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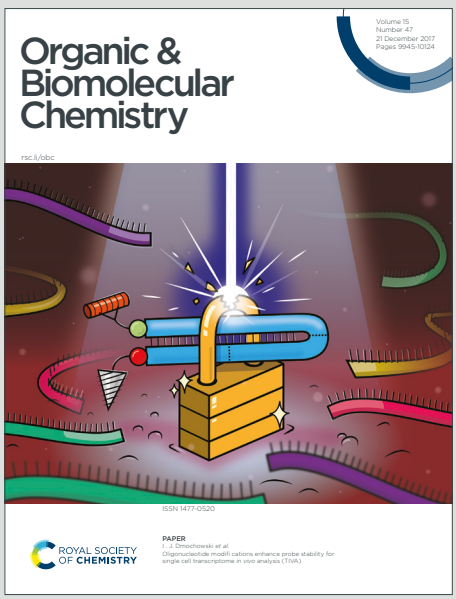

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ARTICLE

Rh(I)-catalyzed enantioselective and scalable [4+2] cycloaddition of 1,3-dienes with dialkyl acetylenedicarboxylates

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An asymmetric intermolecular [4+2] cycloaddition of 1,3-dienes with dialkyl acetylenedicarboxylates, which was catalyzed by rhodium(I) - chiral phosphoramidite complex, was developed. This protocol provided a highly enantioselective access to prepare the carbonyl substituted cyclohexa-1,4-dienes with up to 96% yield and > 99% ee. Notably, a cycloaddition on 10 g scale gave the product in 92% yield and with 99% ee, which showed a great potential in the scale-up synthesis of carbonyl substituted cyclohexa-1,4-dienes. In addition, the oxidative aromatizations and hydrolysis of the products were also investigated.

Introduction

Carbonyl substituted cyclohexa-1,4-dienes have received increasing attentions due to their extensive applications in organic chemistry. As versatile functional units, the carbonyl substituted cyclohexa-1,4-diene derivatives have been utilized to construct the selective fluorogenic probes for the thiols in peptides and proteins (Figure 1, **1a**),[1] chiral diene ligands in the rhodium catalyzed asymmetric transformations (Figure 1, **1b**),[2] and hydrogen sources in the palladium-catalyzed hydrogenation of olefins (Figure 1, **1c**).[3] More importantly, the functional groups in the carbonyl substituted cyclohexa-1,4-dienes can be modified easily to construct other significant fragments. Inspired by these modifications, a diversity of the carbonyl substituted cyclohexa-1,4-dienes (Figure 1, **1d** - **1i**) have been used as important synthetic intermediates in the natural product synthesis.[4-10]

As promising moieties in organic chemistry, the cyclohexa-1,4-dienes are mainly prepared through the Birch reductions of aromatic rings,[11] the [4+2] cycloadditions of 1,3-dienes with alkynes,[12] the oxidations of phenols,[13] and the electroreductions of aromatic compounds.[14] Among these methods, the [4+2] cycloaddition reactions might be the appealing synthetic methods due to their mild conditions, high functional group tolerance, and good atom economy.

Actually, several [4+2] cycloaddition reactions have been employed for the catalytic asymmetric synthesis of substituted cyclohexa-1,4-dienes in intramolecular or intermolecular manners. As a pioneering study, Livinghouse and co-workers have reported an example of asymmetric synthesis of the trim-

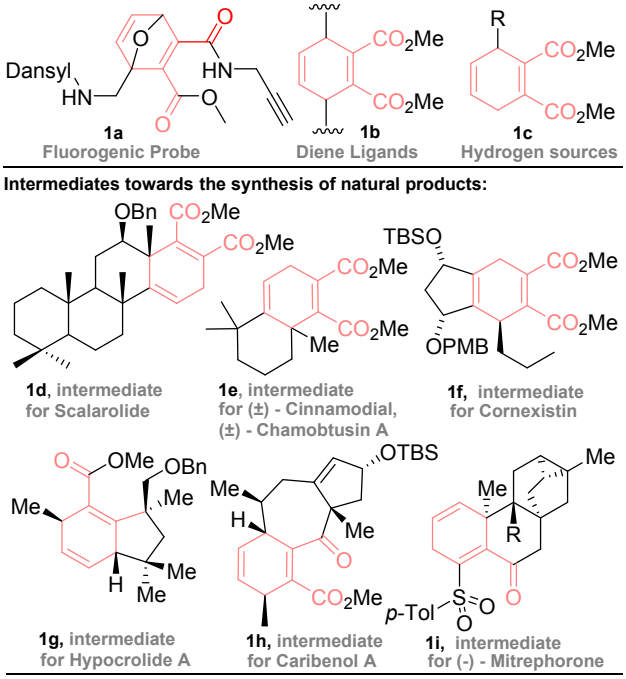

Figure 1 Representative compounds containing substituted cyclohexa-1,4-dienes.

-ethylsilyl substituted cyclohexa-1,4-diene, which suffered from an intramolecular [4+2] cycloisomerization reaction catalyzed by Rh(I)-(+)-DIOP complex with giving 87% ee (Scheme 1, A).[15] After that, Gilbertson and co-workers realized a similar cycloisomerization of dieneynes in the present of chiral Rh(I)-bisphosphine complexes with up to 95% ee (Scheme 1, A).[16] Next, Mikami and co-workers disclosed that the chiral diene-Rh(I)-chiral diphosphine complex was a highly efficient catalyst for the intramolecular [4+2] cycloaddition with up to 98% ee (Scheme 1, A).[17] Notably, Hayashi and co-workers also established highly efficient Rh(I)-chiral diene catalysts for the intramolecular [4+2] cycloaddition with up to > 99% ee (Scheme

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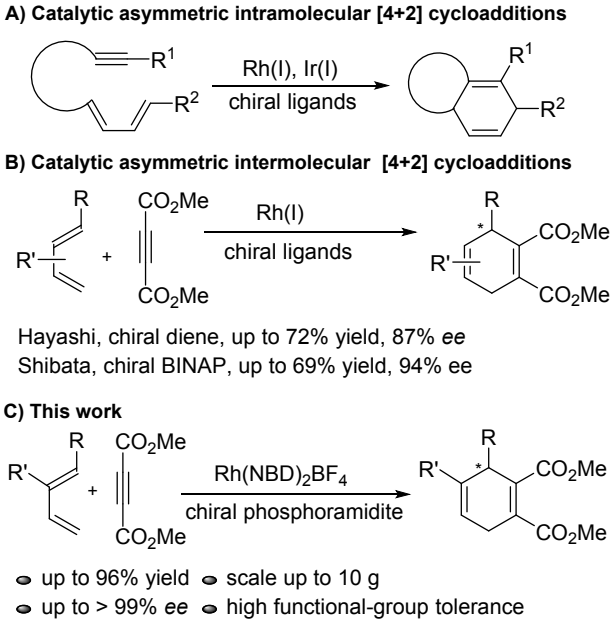


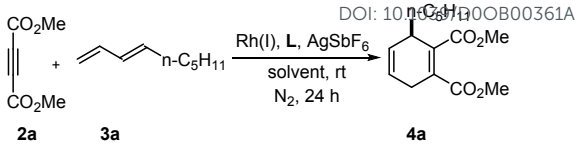
Scheme 1 Catalytic asymmetric synthesis of substituted cyclohexa-1,4-dienes.

1, A).[18] As a breakthrough, his catalytic system could also be used for two examples in the intermolecular [4+2] cycloadditions of 1,3-dienes and dimethyl acetylenedicarboxylate with up to 87% ee (Scheme 1, B). Recently, Shibata and co-workers presented a Rh(I)-BINAP catalyzed intermolecular [4+2] cycloaddition with good enantioselectivities, in which one example achieved the high enantioselectivity (94% ee) (Scheme 1, B).[19] Compared with the intramolecular [4+2] cycloadditions, the intermolecular cycloadditions constructed the substituted cyclohexa-1,4-dienes through convergent synthesis, which circumvented extra synthetic steps to connect the diene and alkyne moieties to prepare the enynes in the intramolecular cycloadditions. To our knowledge, only two reports focused on the asymmetric intermolecular [4+2] cycloadditions, and they have only achieved moderate to good enantioselectivities with limited substrates and functional groups. In fact, accessing the practical and scalable asymmetric intermolecular [4+2] cycloaddition has remained an unmet challenge. Herein, we report a catalytic asymmetric cycloaddition of 1,3-dienes and dialkyl acetylenedicarboxylates catalyzed by Rhodium(I)-chiral phosphoramidite complex with excellent enantioselectivies and good functional group compatibility.

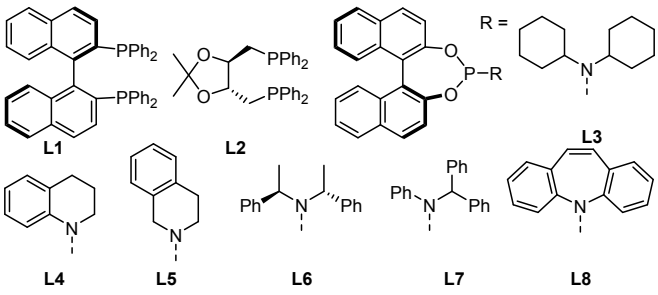
Results and discussion

To begin our investigations, we opted for the dimethyl acetylenedicarboxylate **2a** and diene **3a** as model substrates for this [4+2] cycloaddition in toluene at 25 °C (Table 1). We initially selected the $[Rh(COD)Cl]_2$ as the rhodium catalyst and screened several chiral ligands (Table 1, entry 1-8). Fortunately, the chiral phosphoramidite ligand **L5**, which was reported by Feringa group,[20] has proved to be effective in this asymmetric transfor-

Table 1 Optimization of reaction conditions[a]



2a 3a 4a



Entry	Rh(I)	L	Solvent	Yield[b] %	Ee[c] %
1	$[Rh(COD)Cl]_2$	**L1**	Toluene	trace	--
2	$[Rh(COD)Cl]_2$	**L2**	Toluene	N.R.	--
3	$[Rh(COD)Cl]_2$	**L3**	Toluene	16	2
4	$[Rh(COD)Cl]_2$	**L4**	Toluene	15	0
5	$[Rh(COD)Cl]_2$	**L5**	Toluene	77	98
6	$[Rh(COD)Cl]_2$	**L6**	Toluene	N.R.	--
7	$[Rh(COD)Cl]_2$	**L7**	Toluene	N.R.	--
8	$[Rh(COD)Cl]_2$	**L8**	Toluene	67	54
9	$Rh(COD)_2BF_4$	**L5**	Toluene	82	96
10	$[Rh(COE)Cl]_2$	**L5**	Toluene	71	98
11	$[Rh(NBD)Cl]_2$	**L5**	Toluene	30	98
12	$Rh(NBD)_2BF_4$	**L5**	Toluene	96	99
13	No Rh(I)	**L5**	Toluene	trace	--
14[d]	$Rh(NBD)_2BF_4$	**L5**	Toluene	59	99
15[e]	$Rh(NBD)_2BF_4$	**L5**	Toluene	3	85
16[f]	$Rh(NBD)_2BF_4$	**L5**	Toluene	12	13
17	$Rh(NBD)_2BF_4$	**L5**	DCE	89	95
18	$Rh(NBD)_2BF_4$	**L5**	Et_2O	7	87
19	$Rh(NBD)_2BF_4$	**L5**	THF	N.R.	--
20	$Rh(NBD)_2BF_4$	**L5**	CH_3CN	N.R.	--

[a] Reaction conditions: **2a** (0.2 mmol), **3a** (0.6 mmol), Rh(I) (10 mol%), **L** (12 mmol%) and $AgSbF_6$ (20 mol%) in solvent (3 mL) under N_2 at 25 °C. [b] Isolated yields. [c] Determined by HPLC. [d] Open to air. [e] H_2O (5 μL) was added. [f] No $AgSbF_6$. Rh(I) = rhodium(I) complexes. DCE = 1,2-Dichloroethane. Et_2O = Diethyl ether. THF = Tetrahydrofuran.

-mation, providing a good yield (77%) with an excellent enantioselectivity (98% ee) (Table1, entry 5). Although the yield was a weak point for improvement, the good asymmetric induction still provided a clue for the further screening. With the optimal ligand **L5** in hand, we investigated the effect of different

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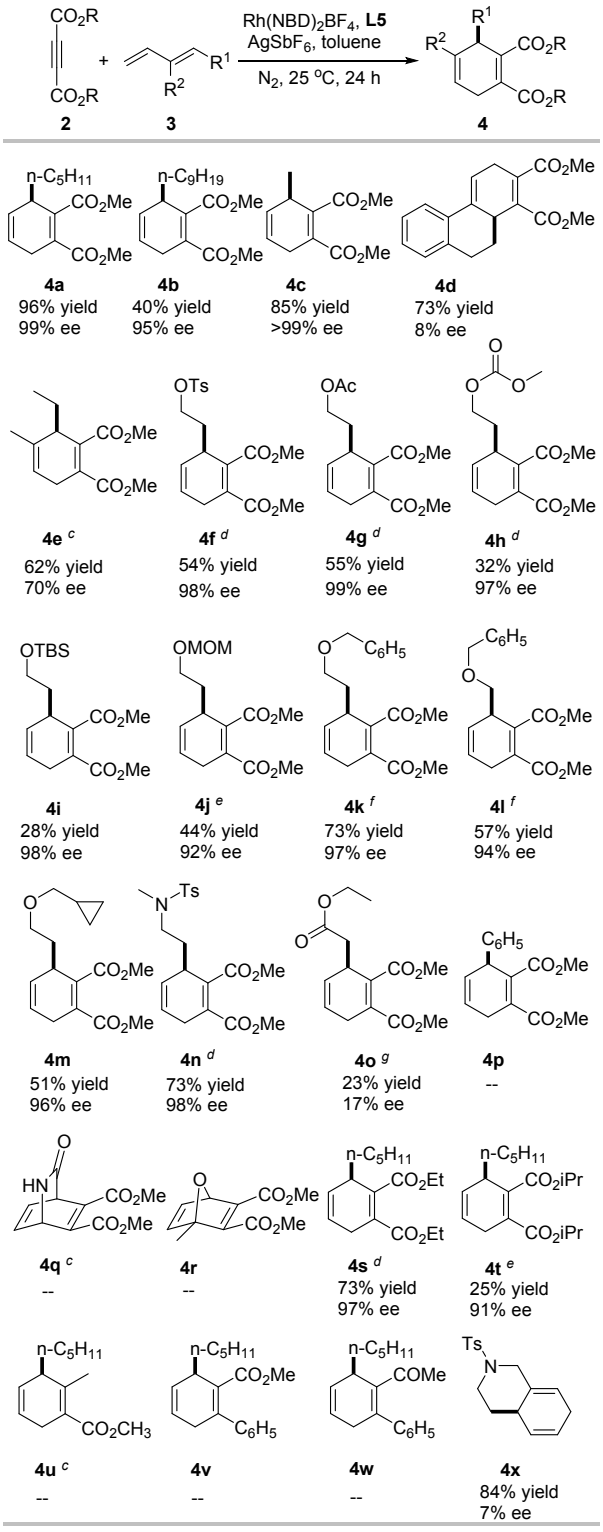
rhodium(I) complexes (Table 1, 9-12). Very pleasingly, we found that the $Rh(NBD)_2BF_4$ was the most effective rhodium(I) complex for this cycloaddition, affording **4a** in 96% yield and with 99% ee. To get a better understanding of the nature of the catalytic system, further control experiments were conducted. As expected, the reaction couldn't proceed smoothly in the absence of rhodium(I) complexes (Table 1, entry 13). When the reaction was carried out under air, the yield would decrease to 59% (Table 1, entry 14). If H_2O was added into the reaction, the reactivity would be depressed sharply (Table 1, entry 15). Additionally, both the reactivity and enantioselectivity would decrease dramatically without adding $AgSbF_6$ into the catalytic system (Table1, entry 16), and this result implied that the hexafluoroantimonate anion could improve the reaction rate and enantioselectivity of the cycloaddition, which was consistent with the remarkable accelerating effect of the hexafluoroantimonate anion in Livinghouse's report.[21] In the end, our efforts to evaluate the effect of the solvents revealed that the toluene was the optimal solvent (Table 1, 17-20). In summary, the condition of entry 12 in Table 1 was the best option.

With the optimized conditions in hand, we screened the asymmetric [4+2] cycloaddition of **2a** with a wide range of 1,3-dienes (Table 2). In general, the steric effect of substrates was a critical factor for the reaction both in reactivity and enantioselectivity. Compared to the model reactions, increasing the length of linear 1,3-diene depressed the reactivity and enantioselectivity (Table 2, **4b**). In contrast, reducing the length of linear 1,3-diene resulted in a depressed reactivity due to the low boiling point of the 1,3-diene although the excellent enantioselectivity was obtained as well (Table 2, **4c**). Next, investigating the steric effect of substituents in the branched 1,3-dienes leaded to slightly diminished yields and drastically decreased enantiomeric excesses (Table 2, **4d** and **4e**). Subsequently, to evaluate the functional group tolerance, the masked alcohol moieties, protected amine, esters, and phenyl group were introduced into the 1,3-dienes (Table 2, **4f** - **4p**). Gratifyingly, the catalytic system showed good functional group tolerance with the -OTs, -OAc, $-OCO_2CH_3$, -OTBS, -OMOM, -OBn, the cyclopropyl, -N (CH_3) Ts and $-CO_2Et$. Deserved to be mentioned, introducing the protected groups with large steric hindrance would lead to lower reactivity. One strategy to promote the reactivity was using 1,2-dichloroethane as a co-solvent, and with employing this strategy, the products **4f**, **4g**, **4h**, **4j**, and **4n** were obtained in moderate to good yields. Another way to improve the reactivity was to increase the reaction temperatures, and the products **4k**, **4l** and **4o** were also obtained under higher temperatures. As for some dienes containing oxygen atoms, the reaction systems would turn black and the dimethyl acetylenedicarboxylate **2a** couldn't convert to the products **4g**, **4h**, **4i**, **4j**, and **4o** completely. Moreover, the reactivity of (*E*)-buta-1,3-dien-1-ylbenzene was also examined in the cycloaddition. But the products **4p** was not isolated, due to the complexed reaction systems.

Apart from the linear and branched dienes, pyridin-2(1*H*)-one and 2-methylfuran were attempted to use as cyclic dienes to construct bridged-ring products **4q** and **4r** in the cycloaddition respectively. When the pyridin-2(1*H*)-one was subjected to the reaction, the reaction system turned to be complexed and the product **4q** was not isolated. When 2-methylfuran was utilized in the cyclization, it was found that the 2-methylfuran didn't reactive with (*E*)-nona-1,3-diene **3a** under

Table 2 Substrate scope of enantioselective [4+2] cycloadditions[a,b]

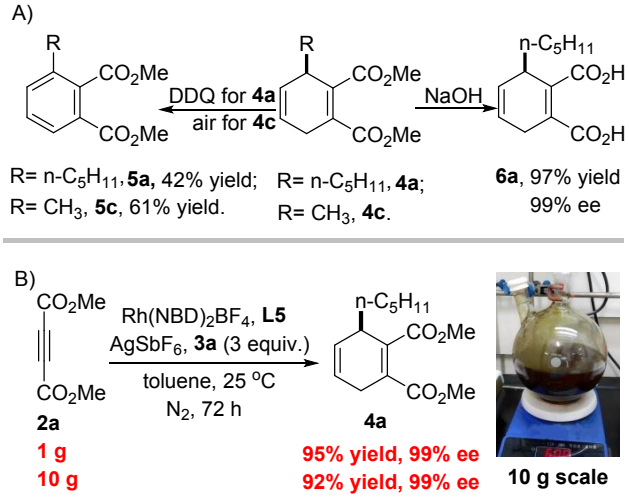


[a] Reaction conditions: **2** (0.2 mmol), **3** (0.6 mmol), $Rh(NBD)_2BF_4$ (10 mol%), **L5** (12 mol%), and $AgSbF_6$ (20 mol%), in toluene (3 mL) under N_2, 24 h. [b] Isolated yield. [c] In 1,2-dichloroethane (3 mL) at 25 °C, 24 h [d] In toluene (2 mL) and 1,2-dichloroethane (1 mL) at 25 °C,72 h. [e] In toluene (2 mL) and 1,2-dichloroethane (1 mL) at 50 °C,72 h. [f] in toluene (3 mL) at 50 °C, 72 h. [g] in toluene (3 mL) at 110 °C, 72 h. -- Not isolated.

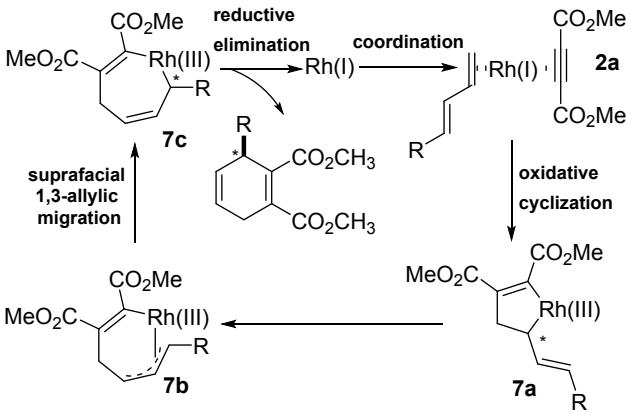
the standard conditions.

After screening various dienes, the effect of different substituted alkynes was investigated. Firstly, two dialkyl acetylenedicarboxylates were employed in the cycloaddition and the results implied that larger steric hinderance of the acetylenedicarboxylate would result in lower reactivity (Table 2, **4s** and **4t**). Then, methyl 2-butynoate, methyl 3-phenylpropiolate and 4-phenylbut-3-yn-2-one were utilized as starting materials in the cycloaddition. Unfortunately, they didn't react with (*E*)-nona-1,3-diene **3a** and the corresponding products **4u**, **4v** and **4w** were not obtained. Additionally, we attempted to employ this rhodium(I)-chiral phosphoramidite complex to catalyze the intramolecular [4+2] cycloaddition. But only a significantly low enantioselectivity was obtained (Table 2, **4x**).

Further transformations of the Enantio-enriched products were performed. Since the construction of the polysubstituted benzenes has emerged as powerful methods in the total synthesis of Daphenylline,[22] and Clostrubin,[23] the dimerization of Artemisinin,[24] and the macrocyclic ring formation of conjugated macrocycles,[25] the oxidative aromatization was carried out firstly to give the 1,2,3-tri-substituted benzene **5a** in 42% yield with using DDQ as an oxidant. Interestingly, **4c** could be converted to **5c** in 61% yield just under air for a month (Scheme 2, A). Except for the oxidations, the hydrolysis of **4a** was also performed, resulting in the dicarboxylic acid **6a** in 97% yield with 99% ee (Scheme 2, A), which has a potential to synthesize the glycosidase inhibitor analogues.[26]



Scheme 2 Derivatizations and large-scale experiments.



Scheme 3 A Plausible mechanism for the [4+2] cycloaddition.

To evaluate the practicability and explore the potential of this synthetic method, the scale-up reactions were conducted (Scheme 2, B). Initially, 1 g of **2a** was subjected to this cycloaddition, resulting in the product **4a** in 95% yield and with 99% ee, in which the yield and enantioselectivity were successfully maintained. Encouraged by this perfect result, an increased scale reaction on 10 g of **2a** was performed. To our delight, the larger scale reaction also proceeded smoothly, affording **4a** in 92% yield and with 99% ee. Notably, the superabundant **3a** was recyclable through column chromatography. Based on the good scalability, this robust cycloaddition showed a great potential in synthetic chemistry.

A plausible mechanism for this rhodium(I)-catalyzed [4+2] cycloaddition is showed in Scheme 3.[15, 18, 27] Firstly, the pre-prepared rhodium (I)-complex coordinates with dimethyl acetyl-enedicarboxylate **2a** and 1,3-diene. After an oxidative cyclization, the rhodacyclopentene species **7a** is formed, which predominates the steric selectivity of this transformation. Next, a suprafacial 1,3-allylic migration[18] occurs to form a rhodacycloheptadiene intermediate **7c** through a metal-mediated η3-complex **7b**. Finally, the cycloadduct is obtained in the process of reductive elimination, along with the regeneration of rhodium (I)-complex.

Conclusions

In summary, we have developed a rhodium(I)-chiral phosphoramidite complex catalyzed intermolecular [4+2] cycloaddition. The reaction was tolerated with a range of functional groups and performed under mild conditions with up to 96% yield and > 99% ee, thereby providing a practical method for direct synthesis of the substituted cyclohexa-1,4-dienes in an asymmetric fashion. The scale-up reactions and derivatizations of products were also performed respectively. Further investigations to extend this protocol into natural product synthesis are ongoing in our laboratory. The results will be reported in due course.

Experimental section

General procedure:

A Schlenk tube equipped with a stir bar was charged with $Rh(NBD)_2BF_4$ (3.73 mg, 0.02 mmol), **L5** (10.7 mg, 0.024 mmol) and $AgSbF_6$ (13.7 mg, 0.04 mmol) under nitrogen atmosphere. Then corresponding solvent was added to the tube via syringe and the resulting mixture was stirred at 25 °C for 1 h. The reaction was started by addition of the 1,3-dienes (0.6 mmol) and substituted alkynes (0.2 mmol) separately *via* syringe. The reaction was allowed to stir at the corresponding temperature. When the reaction was completed, the solvent was evaporated to give a crude product, which was purified with column chromatography on silica gel or prepared TLC.

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Procedure for the [4+2] cycloaddition on 10 g scale:

To a flame-dried 2 L two-necked flask equipped with a stir bar was charged with the chiral phosphoramidite **L5** (3.78 g, 8.44 mmol), $Rh(NBD)_2BF_4$ (2.63 g, 7.03 mmol) and $AgSbF_6$ (4.83 g, 14.07 mmol) under N_2. After addition of the anhydrous toluene (50 mL) to the flask, the resulting mixture was stirred for 4 h at 25°C and then another 950 mL of anhydrous toluene was added to the flask. The reaction system was cooled to 0 °C, then the (*E*)-1,3-nonadiene (26.20 g, 211.11 mmol) and dimethyl acetylenedicarboxylate (10 g, 70.37 mmol) were added to the flask via syringe, respectively. The reaction system was allowed to warm to 25 °C and stir at 25 °C for 72 h. When the reaction was completed, it was quenched with water. After purification of the crude product, a light brown liquid was obtained.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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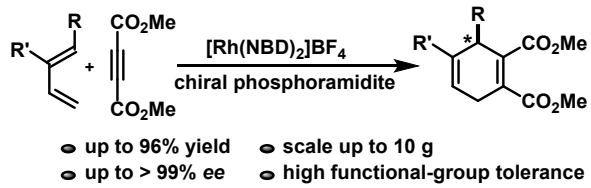

- up to 96% yield
- up to > 99% *ee*
- scale up to 10 g
- high functional-group tolerance

A highly enantioselective and scalable intermolecular [4+2] cycloaddition to construct the substituted cyclohexa-1,4-dienes.