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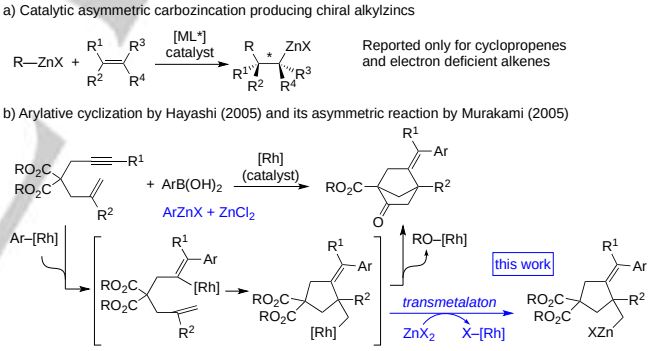
Asymmetric Synthesis of Alkylzincs by Rhodium-Catalyzed Enantioselective Arylative Cyclization of 1,6-Enynes with Arylzincs

Jiahua Chen[b] and Tamio Hayashi*[a,b]

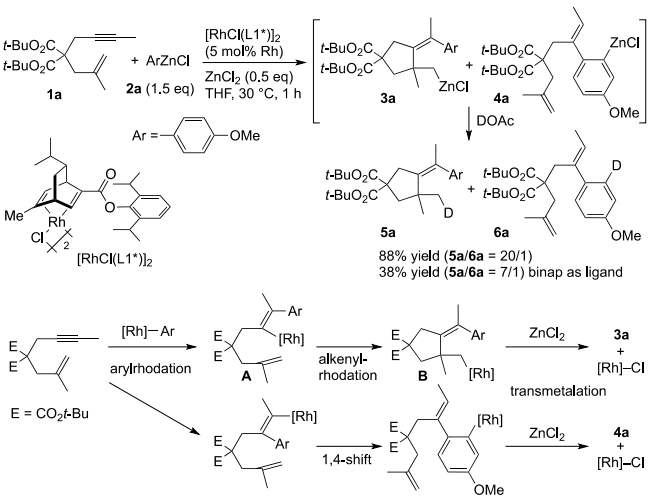
Abstract: A chiral diene–rhodium complex was found to catalyze the reaction of 1,6-enynes with ArZnCl to give high yields of 2-(alkylidene)cyclopentylmethylzincs with high enantioselectivity (95–99% ee). The enantioenriched alkylzincs were readily converted in one-pot into a wide variety of functionalized products by taking advantages of their unique reactivity. The catalytic cylcle involves arylrhodation of alkyne, intramolecular alkenylrhodation of alkene, and transmetalation of the alkyl-rhodium intermediate into alkylzinc.

Organozincs are organometallic reagents conveniently used for organic synthesis because of their unique features covering both high functional group compatibility and high reactivity towards electrophiles in the presence of metal catalysts at the same time.[1] As such, enantioenriched chiral alkylzincs are very useful for the synthesis of functionalized chiral molecules including biologically active compounds.[1] They have been obtained mainly from enantioenriched alkyl halides by insertion of zinc metal or halide-zinc exchange, or from other alkylmetals by transmetalation.[1,2] Catalytic enantioselective carbozincation of alkenes would be one of the promising methods of synthesizing chiral alkylzincs (Scheme 1a), but, unfortunately, this type of asymmetric reaction has not been well developed[3] except for the addition to cyclopropene derivatives[4] and electron deficient alkenes.[5] On the other hand, Murakami[6] and we[7] independently reported rhodium-catalyzed arylative cyclization of a malonate-tethered 1,6-enyne with $ArB(OH)_2$ producing a bicyclo[2.2.1]heptanone derivative. The catalytic cycle involves an alkyl-Rh species which is formed by carborhodation of alkene[8,9] and attacks ester carbonyl to result in the formation of ketone (Scheme 1b). If the $ArB(OH)_2$ is replaced by ArZnX and the transmetalation with ZnX_2 takes place for the alkyl-Rh intermediate, the overall reaction would be a new type of catalytic carbozincation giving alkylzinc product. During our studies on the arylzincation of carbon–carbon multiple bonds,[3,10] we found that the catalytic asymmetric carbozincation giving chiral alkylzincs shown in Scheme 1b is realized in the presence of a chiral diene/Rh catalyst and zinc chloride.

As shown in Scheme 2, 1,6-enyne **1a** was allowed to react with 4-$MeOC_6H_4ZnCl$ (**2a**) and $ZnCl_2$[11] in the presence of 5 mol% of a chiral diene/Rh catalyst, $[RhCl(L1^*)]_2$, at 30 °C for 1 h, and the reaction mixture was quenched with DOAc to give 88% yield of cyclopentane derivative **5a** together with a minor amount of side product **6a** (**5a**/**6a** = 20/1). The deuterium was found at one of the two methyl groups in **5a** and at ortho position to the alkenyl group on the phenyl ring in **6a**. With bisphosphine ligand, binap, the reaction was slower and the **5a**/**6a** selectivity was lower. The results on the deuterium quenching studies clearly demonstrate that alkylzinc **3a** and arylzinc **4a** were produced by the Rh-catalyzed arylzincation of **1a**. Based on the reaction pathways reported for Rh-catalyzed arylation of alkynes[6,7,12] and cyclization reactions,[9a–c] addition of an aryl–Rh intermediate to alkyne in **1a** followed by addition of the resulting alkenyl–Rh **A** to alkene generates the alkyl–Rh intermediate **B**. Transmetalation between **B** and $ZnCl_2$[10] produces alkylzinc **3a** and a Cl–Rh species, the latter undergoing the reaction with ArZnCl regenerating aryl-Rh species. When the regiochemistry at the arylrhodation of alkyne is opposite, the alkenyl–Rh intermediate **C** cannot participate in the intramolecular addition to alkene. Instead, 1,4-Rh shift takes place from alkenyl to the phenyl ring,[12,13] and transmetalation of aryl–Rh species **D** with $ZnCl_2$ produces arylzinc **4a**.[10]



Scheme 1. Catalytic asymmetric carbozincation producing chiral alkylzincs.



Scheme 2. Rhodium-catalyzed asymmetric arylative cyclization producing alkylzincs.

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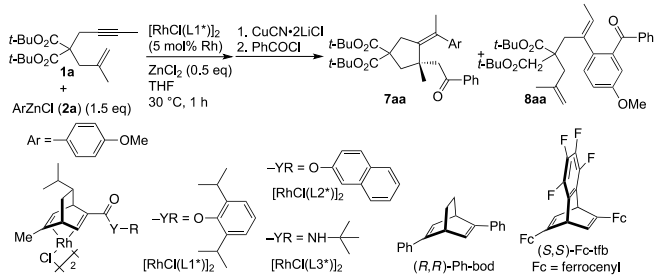
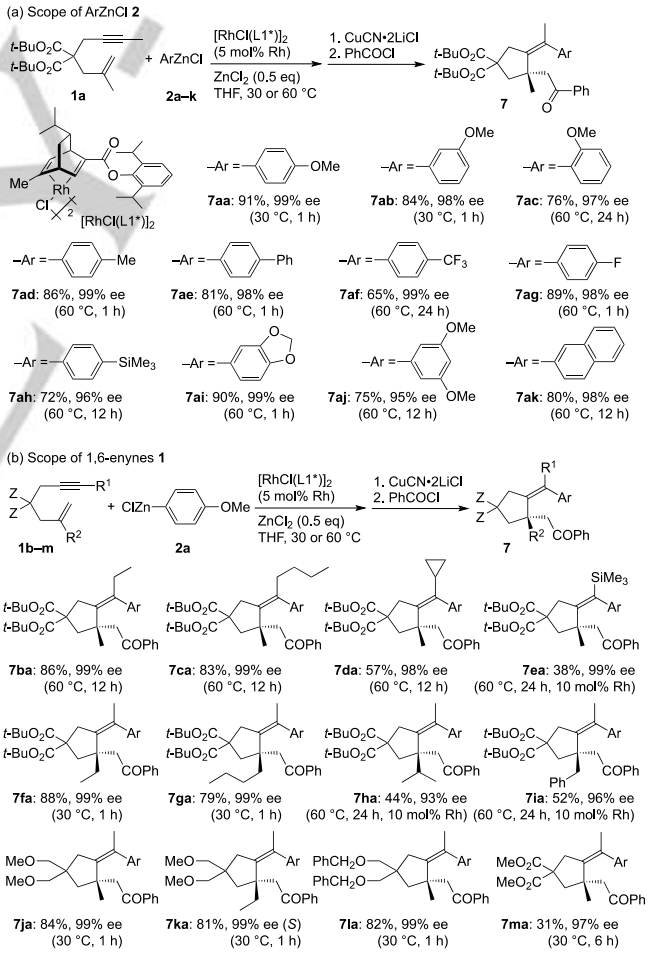
Table 1. Catalytic asymmetric arylative cyclization of enyne **1a** with 4-methoxyphenylzinc chloride (**2a**).[a]



Entry	Variations from standard conditions (shown above)	Yield (%)[b] of **7aa**	% ee[c] of **7aa**	Ratio[d] of **7aa**:**8aa**
1	none	91	99 (*S*)	20:1
2	$[RhCl(L2^*)]_2$	70	96 (*S*)	14:1
3	$[RhCl(L3^*)]_2$	85	98 (*S*)	10:1
4	$[RhCl(coe)_2]_2$ + (*R*,*R*)-Ph-bod	12	94 (*S*)	5:1
5	$[RhCl(coe)_2]_2$ + (*S*,*S*)-Fc-tfb	62	91 (*S*)	50:1
6	$[RhCl(coe)_2]_2$ + (*R*)-binap	35	99 (*S*)	10:1
7	$[RhCl(coe)_2]_2$ + (*R*)-segphos	63	98 (*S*)	4:1
8	$[RhCl(coe)_2]_2$ + (*R*)-DTBMsegphos	<5	—	—
9	$ZnCl_2$ (0.0 equiv)	44	99 (*S*)	20:1
10	$ZnCl_2$ (0.1 equiv)	88	99 (*S*)	20:1
11	$ZnCl_2$ (1.0 equiv)	68	99 (*S*)	20:1
12	ArZnBr + $ZnBr_2$ (0.5 eq)	75	99 (*S*)	20:1
13	24 h instead of 1 h	84	99 (*S*)	20:1
14	0 °C instead of 30 °C	24	99 (*S*)	22:1
15	60 °C instead of 30 °C	76	99 (*S*)	17:1

[a] Reaction conditions: Enyne **1a** (0.20 mmol), ArZnCl (**2a**) (0.30 mmol), $ZnCl_2$ (0.10 mmol), and Rh catalyst (5 mol% of Rh) in THF (2.0 mL) at 30 °C for 1 h. To the reaction mixture was added CuCN•2LiCl (0.36 mmol) and subsequently benzoyl chloride (0.36 mmol). For the details, see text and Supporting Information. [b] Isolated yield. [c] The % ee was determined by HPLC on a chiral stationary phase column. [d] The ratio of **7aa**:**8aa** was determined by ^{1}H NMR of the crude reaction mixture.

Although the alkylzinc product **3a** itself is not very reactive toward electrophiles other than proton, the Cu-mediated acylation[1,2,14] developed by Knochel proceeded well to give a high yield of the benzoylation product **7aa** which is readily analyzed for its enantiomeric purity. Thus, the reaction mixture resulting from arylzincation of **1a**, which contains **3a**, was treated first with CuCN and then with PhCOCl to give phenyl ketone **7aa** in 91% yield with 99% ee (reaction scheme in Table 1). Some of the results obtained at optimization of the reaction conditions for higher yield and enantioselectivity in the reaction of enyne **1a** with ArZnCl **2a** are shown in Table 1. The chiral diene ligand L1*,[15,16] which bears a bulky ester group, was found to be most effective in both the chemo- and enantioselectivities (entry 1). Other chiral diene ligands, L2*,[17] L3*,[18] Ph-bod,[19] and Fc-tfb,[20] are less effective giving the product **7aa** in a lower yield or with lower **7aa**/**8aa** selectivity and/or enantioselectivity (entries 2–5). Rhodium complexes with binap[21] and segphos[22] ligands also catalyzed the reaction, but the yields and/or the selectivity are lower (entries 6 and 7). The reaction did not take place with bulky DTBMsegphos[22] (entry 8). The presence of $ZnCl_2$ is necessary for the reaction to proceed efficiently, which is probably because $ZnCl_2$ participates in the catalytic cycle at the transmetalation step giving the final alkylzinc product[10] (See Scheme 2). While the high yield (91%) of **7aa** was obtained under standard conditions with 0.5 equiv of $ZnCl_2$ (entry 1), the reaction was slower in the absence of excess $ZnCl_2$ (entry 9), and a large excess of $ZnCl_2$ retarded the reaction (entry 11). The % ee of **7aa** was kept high (99% ee) irrespective of the amount of $ZnCl_2$ (entries 1 and 9–11). The use of ArZnBr/$ZnBr_2$ instead of ArZnCl/$ZnCl_2$ did not affect the enantioselectivity or **7aa**/**8aa** selectivity, although the yield was somewhat lower (entry 12). A prolonged reaction time (24 h) did not cause a significant change, demonstrating that the alkylzinc product **3a** is stable under the present reaction conditions (entry 13). The 30 °C is the reaction temperature of choice. At lower temperature (0 °C) the reaction is much slower, although the **7aa**/**8aa** selectivity is slightly higher (entry 14).



[a] Yields are based on the amount of 1,6-enynes **1** used.

Scheme 3. Asymmetric arylation/cyclization producing alkylzincs catalyzed by $[RhCl(L1^*)]_2$.[a]

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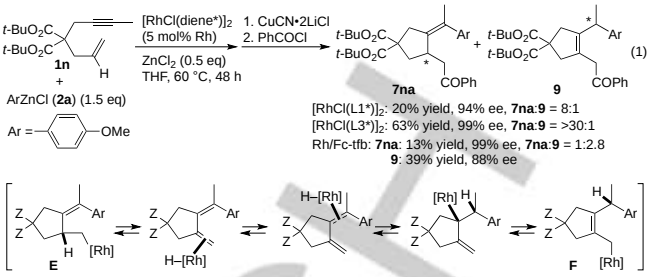
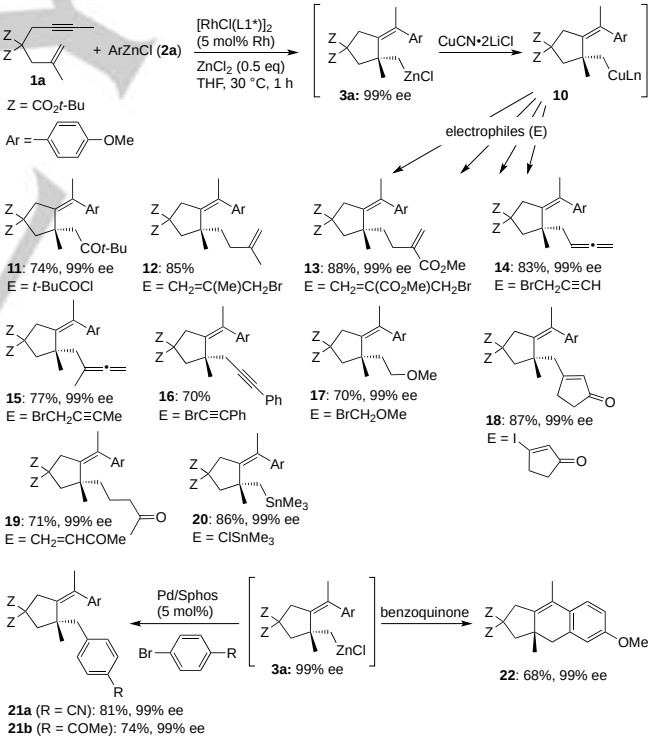
The conditions using chiral diene ligand L1* optimized for the reaction of **1a** with **2a** (entry 1 in Table 1) were applied to several other 1,6-enynes **1** and arylzincs **2** (Scheme 3). The results are summarized in Scheme 3. The arylzinc reagents substituted with MeO group at meta and ortho positions gave high yields of the corresponding phenyl ketones, **7ab** and **7ac**, respectively, although the enantioselectivity is slightly lower than **7aa** where the MeO substitution is at para position. The aryl groups bearing Me (**7ad**), Ph (**7ae**), CF_3 (**7af**), F (**7ag**), and $SiMe_3$ (**7ah**), at para-position were all successfully introduced into the products with high enantioselectivity (96–99% ee). For those zinc reagents whose reactions are slow, the reaction temperature was increased to 60 °C. Reactions of disubstituted phenylzincs and 2-naphthylzinc proceeded well to give the arylative cyclization products **7ai**, **7aj** and **7ak** of high % ee.

As a substituent R^1 at the alkyne terminus of 1,6-enyne **1**, primary alkyl and cyclopropyl groups are tolerable to give the corresponding products **7ba**, **7ca**, and **7da** with high % ee. Aromatic groups as R^1 at the alkyne terminus cause the opposite regiochemistry at the arylrhodation of alkyne,[10a] and hence the target alkylzincs were not formed. The 1,6-enyne substrate **1e** bearing trimethylsilyl group as R^1 gave the target product **7ea** with high ee albeit in a lower yield. The asymmetric arylative cyclization took place without serious problems for those 1,6-enyne substrates where the R^2 groups at 2-position of the alkene moiety are primary alkyls (**7fa** and **7ga**), a secondary alkyl (**7ha**), and a benzyl (**7ia**). Dimethyl and dibenzyl ethers at the carbon connecting propargyl and allyl groups underwent the arylative cyclization well (**7ja**, **7ka**, and **7la**), the yields and selectivity being as high as the *t*-butyl esters. The absolute configuration and *Z* geometry of the double bond was determined by X-ray crystal analysis of **7ka**. The yield of **7ma** was low (31%) in the reaction of methyl ester in place of *t*-butyl ester. It is because a bicyclo[2.2.1]heptanone derivative is formed as a side product by the intramolecular attack of alkylrhodium intermediate **B** to the ester carbonyl[6,7] (Scheme 1b).

The reaction of **1n**, which has an unsubstituted allyl group as the alkene moiety, gave us some information on the stability and reactivity of the alkylrhodium intermediate bearing a β-hydrogen (eq 1). High enantioselectivity (99% ee) and selective formation of the target product **7na** were observed in the reaction with the diene ligand L3*. With ligand L1*, which is used for other 1,6-enynes, the yield of **7na** was lower and the olefin isomer **9** was formed as a minor product. It is remarkable that the use of Fc-tfb ligand gave the olefin isomer **9** as a main product (**7na/9** = 1/2.8) and that high % ee was observed in **9** (88% ee) as well as in **7na** (99% ee). The product **9** should be formed through isomerization of homoallylic Rh intermediate **E** to allylic intermediate **F**, before transmetalation giving the corresponding homoallylic or allylic zinc species. It is most likely that the isomerization proceeds through several steps consisting of β-hydrogen elimination, migration of hydrido-rhodium to the other double bond, hydrorhodation, and allylic 1,3-shift. The high % ee of the isomerized product **9** may indicate that the hydrido-rhodium does not move from one coordination site to the other during those steps for isomerization.[23]

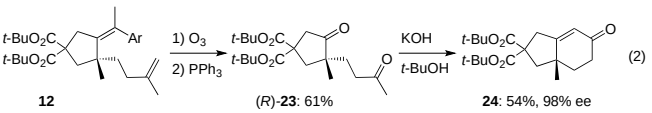


In addition to the benzoylation shown in Scheme 3, the enantioenriched alkylzinc **3a** was readily functionalized in one-pot by reaction with various types of electrophiles (Scheme 4). Thus, the copper-mediated reaction reported by Knochel[1,2,13] covers acylation (giving **11**), allylation (**12** and **13**), allenylation (**14** and **15**), alkynylation (**16**), coupling with alkyl and alkenyl halides (**17** and **18**), conjugate addition (**19**), and stannylation (**20**). Palladium-catalyzed cross-coupling of alkylzinc **3a** with aryl bromides giving **21a** and **21b** was also successful.[24] Treatment of **3a** with benzoquinone resulted in the oxidative cyclization giving tricyclic product **22**. It should be noted that all the reactions shown in Scheme 4 are one-pot reactions and the yields are based on enyne **1a** employed. The enantiomeric purities were all kept 99% as expected. As one example of transformation of the products obtained in Scheme 4, the synthesis of [4.3.0]bicyclic enone **24** is shown in equation 2.



[a] Yields are based on the amount of **1a**.

Scheme 4. Functionalization of the alkylzinc **3a** (99% ee) obtained by the Rh-catalyzed asymmetric arylation/cyclization.[a]



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Keywords: enantioenriched alkylzinc • asymmetric carbometalation • chiral diene ligand • rhodium catalyst

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Layout 2:

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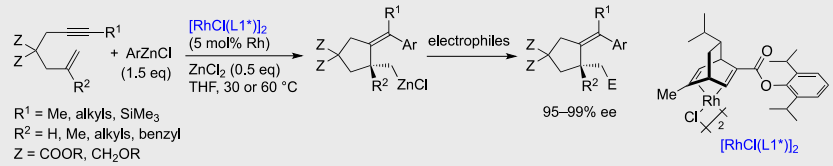

A chiral diene–rhodium complex was found to catalyze the reaction of 1,6-enynes with ArZnCl to give high yields of 2-(alkylidene)cyclopentylmethylzincs with high enantioselectivity (95–99% ee). The enantioenriched alkylzincs were readily converted in one-pot into a wide variety of functionalized products by taking advantages of their unique reactivity.

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