effectively render "invisible" signals other than those of the probe and, if the label could be easily incorporated, lead to a further simplification of the screening method.

The approach demonstrated here provides a general and rapid means for detecting active molecules, especially when these are constituents of a combinatorially generated library. The method could conceivably be automated, and thereby transformed into a routine, high-throughput technique of even greater potential in the process of drug discovery.[22]

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Highly Enantioselective Rh-Catalyzed Intramolecular Alder–Ene Reactions for the Syntheses of Chiral Tetrahydrofurans**

Aiwen Lei, Minsheng He, Shulin Wu, and Xumu Zhang*

Dedicated to Professor Robert H. Grubbs on the occasion of his 60th birthday

Alder–ene reactions are a powerful way to construct carbon–carbon bonds. The intramolecular version of these reactions can provide efficient routes to produce a variety of heterocyclic and carbocyclic compounds.[1] Since the thermal Alder–ene reaction requires high temperature, it has found limited applications in organic syntheses. In contrast, transition-metal-catalyzed Alder–ene reactions can be performed under mild conditions and therefore are widely applied to organic syntheses.[2] However, the enantioselective processes of metal-catalyzed Alder–ene reactions are relatively unexplored and the development of highly efficient catalysts still remains a great challenge.[3] Recently, we have developed Rh-catalyzed intramolecular Alder–ene reactions of enynes using a $[\{Rh(diphos)Cl\}_2]$ precursor.[4] Enantioselectivities between 65–98 % *ee* were obtained by using 1,2-bis(phospholano)benzene (Duphos), (2*R*,2′*R*)-bis(diphenylphosphanyl)-(1*R*,1′*R*)-dicyclopentane (BICP), or the related (2*R*,2′*R*)-bis(diphenylphosphinite)-(1*R*,1′*R*)-dicyclopentane (BICPO) as chiral ligands.[4a] Herein, we report a significant improvement of the catalytic system for these reactions. The new catalysts are prepared in situ by simply mixing a commercially available metal precursor and a ligand. Over 99 % *ee* has been achieved for a number of substrates.

To achieve high enantioselectivities for Rh-catalyzed Alder–ene reactions, we have screened a number of chiral phosphane ligands. The enyne **1a** was chosen as a standard substrate to optimize the reaction conditions and the results are given in Table 1. In the absence of phosphane ligand, $[\{Rh(cod)Cl\}_2]$ was an ineffective catalytic precursor at either room temperature or 65 °C (Table 1, entries 1 and 2). However, $[\{Rh(nbd)Cl\}_2]$ (nbd = norbornadiene) can be used as a catalyst precursor at 65 °C (Table 1, entry 6). Using the C_n-Tunaphos ligands developed by our group,[5] high efficiency was observed. When *rac*-C_4-Tunaphos was used as the ligand in the presence of $[\{Rh(cod)Cl\}_2]$ and $AgSbF_6$, high conversion (100 %) and a high yield (98 %) were obtained at room temperature within 20 min (Table 1, entry 9). Control experiments indicated that there were big differences between this new catalytic system and the earlier protocol developed by us using $[\{Rh(diphosphane)Cl\}_2]$ as catalytic precursor. We previously reported that $[\{Rh(BINAP)Cl\}_2]$ (BINAP = 2,2′-

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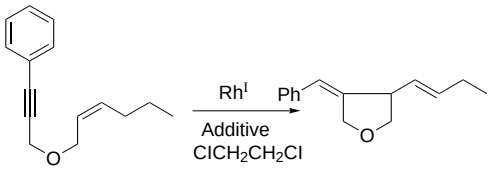
Table 1. Rh-catalyzed Alder–ene reaction of **1a**.[a]



1a **2a**

Entry	Rh^I	*T*	Additive	Conversion [%][b]
1	$[\{Rh(cod)Cl\}_2]$	RT	$AgSbF_6$	< 5
2	$[\{Rh(cod)Cl\}_2]$	65 °C	$AgSbF_6$	< 5
3	$[Rh(cod)_2]SbF_6$	RT	none	< 5
4	$[Rh(cod)_2]SbF_6$	65 °C	none	< 5
5	$[Rh(nbd)Cl]_2$	RT	$AgSbF_6$	< 5
6	$[Rh(nbd)Cl]_2$	65 °C	$AgSbF_6$	100(65)
7	$[Rh(nbd)_2]SbF_6$	RT	none	< 5
8	$[Rh(nbd)_2]SbF_6$	65 °C	none	100(60)
9	$[\{Rh(cod)Cl\}_2]$/*rac*-C_4-Tunaphos	RT	$AgSbF_6$	100(98)
10	$[\{Rh(cod)Cl\}_2]$/*rac*-BINAP	RT	$AgSbF_6$	100(99)
11	$[\{Rh(cod)Cl\}_2]/PPh_3$	RT	$AgSbF_6$	< 5
12	$[RhCl(PPh_3)_3]$	RT	$AgSbF_6$	< 5
13	$[\{Rh(cod)Cl\}_2]$/dppb	RT	$AgSbF_6$	< 5
14	$[\{Rh(cod)Cl\}_2]$/dppbO	RT	$AgSbF_6$	< 5
15	$[\{Rh(cod)Cl\}_2]$/*rac*-BICPO	RT	$AgSbF_6$	< 5

[a] All reactions were performed using 10 mol % Rh^I in 0.2 mmol scale. dppb = 1,4-bis(diphenylphosphanyl)butane, dppbO = 1,4-bis(diphenylphosphinite)butane. [b] Conversion was detected by GC, and isolated yield was reported in parentheses.

bis(diphenylphosphanyl)-1,1′-binaphthyl) was inactive towards the Alder–ene reaction. In contrast to our earlier report, *rac*-BINAP was found to be an efficient ligand in this new catalytic system for Rh-catalyzed Alder–ene reactions; 100 % conversion and 99 % yield were obtained within 5 min at room temperature by simply mixing $[\{Rh(cod)Cl\}_2]$ and *rac*-BINAP (Table 1, entry 10).[6] Further changes in catalysts and ligands showed that some systems did not work (Table 1, entries 11–15).[7]

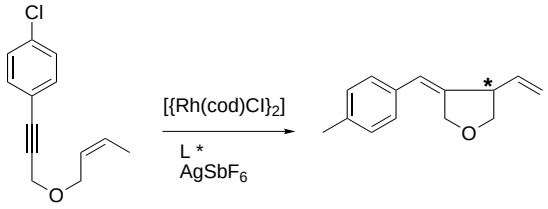
Encouraged by these results, we focused our studies on the asymmetric Rh-catalyzed Alder–ene reaction. All C_n-Tunaphos[5] ($n = 1$–6) were effective ligands, and highly enantioselective products (> 99 % *ee*) were obtained (Table 2, entries 1–6). It is noteworthy that extremely high enantioselectivities were achieved when (*S*)-C_3-, (*S*)-C_4-Tunaphos, and (*S*)-BINAP were used as ligands (Table 2, entries 3,4, and 8).

With the optimized conditions in hand, we screened the reaction with a variety of enyne substrates (Table 3). Using enantiomerically pure BINAP as the ligand, high enantioselectivities were achieved with most tested substrates (Table 3, entries 1–6). Reactions of an enyne bearing an aryl terminal group were completed within 20 min at room temperature; high yields and over 99 % *ee* were achieved. Enyne substrates with an alkyl group were more reactive than enyne substrates with an aryl terminus (Table 3, entries 8 and 9); these reactions were completed less than 5 min.

To broaden the substrate scope, we introduced ketone (Table 4, entries 1, and 2), ester (Table 4, entry 3), alcohol [Eq. (1)], and ether groups [Eq. (2); MOM = methoxymethyl] at the alkyne carbon terminus. As expected, high yields and enantioselectivities were obtained.

The vinyl propargyl ether **18** was obtained in high yield (91 %) and enantioselectivity (99.3 % *ee*) from the cycloiso-

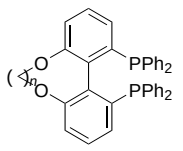
Table 2. Highly enantioselective Alder–ene reactions of enyne **1b** catalyzed by rhodium complex.[a]



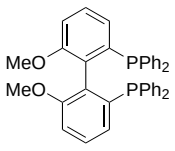
1b (+)-**2b**

Entry	L*	Conversion[b]	*ee* [%][c]
1	**3**	100	99.2
2	**4**	80	99.3
3	**5**	100	> 99.9
4	**6**	100	> 99.9
5	**7**	100	99.2
6	**8**	100	99.3
7	**9**	100	98.3
8	**10**	100	> 99.9

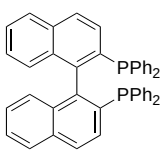
[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Conversion was detected by GC. [c] Determined by GC with chiral select 1000.



n = 1 (*S*)-C_1-Tunaphos **3**
n = 2 (*S*)-C_2-Tunaphos **4**
n = 3 (*S*)-C_3-Tunaphos **5**
n = 4 (*S*)-C_4-Tunaphos **6**
n = 5 (*S*)-C_5-Tunaphos **7**
n = 6 (*S*)-C_6-Tunaphos **8**



(*S*)-**9**



(*S*)-**10**

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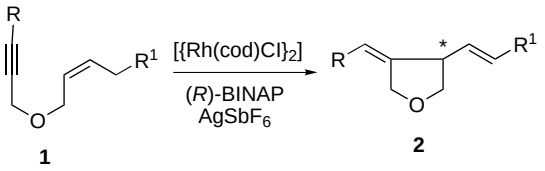
Table 3. Highly enantioselective Alder–ene reactions of enynes **1** catalyzed by a rhodium complex using BINAP as ligand.[a]

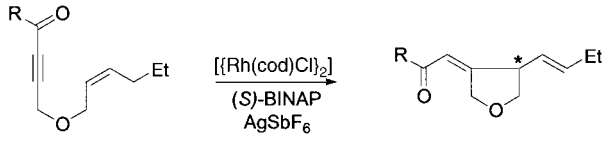


1 **2**

Entry	**1**	R	R^1	**2**	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	Et	(−)-**2a**	96	> 99.5
2	**1b**	Ph	H	(−)-**2b**	96	> 99.5
3	**1c**	C_6H_4(*o*-Cl)	H	(−)-**2c**	95	99.0
4	**1d**	C_6H_4(*m*-Cl)	H	(−)-**2d**	92	99.5
5	**1e**	C_6H_4(*p*-Cl)	H	(−)-**2e**	95	> 99.9
6	**1f**	C_6H_4(*p*-Me)	H	(−)-**2f**	94	99.9
7	**1g**	C_6H_4(*p*-CF_3)	H	(−)-**2g**	93	99.1
8	**1h**	Me	Me	(−)-**2h**	82	> 99.9
9	**1i**	*n*Bu	H	(−)-**2i**	89	> 99.9

[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Yield of isolated product. [c] Determined by GC and HPLC.

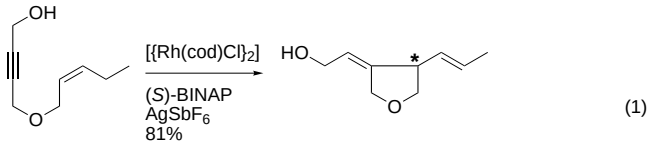
Table 4. Highly enantioselective Alder–ene reactions of functional enyne **11** catalyzed by rhodium in the presence of BINAP.[a]



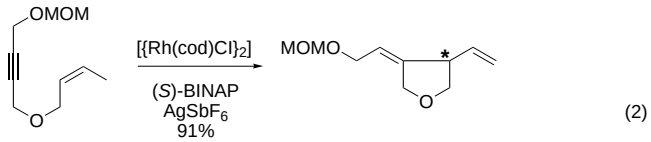
11 **12**

Entry	**11**	R	**12**	Yield [%][b]	*ee* [%][c]
1	**11a**	Me	(+)-**12a**	86	99.5
2	**11b**	Ph	(+)-**12b**	99	> 99.9
3	**11c**	EtO	(+)-**12c**	82	> 99.9

[a] All reactions were performed using 10 mol % Rh^I and 12 mol % BINAP in 0.2 mmol scale. [b] Yield of isolated product. [c] Determined by GC with chiral select 1000.

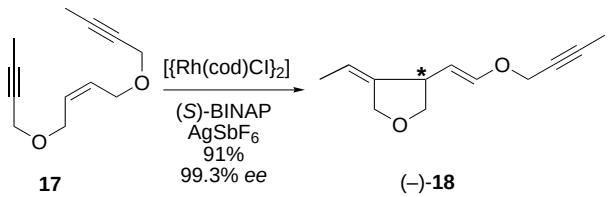


13 **(+)-14** (1)



15 **(+)-16** (2)

merization of yne–ene–yne **17** [Eq. (3)]. Since vinyl ethers and vinyl acetates are important functionalities in organic syntheses, we incorporated these groups by designing an array

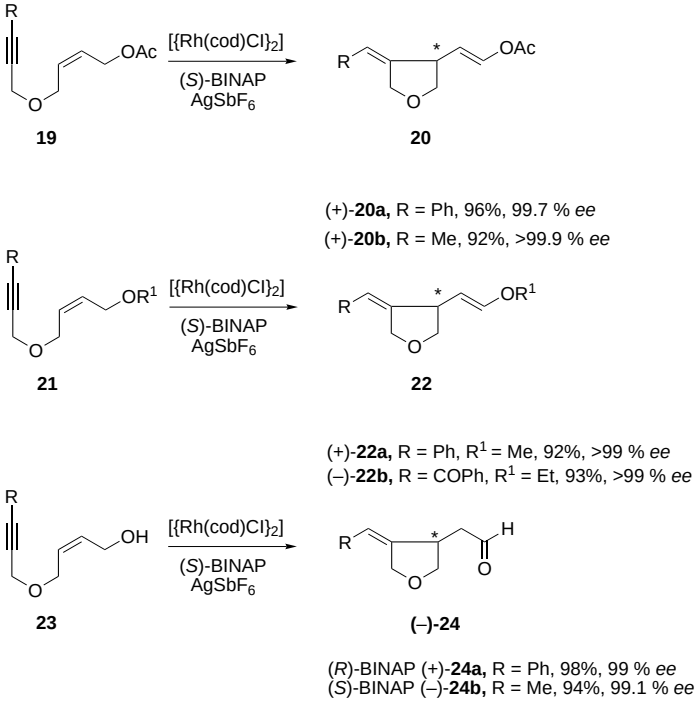


17 (−)-**18** (3)

of substrates (Scheme 1). In two cases, aldehydes were formed after the enynes cycloisomerization.

To test the catalytic efficiency of the reaction, a low catalyst loading was employed: In the presence of 1 mol % [{Rh(cod)Cl}$_2$] and 2 mol % (*S*)-BINAP, the cycloisomerization of **1h** was complete at room temperature within 2 min in 99 % conversion (turnover frequency (TOF): 1500 h^{-1}). The product (+)-**2h** was obtained in over 99.9 % *ee*. Further experimentation showed that the reaction could be done with lower catalyst loading. In the presence of 0.4 mol % [{Rh(cod)Cl}$_2$] and 0.8 mol % (*S*)-BINAP, this reaction was complete within 35 min with no decrease in enantioselectivity.

In conclusion, we have developed a highly efficient Rh-catalyzed Alder–ene reaction for preparing a variety of chiral



Scheme 1. Highly enantioselective Alder–ene reactions of enynes substituted at the allylic terminus.

tetrahydrofurans using an air-stable [{Rh(cod)Cl}$_2$] precursor with commercially available BINAP or the C_n-Tunaphos ligands. Functionalized tetrahydrofurans were obtained in high yields and over 99 % *ee* for all the substrates we tested. Syntheses of other functionalized carbocycles and heterocycles such as lactams and pyrrolidines are in progress and will be reported in due course.

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Experimental Section

The procedure for the asymmetric alder–ene reaction of **1b** catalyzed by rhodium (**2b**):[4] In a dried Schlenk tube, [{Rh(cod)Cl}$_2$] (4.9 mg, 0.01 mmol) and (*S*)-BINAP (13.8 mg, 0.022 mmol) were dissolved in freshly distilled 1,2-dichloroethane (2 mL), then freshly prepared **1b** (37.2 mg, 0.2 mmol) was added to the solution at room temperature under nitrogen. After the mixture had been stirred for 1 min, $AgSbF_6$ (0.04 mmol) was added, and the reaction was complete within 5 min. The reaction mixture was directly subjected to column chromatography. Compound **2b** (35.8 mg, 96% yield, >99.9% *ee*) was obtained. The *ee* value was determined by GC with chiral select 1000 at 150 °C. $[\alpha]_D = 23.85$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$–7.29 (m, 2H), 7.22–7.18 (m, 1H), 7.12–7.10 (m, 2H), 6.24(s, 1H), 5.70–5.65 (m, 1H), 5.2–5.16 (m, 2H), 4.77 (d, $J = 14.0$ Hz, 1H), 4.64 (d, $J = 14.0$ Hz, 1H), 4.15 (t, $J = 7.7$ Hz, 1H), 3.60–3.48 ppm (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 144.1$, 137.6, 137.1, 128.9, 128.3, 127.1, 122.5, 118.1, 72.8, 70.7, 51.1 ppm.

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[6] Using [{Rh(BINAP)Cl}$_2$] as catalyst precursor and $AgSbF_6$ as additive, the reaction of **1a** yielded **2a** in less than 5% conversion within 20 min at room temperature. This was consistent with the low reactivity observed in ref. [4b].

[7] Compared with our earlier system, [{Rh(dppb)Cl}$_2$] and [{Rh(dppbo)Cl}$_2$] were effective catalytic precursors for the Alder–ene reaction.[4] This clearly indicates the differences between our previous catalyst and the new catalytic system.

Radical Carboazidation of Alkenes: An Efficient Tool for the Preparation of Pyrrolidinone Derivatives**

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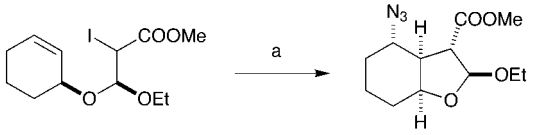
The use of free radical reactions in multistep synthesis has steadily increased over the last years, mainly because of their compatibility with a large number of functional groups and their high potential for performing sequential transformations.[1] Recently, we developed a novel method that allows the efficient formation of carbon–nitrogen bonds by reaction of radicals with sulfonyl azides.[2,3] Since sulfonyl azides possess an electrophilic character, this azidation process is particularly efficient with nucleophilic radicals and does not occur with ambiphilic or electrophilic radicals. For instance, the cyclization depicted in Scheme 1 can be performed by



Scheme 1. Radical cyclization–azidation process. a) $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), *t*BuON=NO*t*Bu (3 mol%), benzene.

mixing all the reagents at once under relatively concentrated conditions (0.5 M substrate) without the formation of even traces of noncyclized products.

This observation let us speculate that the reaction could also be accomplished in intermolecular processes. Here we report our first results on the intermolecular addition of radicals to unactivated alkenes followed by azidation. This reaction sequence represents a formal carboazidation of alkenes, and it is the key process for an efficient three-component synthesis of pyrrolidinone, pyrrolizidinone, and indolizidinone derivatives.

In a first series of experiments, we tested the feasibility of the reaction starting from terminal alkenes and different radical precursors that are known to be efficient in radical atom or group transfer reactions (Scheme 2, see also Table 1).[4] A one-pot procedure similar to that used for intramolecular reactions gave promising results: The radical precursors are treated with phenylsulfonyl azide (3 equiv),

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