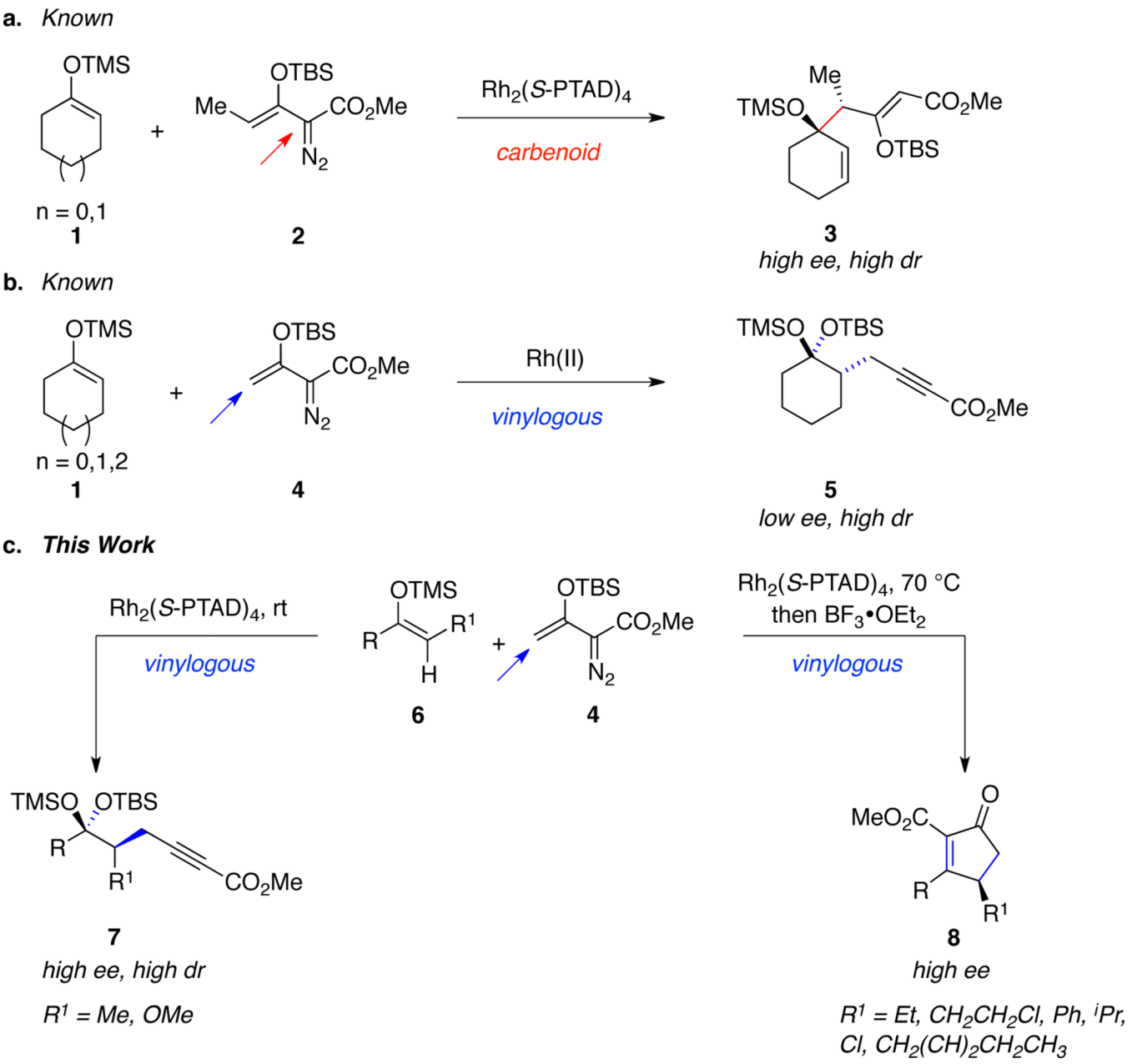

Scheme 1.
Comparison of Known Carbenoid (a) and Vinylogous (b) Transformations with 1, and the Current Studies (c)

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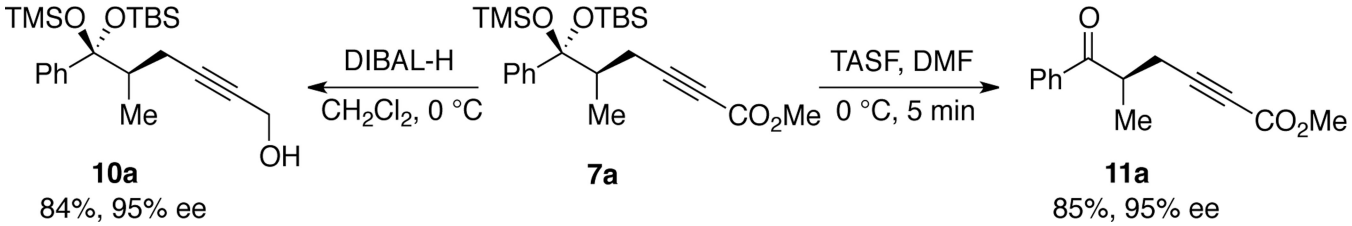

Scheme 2.
Product Derivatizations

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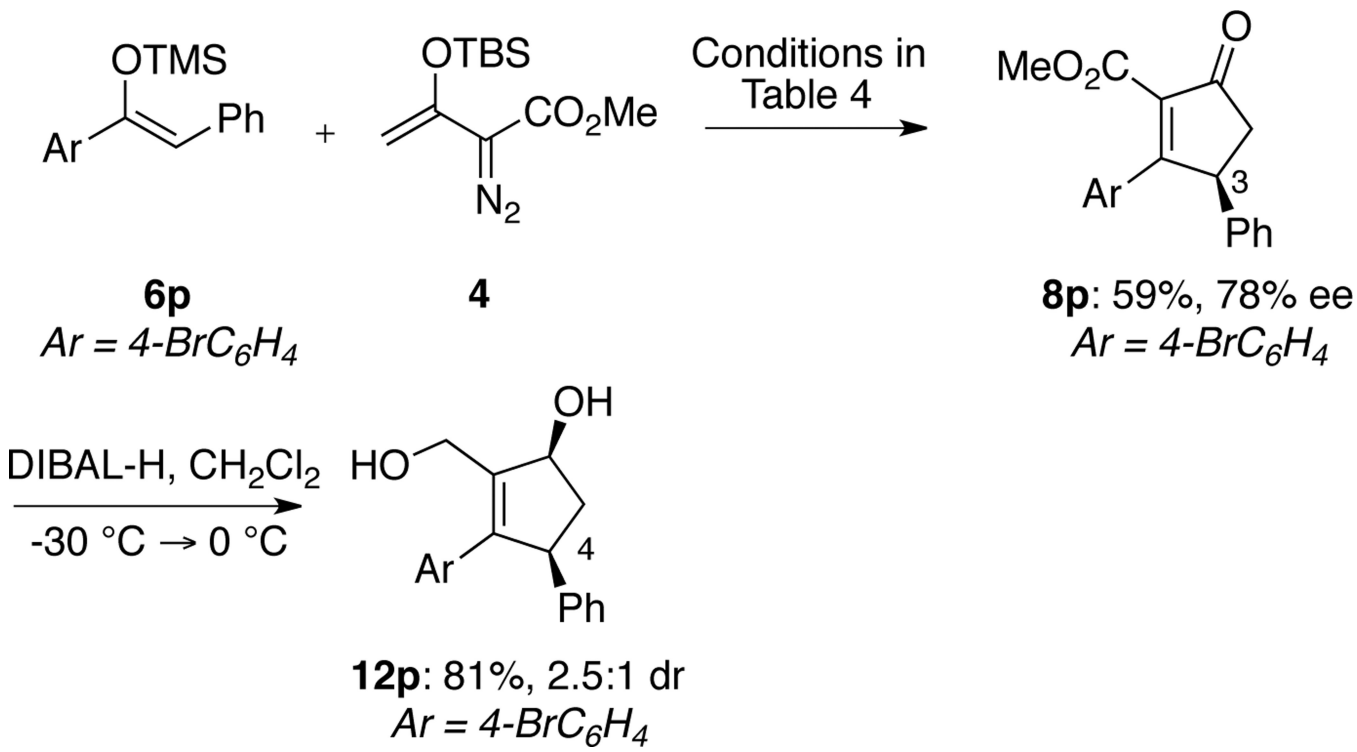

Scheme 3.
Synthesis of 12p

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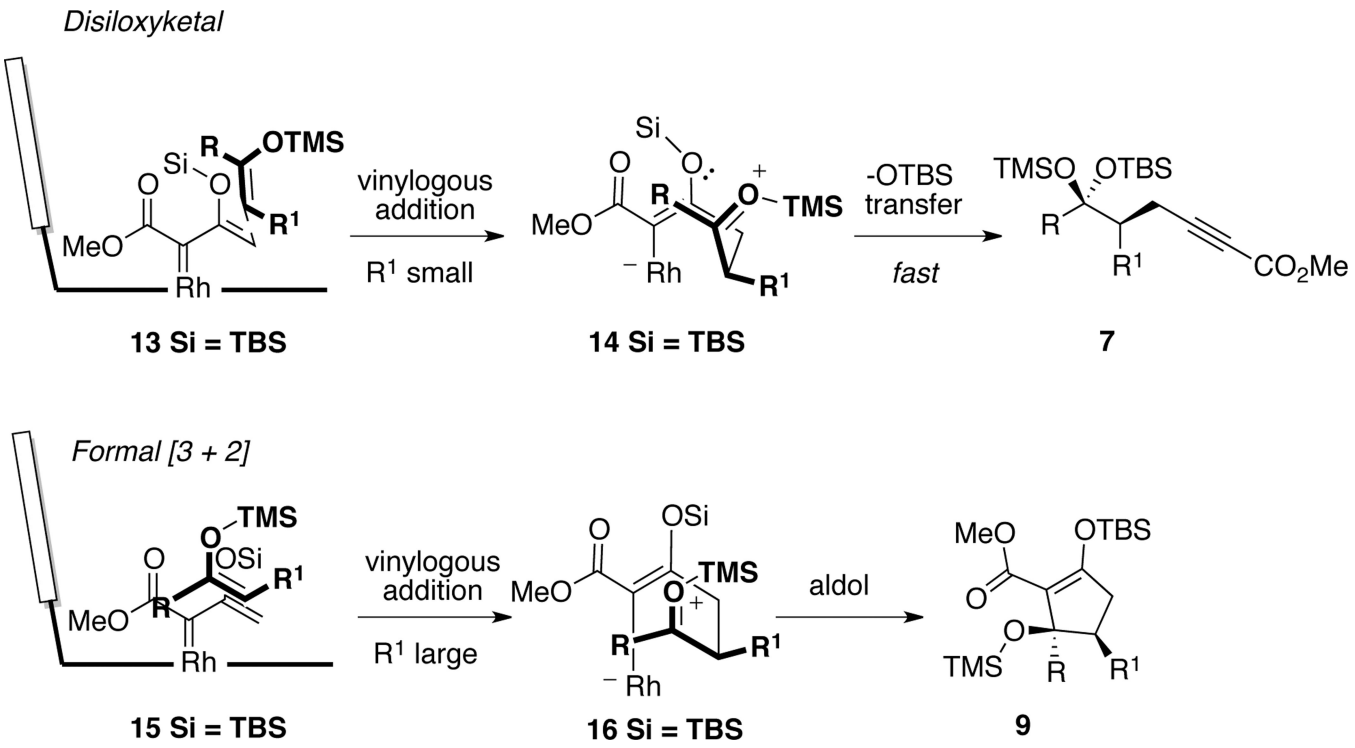

Scheme 4.
Proposed Mechanism for the Formation of 7 and 9

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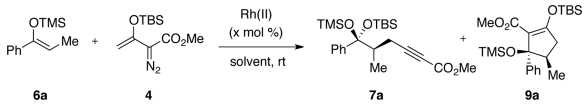
Table 1

Optimization Results with 6a[a,b]



entry	catalyst	solvent	x	% yield 7a (% ee 7a[c])	% yield 9a (% ee 9a[d])
1	Rh_2(*S*-PTAD)$_4$	CH_2Cl_2	2	65 (77)	12 (90)
1	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	2	0	40 (<5)
3	Rh_2(*S*-BTPCP)$_4$	CH_2Cl_2	2	20 (−19)	17 (−22)
4[e]	Rh_2(*S*-PTTL)$_4$	CH_2Cl_2	2	39 (76)	<5 (na)
5[f]	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	2	18 (75)	<5 (na)
6	Rh_2(*S*-PTAD)$_4$	hexanes	2	65 (94)	15 (95)
7	Rh_2(*S*-PTAD)$_4$	pentane	2	76 (94)	14 (95)
8	Rh2$_{(}$*S*-PTAD)$_4$	2,2-DMB	2	84 (95)	7 (97)
9	***Rh_2(S-PTAD)$_4$***	***2,2-DMB***	***1***	***85 (95)***	***8 (97)***

[a]Products **7a** and **9a** were obtained in >20:1 dr as determined by 1H NMR analysis of the crude reaction mixture.

[b]Yield refers to isolated yield after silica gel chromatography.

[c]Determined by chiral HPLC analysis of the corresponding propargylic alcohol.

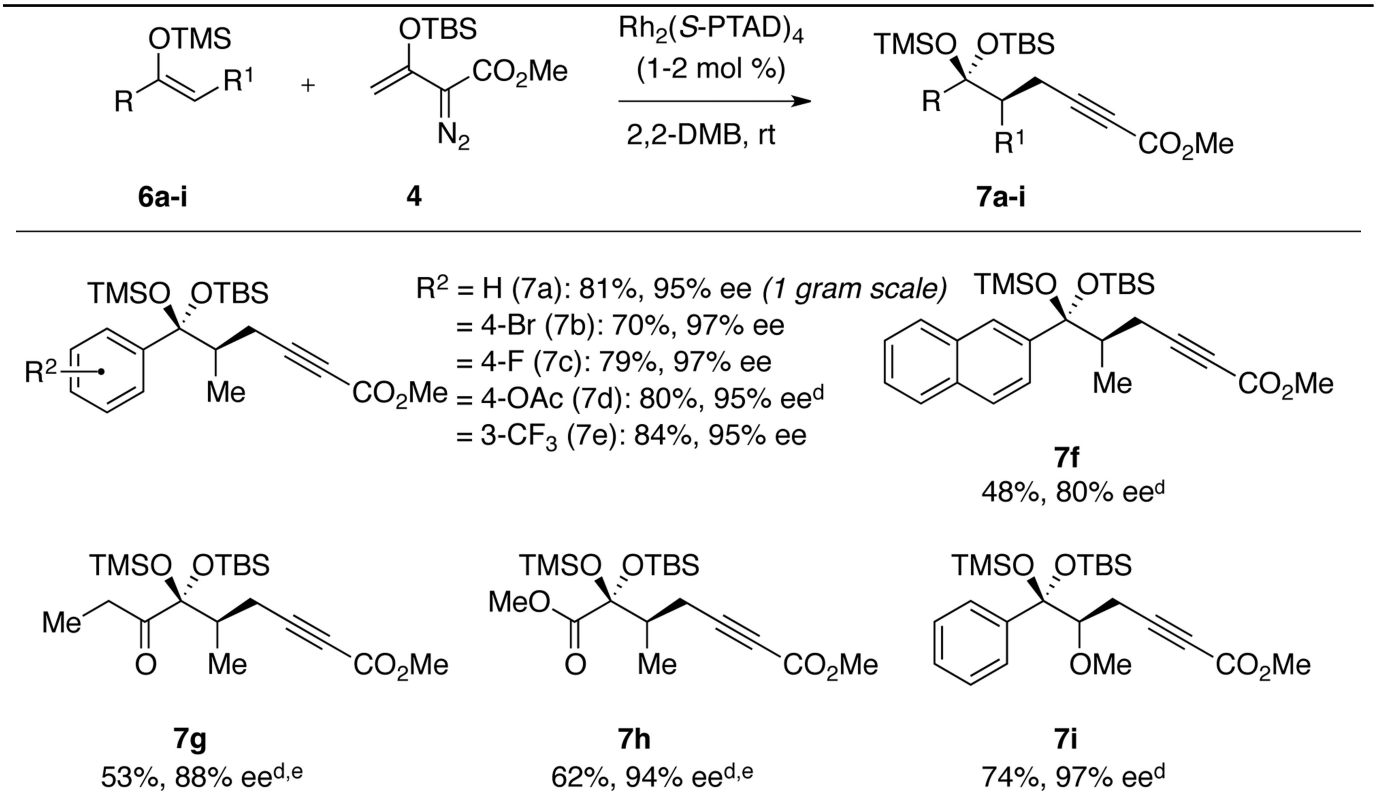
[d]Determined by chiral HPLC analysis.

[e]60% conversion.

[f]40% conversion.

Table 2

Substrate Scope[a,b,c]



[a]Products in >20:1 dr as determined by 1H NMR analysis of the crude reaction mixture.

[b]Yield refers to isolated yield after silica gel chromatography.

[c]Enantioenrichment determined by chiral HPLC analysis of the corresponding propargyl ketone unless otherwise noted.

[d]Determined by chiral HPLC analysis.

[e]Experiment performed at 70 C in hexanes.

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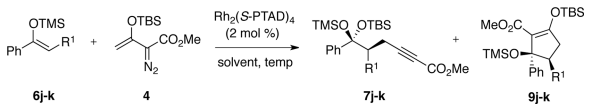
Table 3

Formal [3 + 2] Optimization[a,b]



entry	solvent	temp	R^1	% yield 7 (% ee 7[c])	% yield 9 (% ee 9[d])
1[e]	2,2-DMB	rt	Et (**6j**)	49 (95)	10 (96)
2	2,2-DMB	50 °C	Et (**6j**)	61 (92)	30 (94)
3	hexanes	70 °C	Et (**6j**)	47 (90)	45 (91)
4	hexanes	70 °C	Ph (**6k**)	0	86 (91)

[a]Products **7** and **9** were obtained in >20:1 dr as determined by ^{1}H NMR analysis of the crude reaction mixture.

[b]Yield refers to isolated yield after silica gel chromatography.

[c]Determined by chiral HPLC analysis of the corresponding propargyl ketone.

[d]Determined by chiral HPLC analysis. e75% conversion.

[e]75% conversion.

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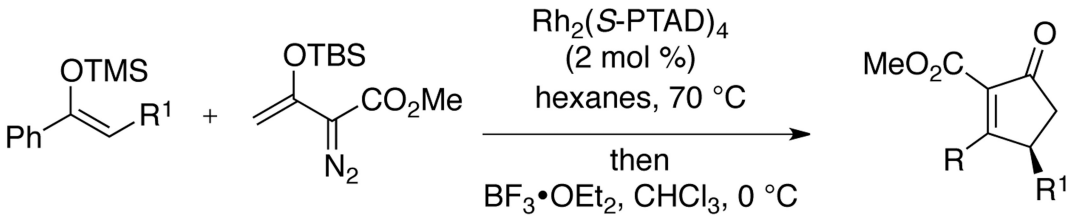
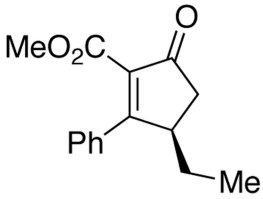
Table 4

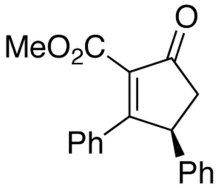
One-Pot Synthesis of Cyclopentenones 8[a,b]



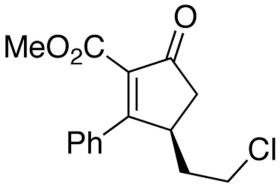
6j-o **4** **8j-o**



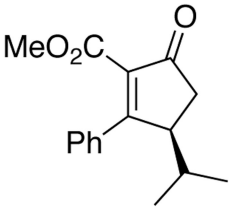
8j
41%, 91% ee



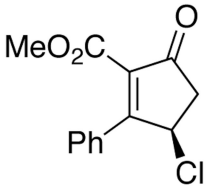
8k
66%, 91% ee



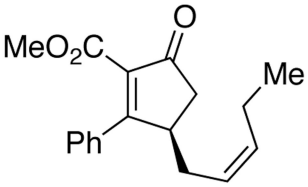
8l
29%, 92% ee



8m
51%, 90% ee



8n
70%, 94% ee



8o
55%, 94% ee

[a]Yield refers to isolated yield after silica gel chromatography.

[b]Enantioenrichment determined by chiral HPLC analysis.