Recent advances in enantioselective [2 + 2 + 2] cycloaddition

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Enantioselective cycloaddition using chiral transition metal catalysts is an atom-economical and efficient synthetic tool for the construction of chiral carbo- and heterocyclic skeletons. This short account discloses our recent results of inter- and intramolecular enantioselective [2 + 2 + 2] cycloadditions of alkyne and/or alkene moiety(ies). Chiral iridium complexes catalyzed the alkyne trimerization for the generation of axial chirality(ies), and chiral rhodium ones catalyzed alkyne–alkyne–alkene cyclization for the generation of a quaternary carbon including spirocyclic system.

Introduction

Transition metal-catalyzed [2 + 2 + 2] cycloaddition of unsaturated motifs, such as alkynes and alkenes, is the most atom-economical protocol for the synthesis of six-membered ring systems, and various types of substrates have been submitted to the inter-, and intramolecular reactions.[1] Among them, cyclotrimerization of alkynes was the first and most developed cycloaddition: thermal [2 + 2 + 2] cycloaddition of acetylene for the formation of benzene was already ascertained in the mid-19th century. The first transition metal complex-mediated [2 + 2 + 2] cycloaddition of acetylene was reported by Reppe *et al.* using a nickel complex.[2] From the synthetic point of view, Yamazaki and co-workers's report of cobalt complex-mediated reaction of diphenylacetylene for the syntheses of hexa-substituted benzene should be recognized as a pioneering work.[3] Vollhardt and co-workers's report of cobalt complex-catalyzed reactions and their use in natural product synthesis drastically raised the significance of [2 + 2 + 2] cycloaddition in organic synthesis.[4] Since then, various transition metal complexes, mainly from group 8–10 elements, such as rhodium, nickel, and palladium, have been reported as efficient catalysts. However, enantioselective cycloaddition had been limited to two examples: Mori and co-workers reported a chiral nickel complex-catalyzed intermolecular reaction of a triyne with acetylene, which generated an asymmetric carbon at the benzylic position of a formed benzene ring by enantiotopic group selection.[5] Starý and co-workers reported a chiral cobalt complex-catalyzed intramolecular cycloaddition of a triyne, which generated helical chirality.[6] These are pioneering works of the enantioselective [2 + 2 + 2] cycloaddition of alkynes; however, their enantioselectivity, yield, and generality of substrates were not sufficient.

In 2004, three groups, including ours, independently reported enantioselective [2 + 2 + 2] cycloadditions using different transition metal catalysts in succession, where axial chirality(ies) was/were generated along with benzannulation.[7] This paper summarizes our strategy and achievements in several enantioselective [2 + 2 + 2] cycloadditions.

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Iridium-catalyzed reaction of alkynes

We had examined iridium-catalyzed carbonylative coupling of [2 + 2 + 1] cycloaddition. In the reaction of enynes using Ir-tolBINAP


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(2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl) catalyst, an enantioselective Pauson–Khand-type reaction proceeded to give chiral bicyclic cyclopentenones.[8] In the reaction of diynes using Ir-DPPP (1,3-bis(diphenylphosphino)propane) catalyst, carbonylative coupling of diynes gave bicyclic cyclopentadienones.[9] In the latter reaction, a hexa-substituted benzene derivative, which was derived from intermolecular [2 + 2 + 2] cycloaddition of two diynes, was formed as a by-product [eqn (1)]. These results prompted us to examine an iridium-catalyzed [2 + 2 + 2] of alkynes for the construction of highly congested benzene compounds.[10]

(1)
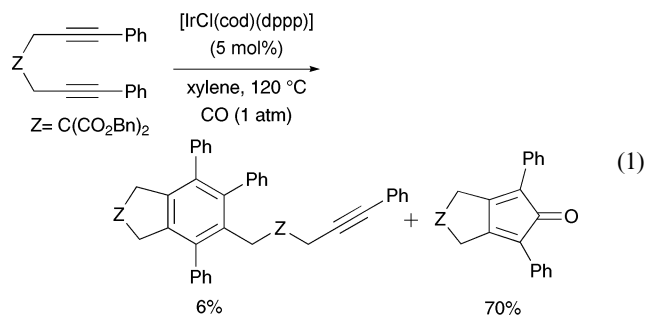
We assumed that the intermolecular coupling of diynes, possessing *ortho*-substituted aryl groups on their termini, and monoalkynes would provide teraryl compounds with two axial chiralities. In the reaction of symmetrical diynes and symmetrical monoalkynes, C_2 symmetrical chiral compounds will be provided (Scheme 1).

Scheme 1
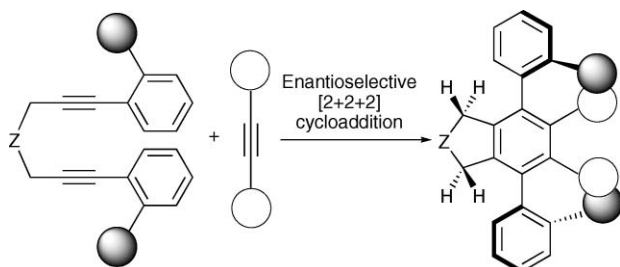
Intermolecular reaction of diynes with monoalkynes

After screening various catalysts, a chiral iridium complex, which was prepared *in situ* from [IrCl(cod)]$_2$ and MeDUPHOS (1,2-bis(2,5-dimethylphospholano)benzene), achieved the highly diastereoselective and enantioselective [2 + 2 + 2] cycloaddition (Table 1).[7b] In the reaction of oxygen, nitrogen, and carbon-tethered 1,6-diynes with naphthyl groups at their termini and 1,4-dimethoxybut-2-yne (**2a**), C_2 symmetrical teraryl compounds with two axial chiralities were obtained. Small amounts of the catalyst also realized excellent enantioselectivity (entry 2). In place of the naphthyl group, other *ortho*-substituted aryl ones, such as 2-methylphenyl and 2-cholorophenyl groups, could also be installed as substituents at the alkyne termini, and excellent *dl/meso* ratio and enantioselectivity were achieved.

A proposed mechanism of asymmetric induction is shown in Scheme 2. The oxidative coupling of the chiral iridium complex with 1,6-diyne provides iridacyclopentadiene, where two axial

**Table 1** Intermolecular reaction of symmetrical diynes and monoalkynes
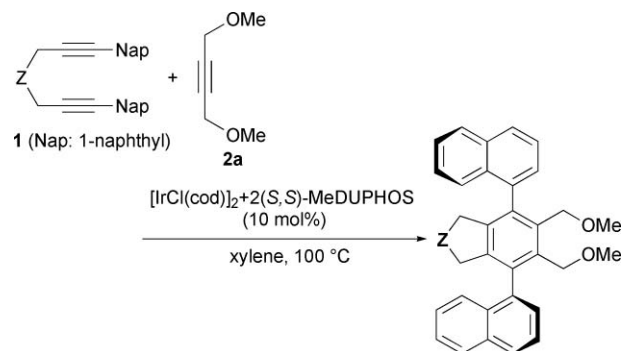
Entry	Z	Yield (%)	dl/meso	Ee (%)
1	O	83	> 95/5	>99
2[a]	O	84	98/2	99
3	NTs	92	> 95/5	99
4	CH₂	96	> 95/5	>99

[a] [IrCl(cod)]$_2$ (0.5 mol%) and MeDUPHOS (1 mol%) were used.
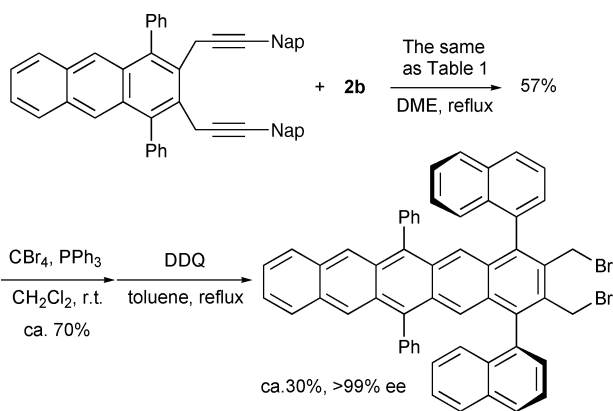
Scheme 2
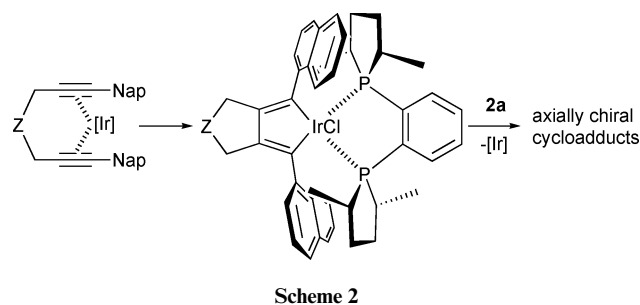
chiralities are induced by steric hindrance between methyl groups of MeDUPHOS and naphthyl ones of the diyne.

The reaction of but-2-yne-1,4-diol (**2b**) and but-2-yn-1-ol (**2c**) efficiently proceeded even at room temperature in 1,2-dimethoxyethane, and axially chiral diol and mono-ol were obtained [eqn (2)].[11] Using the present iridium-catalyzed [2 + 2 + 2] cycloaddition, we first synthesized an axially chiral substituted pentacene derivative (Scheme 3).[12]

(2)

R= CH₂OH: *dl/meso*= >95/5, >99% ee
R= Me: >90% de, >99% ee
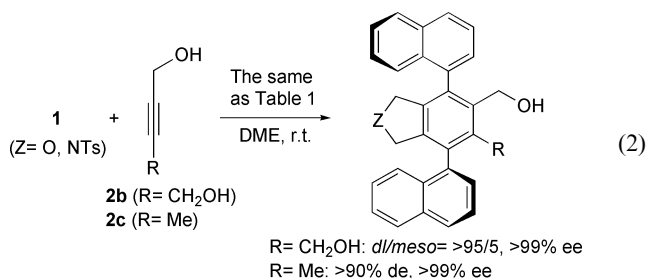
In addition to monoalkynes with oxygen atom(s) at their propargylic position(s), those with a nitrogen atom operated as a good coupling partner for diynes, and an axially chiral amine and amino alcohol were obtained in excellent diastereo- and enantioselectivity [eqn (3)].[11]

Scheme 3

$$(3)$$

1
(Z= CH$_2$, O)

2d (R= Me)
2e (R= CH$_2$OH)

>90% de, >99% ee
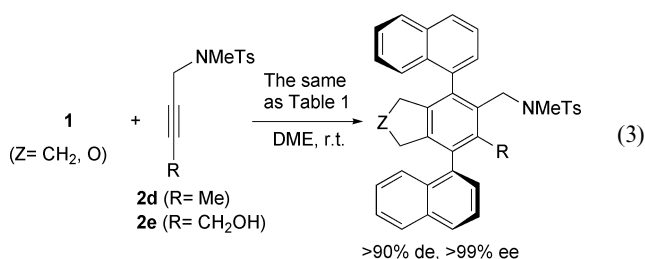
Intramolecular reaction of triynes

We next examined an intramolecular reaction of triynes with *ortho*-substituted aryl groups at their termini. In *ortho*-binaphthylbenzene itself, the single bonds between two aromatic rings are freely rotated even at room temperature; however, in the tricyclic system, two adjacent axial chiralities were generated due to the existence of two fused rings (Table 2).[13] Ir-MeDUPHOS catalyst also worked well, and the corresponding *ortho*-diarylbenzene derivatives were obtained with high enantiomeric excess.

Consecutive intermolecular reaction of poly-ynes

We expanded our notion to consecutive reaction, and submitted oxygen, nitrogen, and ethylene-tethered tetraynes, where two 1,6- or 1,7-diyne moieties were connected with a 1,4-naphthalene

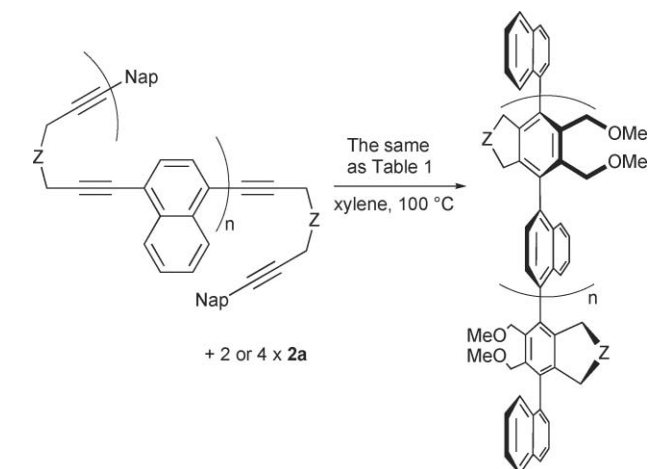**Table 2** Intramolecular reaction of triynes

Ar: *ortho*-substituted aryl
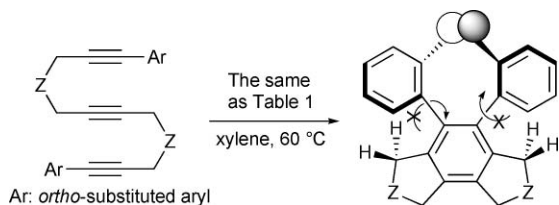
Entry	Z	Ar	Yield (%)	*dl*/*meso*	Ee (%)
1	O	1-Naphthyl	82	5/1	90
2[a]	O	1-Anthracenyl	68	> 20/1	87
3	O	2-Cl-4-NO$_2$-Ph	90	12/1	90
4	NTs	4-MeO-1-Naphthyl	89	2/1	*ca.* 95

[a] The reaction was examined at room temperature.

spacer, to the [2 + 2 + 2] cycloaddition (Table 3).[14] The penta-aryl compounds with consecutive four axial chiralities were obtained with almost perfect enantioselectivity (entries 1–3). Even the reaction of an octayne efficiently proceeded, and the corresponding nona-aryl compound with consecutive eight axial chiralities was obtained in high yield with more than 99% ee (entry 4). A dendritic compound with six axial chiralities was also obtained in one pot from a hexayne with 1,3,5-triethynylbenzene core [eqn (4)].


$$(4)$$

45%, >99% ee
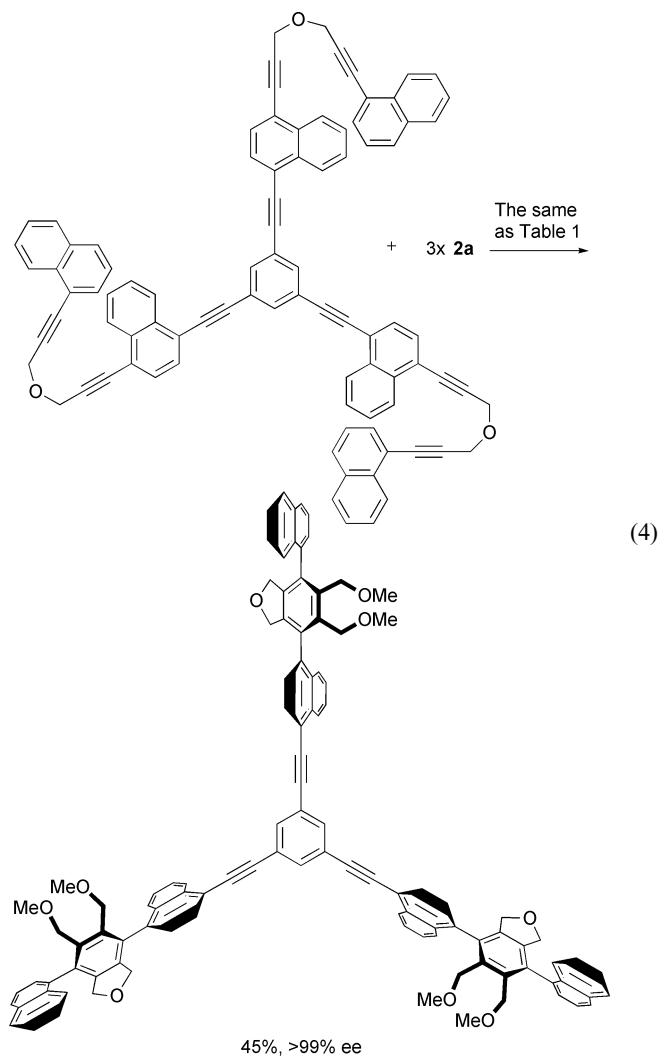
In the reactions mentioned above, axial chiralities were generated between the formed benzene ring and the aromatic ring in the substrate. Next, the reaction of tetraynes with a 1,3-diyne moiety was examined, where axial chirality is generated between the two benzene rings formed in a biaryl system.[15] Iridium-CHIRAPHOS (2,3-bis(diphenylphosphino)butane) complex was the choice of chiral catalyst, and good enantioselectivity was achieved using TBS-protected but-2-yne-1,4-diol **2f** as a coupling partner [eqn (5)].[12]

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Table 3 Consecutive intermolecular reaction of tetraynes and an octayne

+ 2 or 4 × **2a**

Entry	*n*	Z	Yield (%)	Ee (%)
1	1	O	89	>99
2	1	NTs	76	>99
3[a]	1	*cis*-CH=CH[b]	55[c]	>99
4	3	O	92	>99

[a] The reaction was examined at 140 °C. [b] (Z,Z) : (Z,E) : (E,E) = 40 : 10 : 1. [c] [2 + 2 + 2] Cycloadduct was aromatized into a penta-naphthalene using DDQ, and the yield of 2 steps is based on (Z,Z)-isomer of the tetrayne.

Z= C(CO₂Et)₂: 49%, 89% ee

Z= NTs: 76%, 86% ee

(Ee was determined as diols (R = H))

(5)
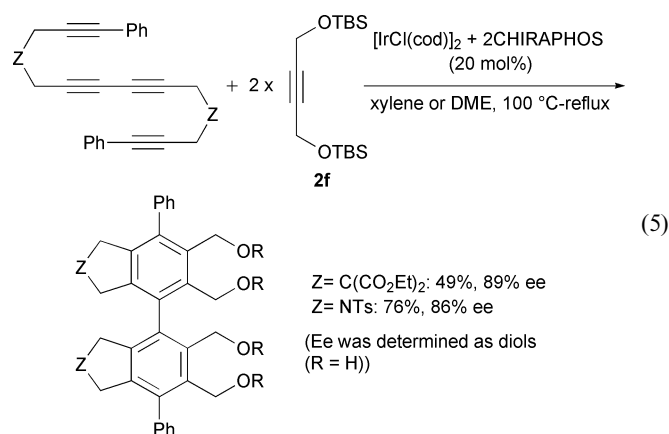
Consecutive intramolecular reaction of hexaynes

An intramolecular and consecutive [2 + 2 + 2] cycloaddition of hexaynes with 1,3-diyne moiety is our most recent challenge. The acyclic and linear molecules were doubly cyclized to biaryl products. As a result, axial chirality was generated between the two benzene rings formed with excellent enantioselectivity using iridium-xylylBINAP (2,2′-bis(di(3,5-xylyl)phosphino)-1,1′-binaphthyl) catalyst [eqn (6)].[12]

Axial chirality in a biaryl system is an important asymmetric skeleton because it is found in efficient chiral ligands and naturally occurring products.[16] As for catalytic and enantioselective synthesis, aryl–aryl couplings, such as nickel-catalyzed Kumada coupling,[17] copper-catalyzed oxidative coupling of 2-naphthol derivatives,[18] and palladium-catalyzed Suzuki coupling,[19] were efficient and established protocols. Therefore, the enantioselective [2 + 2 + 2] cycloaddition of alkynes is a new approach and gives various types of axially chiral multicyclic compounds.


Z= O, R= Ph: 81%, 97% ee

Z= NTs, R= Ph: 52%. 98% ee

Z= O, R= *i*-Pr: 69%, 96% ee

(6)
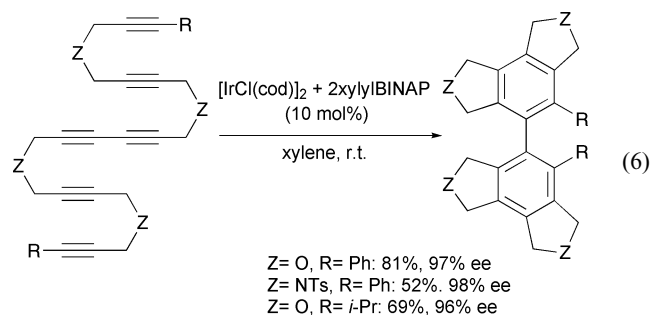
Rhodium-catalyzed reaction of two alkynes and an alkene

Rhodium complexes catalyze various types of cycloadditions, which are represented by [*l* + *m* + *n*] ones.[20] Among them, cationic rhodium complexes are generally more active than the corresponding neutral ones, and many unique and synthetically useful transformations have been achieved.[21] In particular, they have significant advantage in enantioselective reactions because of their stronger coordination to unsaturated motifs, which could achieve higher stereoselectivity. For instance, oxidative coupling of chiral a Rh(I) complex to an enyne is a common scheme for the generation of an asymmetric stereocenter at the ring-fusion carbon of a bicyclic metallacycle (Scheme 4). When R^3 is vinyl, 1,3-allylic rearrangement along with ring expansion and reductive elimination gives [4 + 2] cycloadduct (path **A**).[22] When R^3 is methyl, β-hydrogen elimination and reductive elimination gives ene-type product (path **B**).[23] The CO insertion and reductive elimination gives [2 + 2 + 1] cycloadduct (path **C**, Pauson–Khand-type reaction).[24] We considered that the [2 + 2 + 2] cycloaddition of enynes with a substituent at their olefinic moiety (R^2 is not hydrogen) and alkynes provides an efficient protocol for the construction of a quaternary carbon at the ring-fused position (path **D**).

Intermolecular reaction of enynes with monoalkynes

We screened the cationic rhodium-BINAP derivative complexes as a catalyst for the [2 + 2 + 2] cycloaddition of enynes with monoalkynes because they were already known to work well as catalysts in enantioselective formation of a bicyclic metallacycle (path **B** and **C**).[23b,c,24] the Rh-tolBINAP complex efficiently catalyzed the reaction of various enynes with tethers (Z), substituents at their alkyne termini (R^1), and olefinic moiety (R^2) with monoalkyne **2a**,[25] and the corresponding bicyclic cyclohexa-1,3-dienes were obtained with good to excellent enantiomeric excess (Scheme 5).[26]

In the case of prop-2-yn-1-ol, namely an unsymmetrical alkyne, the regioselectivity was not very high but both regioisomers were obtained in excellent enantiomeric excess [eqn (7)].[26] Acetylene was also inserted, where low partial pressure of acetylene was required for the high yield [eqn (8)].[26]
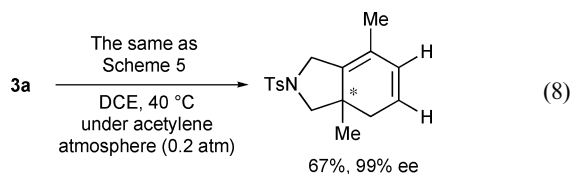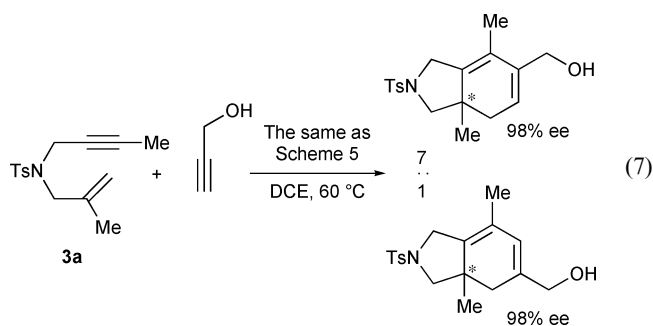
Scheme 4

Scheme 5

(7)

(8)
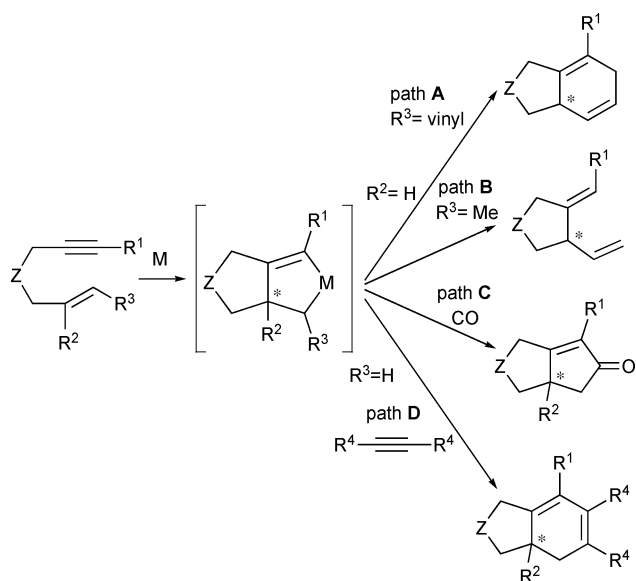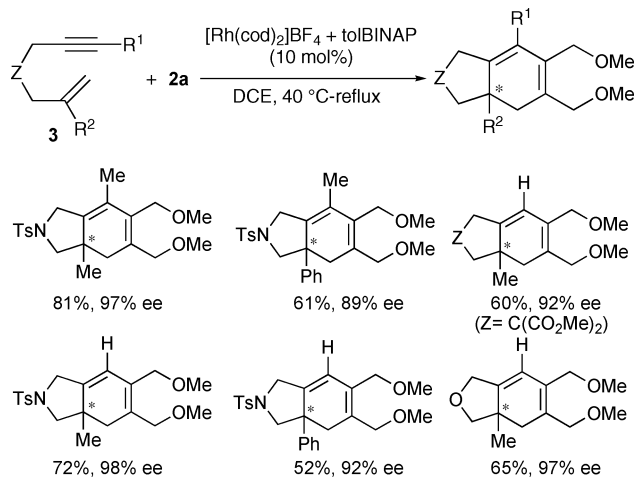
Table 4 Intramolecular reaction of (E)-enediynes[a]

Entry	R^1	R^2	Z	Z'	Yield (%)	Ee (%)
1	E	E	CE_2	CE_2	72	98
2	Me	Me	CE_2	CE_2	81	97
3	E	Me	CE_2	CE_2	82	98
4	n-Bu	n-Bu	NTs	NTs	90	89
5	Me	Me	CE_2	NTs	89	95
6	Me	$BnOCH_2$	CE_2	O	66	91

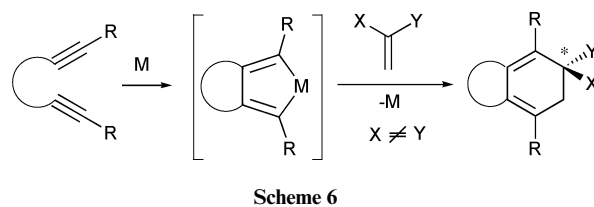[a] $E = CO_2Me$.

Intramolecular reaction of enediynes

We further examined an intramolecular version of alkyne–alkene–alkyne coupling: we chose a carbon-tethered symmetrical (E)-enediyne with unsubstituted alkyne termini as a model substrate, which provides tricyclic compounds with two adjacent asymmetric carbons [eqn (9)].[27] As a result, the choice of chiral ligands was very important, and only H_8-BINAP (2,2'-bis(biphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl) achieved good yield and enantiomeric excess. Other BINAP derivatives, such as tolBINAP and BINAP, gave miserable yield and enantiomeric excess.
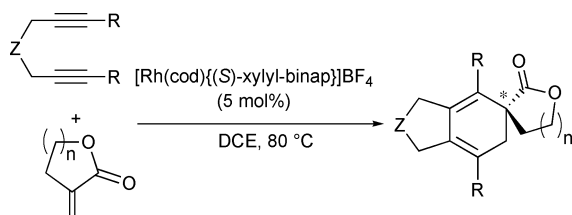

(9)

tolBINAP: 15%, <2% ee
BINAP: 59%, 19% ee
H_8-BINAP: 75%, 76% ee
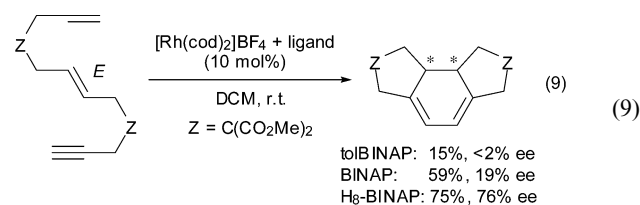
Various carbon-tethered symmetrical (E)-enediynes with substituents at their alkyne termini were transformed into the corresponding C_2-symmetrical tricyclic compounds in excellent enantiomeric excess (Table 4, entries 1 and 2). Carbon-tethered unsymmetrical enediynes, nitrogen-tethered one, and unsymmetrical enediynes with carbon- and nitrogen- or oxygen-tethers also underwent the highly enantioselective intramolecular [2 + 2 + 2] cycloaddition (entries 3–6).[28]

Intermolecular reaction of diynes with alkenes

We next changed the coupling combination from enyne with alkyne to diyne with alkene. In this case, an asymmetric stereocenter is generated at the ring carbon atom when 1,1-disubstituted and unsymmetrical alkene is inserted into the metallacyclopentadiene intermediate (Scheme 6).

Scheme 6

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Table 5 Intermolecular reaction of diynes and α-methylenelactones

Entry	Z	R	n	Yield (%)	Ee (%)
1	C(CO$_2$Bn)$_2$	H	1	81	95
2	C(CO$_2$Bn)$_2$	Me	1	94	99
3	NTs	Me	1	92	97
4	O	Me	1	50	92
5	C(CO$_2$Bn)$_2$	Me	2	93	98
6	C(CO$_2$Bn)$_2$	Me	3	88	97

Table 6 Intermolecular reaction of a diyne and acrylate derivatives
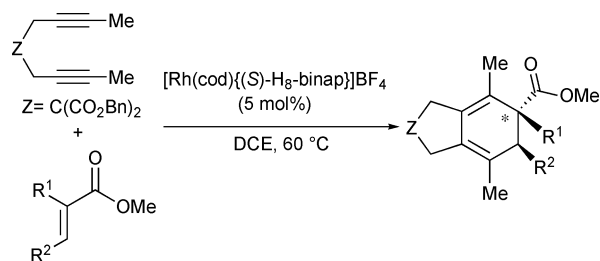
| Entry	R^1	R^2	Yield (%)	Ee (%)
1	Me	H	92	>99
2	Ph	H	54	93
3	H	H	87	91
4	H	Me	77	96

We chose α-methylene lactones as alkenes because they give spirocyclic compounds. The Rh-xylylBINAP complex efficiently catalyzed the reaction, and good to excellent enantioselectivity was achieved in the asymmetric construction of the spirocyclic system (Table 5).[29]

Acrylate derivatives were also good coupling partners: an asymmetric quaternary, tertiary, and two adjacent tertiary carbon stereocenters were readily generated at the ring carbon atom(s) (Table 6).[29]

The asymmetric [2 + 2 + 2] cycloaddition of unsymmetrical diynes with norbornene derivatives, namely symmetrical alkenes was also realized: the Rh-DIFLUORPHOS (5,5′-bis(diphenyl-phosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole) complex catalyzed the highly enantioselective coupling of diynes, possessing an ester functionality at their alkyne terminus and norbornene derivatives (Table 7).[30]

Conclusion

We developed iridium- and rhodium-catalyzed enantioselective [2 + 2 + 2] cycloadditions. The former realized various types of alkyne trimerization along with the generation of axial chiralities. In particular, we demonstrated the synthesis of chiral poly-aryl compounds and a pentacene derivative. The latter realized inter- and intramolecular couplings of two alkynes and an alkene.

Table 7 Intermolecular reaction of unsymmetrical diynes and norbornene
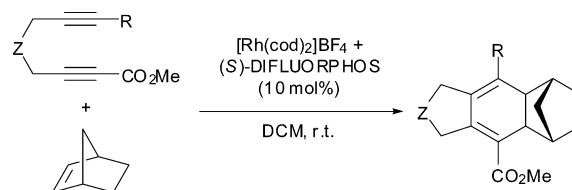
Entry	Z	R	Yield (%)	Ee (%)
1	NTs	Ph	83	96
2	O	Ph	51	95
3	C(CO$_2$Me)$_2$	Ph	71	91
4	C(CO$_2$Me)$_2$	Me	82	99

We mainly focused on the construction of a quaternary carbon stereocenter, including a spirocyclic system. These results opened up a new dimension of enantioselective [2 + 2 + 2] cycloaddition, and will be an important synthetic protocol in asymmetric synthesis.

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