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RESEARCH ARTICLE

Low-Temperature Intramolecular [4+2] Cycloaddition of Allenes with Arenes for the Synthesis of Diene Ligands

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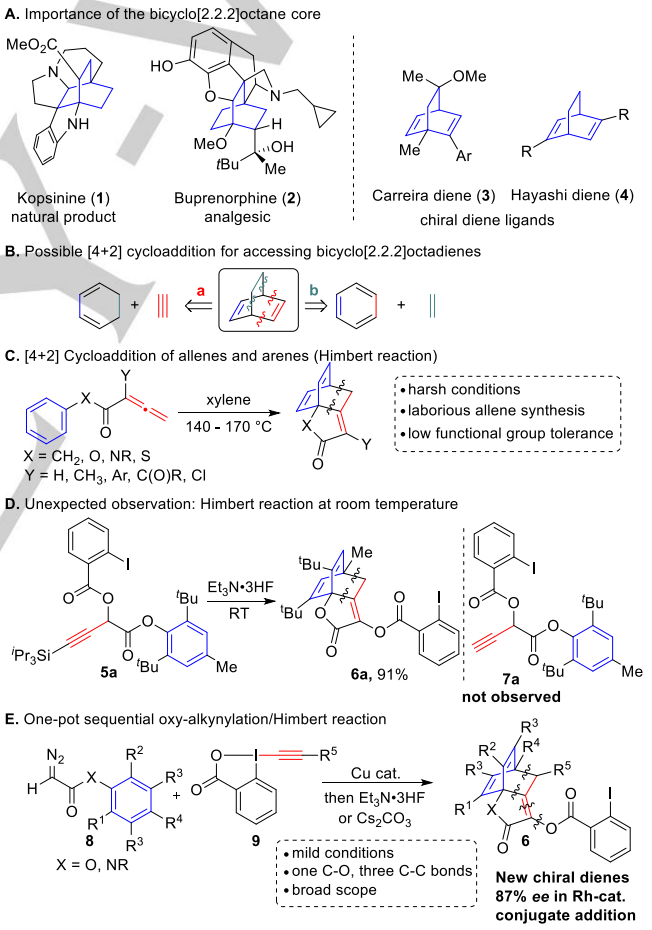
Abstract: The intramolecular [4+2] cycloaddition between arenes and allenes first reported by Himbert gives rapid access to rigid polycyclic scaffolds. Herein, we report a one-pot oxyalkynylation/cycloaddition reaction proceeding under mild conditions (23-90 °C) and providing complex polycyclic architectures with high efficiency, atom and step economy. The bicyclo[2.2.2]octadiene products were obtained with a wide variety of useful functional groups and were successfully applied as chiral ligands for metal catalysis. Computational studies gave a first rationalization of the low activation energy for the cycloaddition based on counter-intuitive favorable dispersive interactions in the transition state.

Introduction

The development of multiple bond-forming transformations to increase molecular complexity and diversity from simple precursors is a constant quest in synthetic chemistry with important applications in the pharmaceutical and agrochemical industries.[1] Among multiple bond-forming transformations, cycloadditions occupy a privileged position.[2,3] They have found applications in the synthesis of natural products,[4] organic materials,[5] and pharmaceutical agents.[6] In particular, the Diels-Alder reaction has been investigated extensively.[7] When using cyclic dienes, it gives access after reduction to bicyclo[2.2.2]octane derivatives, an important class of organic compounds due to their rigidity allowing a precise disposition of functional groups in space. Numerous bioactive natural products, such as the alkaloid kopsinine (**1**),[8] or synthetic compounds, such as the broadly prescribed opioid analgesic buprenorphine (**2**),[9] contain this scaffold (Scheme 1A). Less saturated bicyclo[2.2.2]octadienes constitute another interesting subclass, as they have found broad applications as (chiral) ligands for late transition metal catalysts (Scheme 1A, dienes **3** and **4**).[10] As unsaturated compounds, they are also ideal starting materials for the synthesis of more functionalized saturated derivatives. Two different strategies can be envisioned to access them by a convergent [4+2] cycloaddition (Scheme 1B): reaction of cyclohexadienes with alkynes (**a**), or reaction of arenes with alkenes (**b**). The first approach is now well established.[11] In contrast, the second strategy is less investigated due to the large aromatic stabilization energy of arenes.[12] From the synthetic point of view however, such an approach is highly attractive, as arenes are easier to access than cyclohexadienes.



Scheme 1. A. Importance of the bicyclo[2.2.2]octane core. B. [4+2] cycloadditions for accessing bicyclo[2.2.2]octadienes. C. Himbert reaction. D. Unexpected Himbert reaction at room temperature. E. One-pot oxyalkynylation/Himbert reaction.

In 1982, Himbert and Henn reported an unusual thermal intramolecular [4+2] cycloaddition of allenecarboxanilides to access complex bridged polycyclic architectures.[13] The Himbert and Orahovats groups then studied the scope of allenecarboxylic acid derivatives including esters,[14] amides,[15] thioesters,[16]

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imides,[17] phosphinamides,[18] and phosphinic esters (Scheme 1C).[19] In 2013, Vanderwal and co-workers extended the Himbert cycloaddition to benzyl allenyl ketones.[20] In 2015, Li and co-workers reported a Ugi/Himbert reaction sequence to synthesize strained polycyclic skeletons.[21] Despite its great potential to assembly complex molecules in a single step, the [4+2] cycloaddition of allenes and arenes has found only a few applications in synthetic chemistry.[22] The Himbert reaction often requires high reaction temperatures. Examples at ambient temperature required conformationally constrained amides[17,23] or were performed under light irradiation.[24]

Our group has been interested in electrophilic alkynylation reactions using hypervalent iodine reagents for more efficient and flexible alkyne synthesis.[25] Recently, we developed a copper-catalyzed oxyalkynylation of diazo compounds using ethynylbenziodoxol-(on)e (EBX) reagents.[26] When attempting the deprotection of silyl alkyne **5a** with Et_3N•3HF at room temperature, we did not obtain the expected terminal alkyne **7a**. Instead, polycyclic product **6a** was isolated in excellent yield, probably resulting from a [4+2] cycloaddition of the arene on the *in situ* formed allene (Scheme 1D). The exceptionally mild conditions combined with synthetic accessibility motivated us to investigate this transformation.

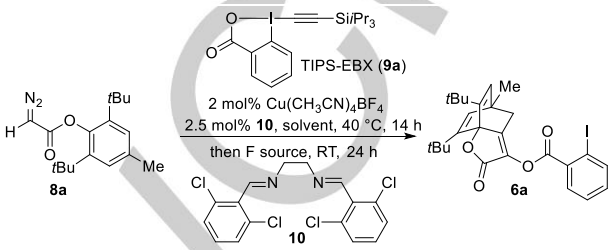
Herein, we report our studies on this fascinating reaction. The cycloaddition proceeded under mild conditions (RT to 90 °C) and exhibited a broad scope of substituents on both arene and allene. By developing a one-pot oxy-alkynylation/cycloaddition process, complex tricyclic compounds are now accessible in a single manipulation from broadly available EBX reagents and diazo esters (Scheme 1E). Preliminary computational studies shed first light on the exceptionally low activation energy of the cycloaddition step, resulting from a combination of attractive interactions from the benzene substituents with the allene and an electronic effect of the oxygen substituent on the allene. This interesting class of heteroatom-substituted allenes has been only rarely investigated so far[27] and the high reactivity observed is promising for other transformations. Furthermore, the iodobenzoyl ester could be easily removed for further modification. Finally, the diene products were effective ligands for rhodium, resulting in quantitative complexation. Preliminary investigations showed that good enantioselectivity can be achieved in rhodium-catalyzed conjugate addition of boronic acids to cyclohexenone using these chiral diene ligands.

Results and Discussion

Optimization and Scope

We started our investigations on developing a one-pot oxy-alkynylation/Himbert reaction by screening various fluoride sources, using 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**8a**) with 1-[(tri*iso*-propylsilyl)-ethynyl]-1,2-benziodoxol-3(*1H*)-one (TIPS-EBX (**9a**)), diimine ligand **10** and $Cu(CH_3CN)_4BF_4$ as the copper source in 1,2-dichloroethane (DCE, Table 1).[26a] Compound **6a** was obtained in 88% yield when Et_3N•3HF was used, whereas trissulfonium difluorotrimethylsilicate (TASF) gave the desired product in 26% yield only (Table 1, entries 1 and 2). The use of tetrabutylammonium fluoride (TBAF) and pyridine hydrofluoride (Py•HF) resulted in decomposition of the oxyalkynylated product (Table 1, entries 3 and 4). One equivalent of Et_3N•3HF was sufficient, whereas a sub-stoichiometric amount led to a lower yield (Table 1, entries 5 and 6). Addition of Et_3N•3HF at the start of the reaction did not lead to the formation of the desired product **6a** (Table 1, entry 7). Among the solvents tested, DCE was the best (Table 1, entries, 5 and 8-10). We were able to reduce the amount of diazo **8a** to 1.2 equivalents without a change in yield (Table 1, entry 11). Finally, the yield could be improved to 94% by lowering the concentration of the reaction (Table 1, entry 12). Furthermore, the reaction proved to be easily scalable, as the yield did not change on gram scale.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Fluoride source (x equiv)	Solvent	Yield[b] (%)
1	Et_3N•3HF (2.0)	DCE	88
2	TASF (2.0)	DCE	26
3	TBAF (2.0)	DCE	<5
4	Py•HF (2.0)	DCE	<5
5	Et_3N•3HF (1.0)	DCE	88
6	Et_3N•3HF (0.5)	DCE	65
7[c]	Et_3N•3HF (1.0)	DCE	<5
8	Et_3N•3HF (1.0)	DCM	46
9	Et_3N•3HF (1.0)	THF	<5
10	Et_3N•3HF (1.0)	PhCl	45
11[d]	Et_3N•3HF (1.0)	DCE	87
12[e]	Et_3N•3HF (1.0)	DCE	94

[a]Reaction conditions: 0.30 mmol diazo ester (**8a**), 0.15 mmol TIPS-EBX (**9a**), copper catalyst (2.0 mol%), **10** (2.5 mol%), solvent (0.05 M). [b]Yield after purification by column chromatography. [c]Et_3N•3HF was added at the start of the sequence. [d]1.2 equiv of diazo ester instead of 2.0 equiv. [e]0.025 M instead of 0.05 M. DCM = dichloromethane, THF = tetrahydrofuran.

With the optimized conditions in hand, the scope of the reaction was first examined using TIPS-EBX (**9a**) and various diazo esters bearing *tert*-butyl substituents in *ortho* positions of the benzene ring (Scheme 2A). *Para*-substituted products **6a-f** with alkyl, ether, bromine or hydrogen substituents were obtained in 83-96% yield, showing that there was no strong steric or electronic effects at this position.[28] In contrast, the *ortho* substituent size had a strong effect on the reaction outcome. When 2,6-di-*iso*-propyl-phenyl 2-diazoacetate (**8g**) was subjected to the standard reaction conditions, we could not observe the desired product **6g**. Heating to higher temperature led to decomposition. This was due to the presence of the copper catalyst. Removal of the catalyst and heating the reaction at 90 °C, gave the product **6g** in excellent yield. This temperature is significantly lower than reported for similar substrates lacking the oxygen substituent on the allene (140 °C).[14a] Diphenyl- and dimethyl-benzene substituted diazo esters could also be used in the reaction (products **6h** and **6i**). The formation of the product **6i** is particularly interesting as a similar *o*-dimethylbenzene substituted allene without *α*-oxygen substitution failed to give the corresponding Himbert product even at 140 °C.[14a] Mono-substituted benzene diazo esters also

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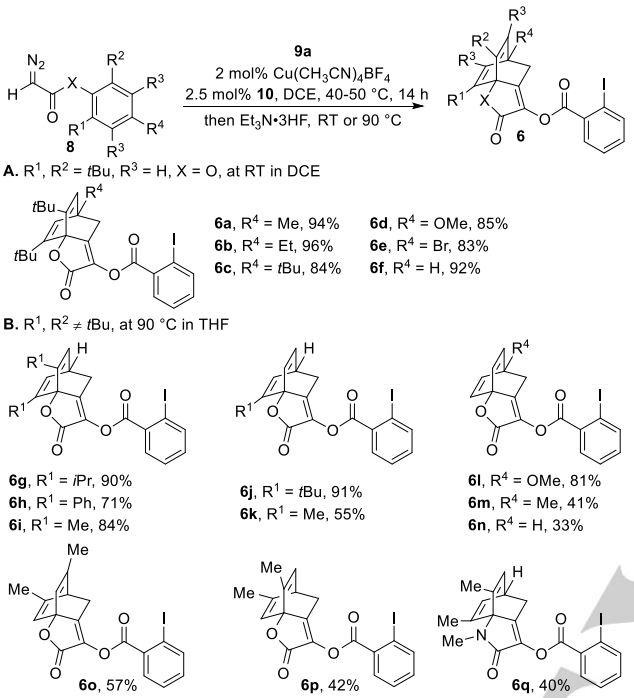
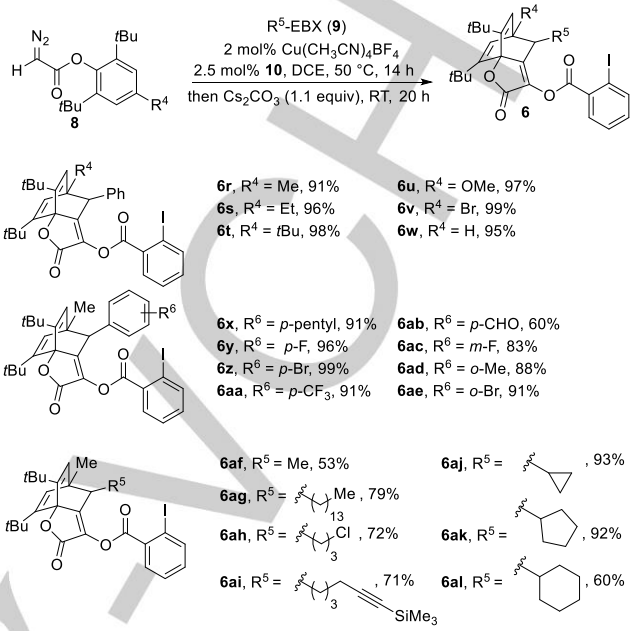
underwent the desired transformation successfully to give products **6j** and **6k** as single diastereoisomers in 91% and 55% yield, respectively.[29] Substitutions at different positions than *ortho* were envisaged: *p*-Substituted and unsubstituted benzene diazo esters gave the corresponding products **6l-n** in moderate to good yield. Dimethyl-substituted benzene diazo esters also gave the desired products **6o** and **6l** in moderate yields. Amide tethered Himbert product **6p** was obtained in 40% yield.



Scheme 2. Scope of diazo esters with TIPS-EBX (**9a**).

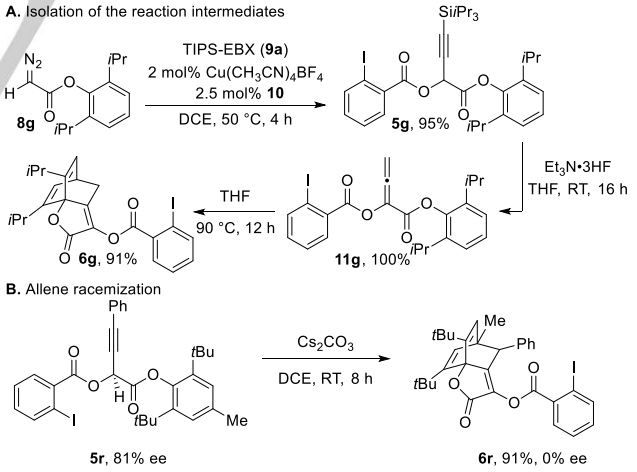
To further increase the molecular complexity of the products, we investigated the reaction of the more reactive *ortho* di-*tert*-butylbenzene substituted diazo esters with functionalized EBX reagents (Scheme 3).[30] Optimization of the reaction conditions showed that it was best to perform the oxyalkynylation at 50 °C and the cycloaddition at room temperature using caesium carbonate as base.[31] The carbonate base is not compatible with the oxyalkynylation and needs to be added afterwards. Under these conditions, the desired product **6q** could be isolated in 91% yield as a single diastereoisomer using 1.1 equiv of Cs_2CO_3 as a base at room temperature.[32] When the reaction was performed on gram-scale, compound **6r** was obtained in 91% yield. Various benzene diazo esters bearing an alkyl chain, an ether, a halogen or a hydrogen substituent in *para* position gave excellent yields (Scheme 3, products **6s-w**). We then turned our attention to the scope of aryl-EBX reagents using **8a**. The desired products **6x-6ae** bearing alkyl, fluorine, bromine, trifluoromethyl or aldehyde in *para*, *meta* or *ortho* position were obtained in 60-99% yield, demonstrating the tolerance of the reaction towards functional groups and substitution patterns. Next, the scope of alkyl-EBX reagents was examined.[33] Methyl- and long alkyl chain- derived EBX reagents worked well in the reaction, giving products **6af** and **6ag** in 53% and 79% yield, respectively. The reaction was also successful in the case of chlorine and alkynyl group bearing alkyl EBX reagents (products **6ah** and **6ai**). The reaction was not limited to linear alkyl-EBX reagents: Cyclo-propyl, -pentyl, and –hexyl substituted products **6aj-l** were obtained in 60-93% yield. The formation of product **6aj** exclusively indicated that radical intermediates were probably not involved in the reaction.



Scheme 3. Scope of diazo esters with different EBX reagents.

Mechanism Investigations

To confirm our hypothesis for a successive oxyalkynylation/allene formation/ [4+2] cycloaddition sequence, we isolated each intermediate before engaging it in the next step using less reactive alkyne **5g** (Scheme 4A).



Scheme 4. Control experiments.

In presence of Et_3N•3HF after removal of the copper catalyst, **5g** was cleanly converted to allene **11g**, which was stable at room temperature. Upon heating to 90 °C, [4+2] cycloaddition then occurred in 91% yield. As allene **11g** is non-chiral, no transfer of chirality is possible when starting from enantioenriched alkynes. However, when using aryl- or alkyl- substituted alkynes, a chiral allene would be formed. We wondered if in this case transfer of

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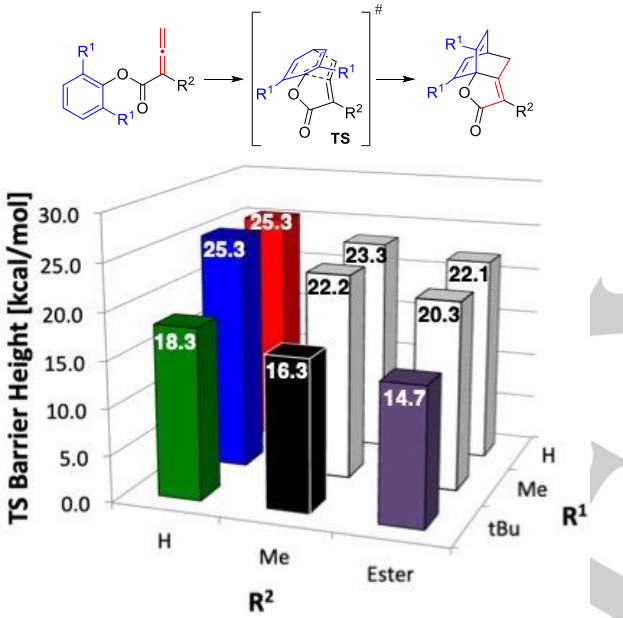
chirality would be possible. However, racemic **6r** was isolated starting from enantioenriched alkyne **5r** (Scheme 4B).[34]

Having established that the reaction most probably proceeds via a [4+2] cycloaddition of the allene with the arene ring, we turned to density functional theory computations (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level, see SI for full computational details) to better understand the observed amazing reactivity. When comparing the transition state energies of nine different cycloadditions in dependence of the substituents on the benzene ring and allene, computations clearly show the favorable nature that bulky *tert*-butyl groups have on the transition state barrier heights (Scheme 5). The free energies with *tert*-butyl groups (14.7-18.3 kcal/mol) were significantly lower than with methyl (20.3-25.3 kcal/mol) or hydrogen (22.1-25.3 kcal/mol), independently from the substituent on the allene. In addition, the reactivity was further enhanced by the carboxy substituent on the allene, although the effect was weaker. These results are in good accordance with the reaction rates observed experimentally.



Scheme 5. Free energies of transition states in dependence of substituents on benzene and allene. Free energies computed at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level). Ester = 2-iodobenzoate. Note that column colors correspond to those of the activation strain model computations shown in Figures 1 and 2.

To gain additional insight, we analyzed the energetic profiles of these nine reactions using the activation strain model.[35] Initially, we speculated that the bulky *tert*-butyl groups in R^1 could diminish the planarity of the benzene ring, lowering the distortion energy and making it easier to break aromaticity. However, the calculation results showed that the presence of the bulky substituents in R^1 causes energetically favorable dispersive interactions at longer C-C distances, whereas no major difference in strain energy was observed (Figure 1). This results in an earlier, lower energy transition state for the *tert*-butyl containing variant relative to methyl or hydrogen. Substitution on the allene is characterized by a more complicated picture in which both the unfavorable strain energy and stabilizing interaction energy are influenced by the substituent (Figure 2). Replacing the hydrogen atom with either a methyl or a carboxy group slightly reduces the strain energy. However, this substitution also results in a less favorable interaction energy for the methyl variant while the ester variant provides a more favorable interaction. Overall, this results in the ester having a lower energy transition state barrier relative to either a hydrogen or methyl group.

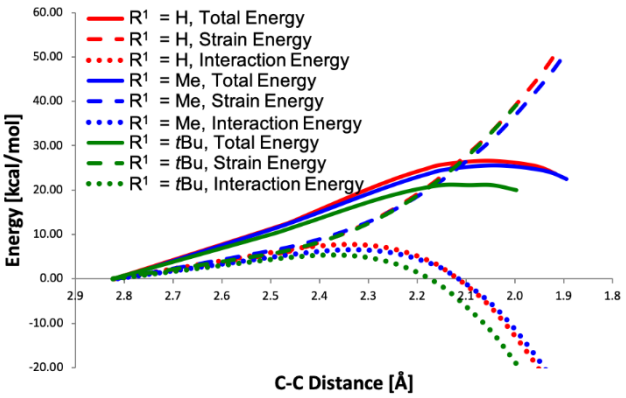


Figure 1. Activation strain model results (computed at the M06-2X/def2-SVP level) in dependence on the R^1 group on the benzene for R^2 = H on the allene. Note that the plots depict electronic energies, as opposed to free energies.

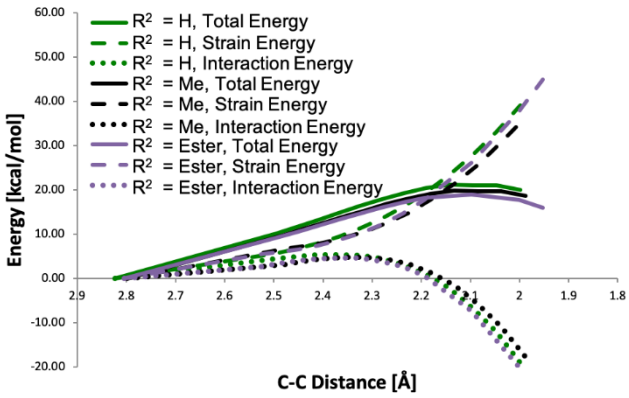


Figure 2. Activation strain model results (computed at the M06-2X/def2-SVP level) in dependence on the R^2 group on the allene for R^1 = *t*Bu on the benzene. Ester = 2-iodobenzoate. Note that the plots depict electronic energies, as opposed to free energies.

Synthetic Applications

The cycloaddition of allene and benzene rings gave access to [6,6,5] ring systems. It is also important to access other polycyclic systems. In this respect, an interesting preliminary result was obtained with furan-derived diazoester **12**: The oxyalkynylation-Himbert sequence gave a new [5,5,6] ring system **13** in 83% yield (Scheme 6A). Furthermore, the iodobenzoyl ester on the product can be cleaved directly after cycloaddition, giving access to ketoesters **14a** and **14b** (in their enol form) on gram-scale in one-pot (Scheme 6B). Bromination of **14a** yielded highly strained cyclopropane **15** in 86% yield.[36] Alcohol **14a** was quantitatively transformed into the corresponding triflate **16** by reaction with triflic anhydride. Palladium catalyzed reduction of **16** gave unsaturated ester **17** in 88% yield. Reaction of triflate **16** with 3-phenylprop-2-yn-1-ol or diethyl phosphonate gave access to products **18** and **19** respectively.

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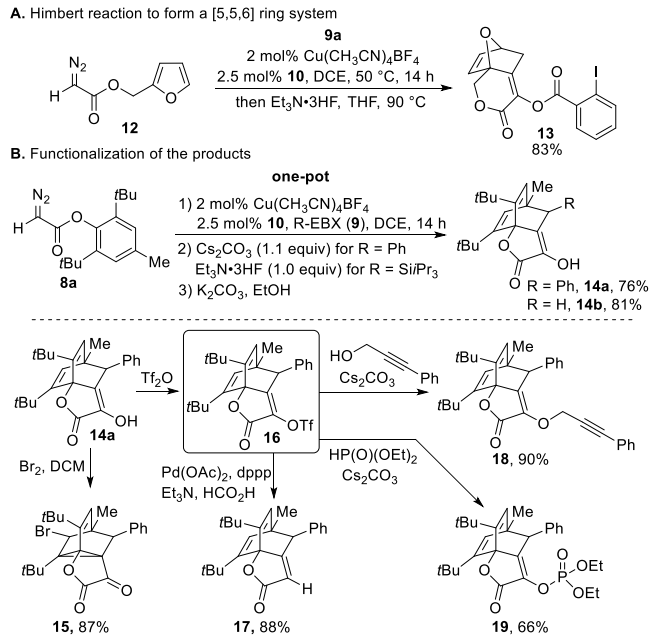
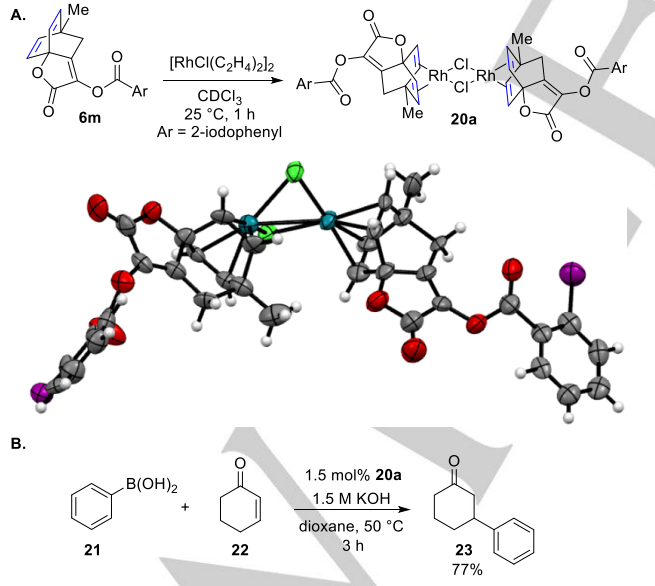


Scheme 6. [4+2] Cycloaddition with furan and product derivatization. Tf = Triflyl.

When considering that bicyclo[2.2.2]octadienes are an important class of ligands for late transition metals,[10] we then attempted the formation of a rhodium complex. The complexation was not successful when using *tert*-butyl substituted dienes, probably due to excessive steric hindrance. In contrast, dimer **20a** was cleanly formed, by just mixing diene **6m** with $[RhCl(C_2H_4)_2]_2$ in chloroform (Scheme 7A). X-ray quality crystals of **20a** could be obtained, allowing us to confirm its structure.[37]

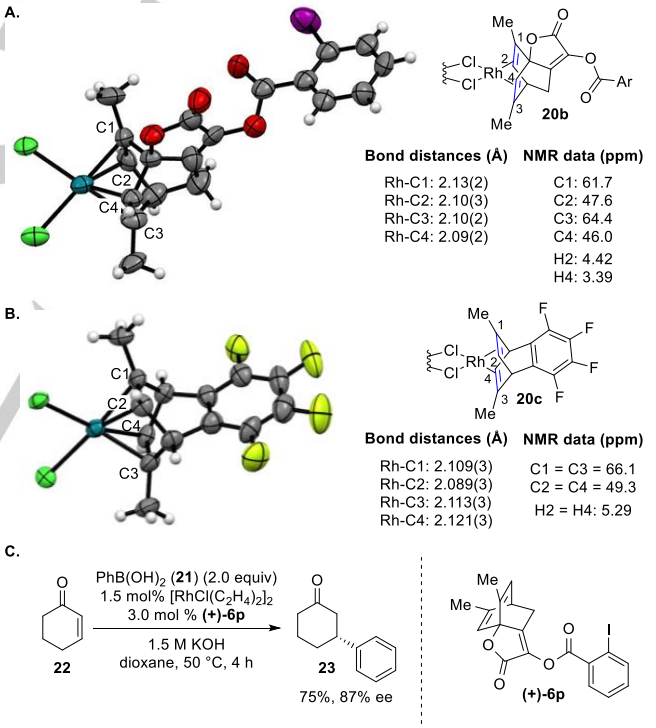


Scheme 7. A. Synthesis and X-ray structure of Rhodium complex **20a**. **B.** Conjugate addition of phenylboronic acid (**21**) on cyclohexenone (**22**) with **20a** as catalyst.

Complex **20a** was a good catalyst for the conjugate addition of phenyl boronic acid (**21**) to cyclohexenone (**22**) under standard conditions (Scheme 7B).[10d]

Next, we envisioned an enantioselective transformation. We decided to take advantage of the pseudo-C2 symmetry of compound **6p**, making it similar to the successful Hayashi-type ligand **4**. Enantiopure (+)-**6p** was isolated by preparative chiral high performance liquid chromatography (HPLC). We were able to obtain a X-ray crystal structure of the corresponding dimeric complex **20b** (Scheme 8A)[38] and we could compare it with the diene complex **20c** reported by Hayashi and co-workers (Scheme 8B).[39] The immediate coordination sphere around the rhodium was not distorted by the lower symmetry of ligand **20b**: all bonds between the metal and the olefins were of same length, and within error margin also identical to those in complex **20c**.[40] In contrast, the ^{13}C and even more the ^{1}H NMR signals on the olefins were clearly separated for complex **20b**, indicating that this ligand will induce a non-symmetrical electronic environment. From this point of view, it is clearly different from the classical Hayashi dienes.

As a proof of concept for its use in asymmetric catalysis, we then used (+)-**6p** as chiral ligand for the rhodium-catalyzed conjugate addition of phenyl boronic acid (**21**) to cyclohexenone (**22**) under standard reported conditions (Scheme 8C).[10d] The resulting β-functionalized ketone **23** was obtained in 75% yield with 87% *ee*. This is promising when considering that the methyl substituent is smaller than the phenyl or benzyl groups used in previous works[10d] and no attempt was made to optimize the reaction conditions.



Scheme 8. A. X-ray structure of Rhodium complex **20b** with bond lengths and ^{1}H and ^{13}C NMR data. **B.** X-ray structure of Hayashi's Rhodium complex **20c** with bond lengths and ^{1}H and ^{13}C NMR data. **C.** Enantioselective conjugate addition with ligand **(+)-6p**. For simplification, only half of the dimeric complexes **20b** and **20c** is shown.

Conclusion

In summary, we have developed a highly efficient strategy for the rapid assembly of bicyclo[2.2.2]octadienes starting from simple diazo esters and EBX reagents via a one-pot sequential oxyalkynylation/[4+2] cycloaddition reaction proceeding between 25 and 90 °C. The reaction tolerated a broad range of functional groups on both diazo esters and EBX-reagents. Isolation of the reaction intermediates support a cycloaddition of an *in situ* formed

allene with the arene ring. The exceptionally low activation energy for the cycloaddition could be rationalized by counter-intuitive favourable dispersive interactions in the transition state, combined with a weaker effect of the carboxy substituent. The obtained products were transformed into useful building blocks and preliminary results indicated that other polycyclic ring systems could also be accessed using this strategy. Importantly, this methodology allows straightforward access to versatile diene ligands for rhodium catalysis with easy variation of the substituents. Pseudo C2-symmetric ligand **6p** could be used in the enantioselective addition of phenyl boronic acid (**21**) to cyclohexenone (**22**) with 87% enantioselectivity. Our future work will focus on catalysis of the cycloaddition step with the goal of developing an enantioselective reaction for a more straightforward access to enantioenriched chiral ligands, and further study the reactivity of this new type of easily accessible "push-pull" allenes.

Acknowledgements

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Keywords: [4+2] cycloaddition • alkynes • diene ligands • hypervalent iodine reagents • diazo compounds

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[30] In the case of less reactive substituted alkynes, the presence of the *tert*-butyl groups was necessary for the success of the cycloaddition.

[31] See Supporting Information for details on the optimization of the reaction conditions.

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[33] The reaction with alkyl-EBXs required 50 °C to form allenes, which undergo spontaneous cyclization to give the corresponding Himbert products.

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RESEARCH ARTICLE

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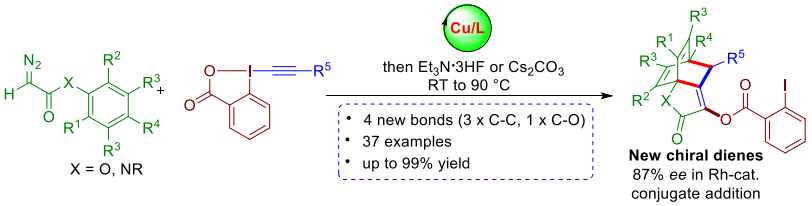

Breaking aromaticity: A highly efficient strategy for the rapid assembly of bicyclooctadienes starting from simple diazo esters and EBX reagents via a one-pot sequential oxyalkynylation/ [4+2] allene-arene cycloaddition reaction at low temperature (23-90 °C) is reported. The obtained products are good chiral ligands for rhodium-catalyzed conjugate addition.

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