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Asymmetric Synthesis of Chiral Cyclopentanes Bearing an All-Carbon Quaternary Stereocenter via Zr-catalyzed Doubled Carboalumination

Shiqing Xu,^{†,[a]} Chuan Wang,^{†,[a,b]} Masato Komiyama,^[a] Yasuhiko Tomonari,^[a] and Ei-ichi Negishi^{*[a]}

Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday

Abstract: Herein we report a Zr-catalyzed enantio- and diastereoselective inter-intramolecular doubled carboalumination of unactivated 2-substituted-1,5-dienes which provides an efficient and direct access to chiral cyclopentanes with generation of two stereocenters including an all-carbon quaternary stereocenter generally in excellent diastereomeric ratios and high enantiomeric excesses. This tandem carboalumination process creates two new C-C bonds as well as a C-Al bond which can be in-situ oxidized with O₂ or hydrolyzed. Furthermore, the obtained chiral cyclopentanes can be readily functionalized to provide various chiral compounds.

In the last decades, zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA) developed by our group has proven to be a powerful tool for asymmetric synthesis of versatile chiral building blocks as well as various natural products containing alkyl-branched tertiary stereocenters, in many cases in enantiomerically pure form with the assistance of either lipasecatalyzed acetylation through kinetic resolution of the initial ZACA products or statistical enantiometric amplification.^[1,2] It is important to note that the previous examples are limited to the construction of chiral tertiary stereocenters. Cyclopentanes bearing an all-carbon quaternary stereocenter can be found in numerous natural products and synthetic biologically active compounds.^[3] However, construction of all-carbon quaternary stereocenters in a highly enantioselective manner, especially from simple starting materials, is still a formidable challenge for organic chemists.^[4] Transition metal-catalyzed intramolecular C-C bond formation reactions provide powerful methods for the synthesis of various carbo- and heterocyclic molecules. Thus, extensive studies have been performed on transition metalcatalyzed cyclizations of α, ω -bifunctional compounds such as diynes, enynes, and dienes.^[5] In contrast, studies of cyclization of dienes through an intermolecular carbometalation followed by a cascade diastereoselective intramolecular carbometalation, especially those cases with the formation of all-carbon guaternary

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centers, are still very rare.^[6] Herein, we report an efficient Zrcatalyzed doubled carboalumination of unactivated 1,5-dienes to provide a variety of chiral cyclopentanes bearing an all-carbon quaternary stereogenic center through the formation of two new C–C bonds as well as a C–Al bond.



Scheme 1. Optimum reaction conditions for the Zr-catalyzed stereoselective doubled carboalumination of 2-phenyl-1,5-hexadiene.

For optimization of the reaction conditions, we used 2-phenyl 1,5-hexadiene (1a) as the standard substrate. After a brief screening of solvents and additives and the tuning of temperature and catalyst loading, the optimal results concerning both enantioselectivity and the efficiency were achieved when the reaction was conducted in chloroform using 3 mol% (-)-Zr(NMI)₂Cl₂^[7] (NMI: 1-neomenthylindenyl) as catalyst and 1 equivalent amount of water as additive (Scheme 1).^[8] Presumably the addition of water to AlMe₃ leads to the generation of MAO or a more active species as a Lewis acid activator or co-activator to assist the formation of the active cationic zirconium complex.^[9] Remarkably, the initial intermolecular ZACA reaction proceeded exclusively at the monosubstitued olefin followed by intramolecular carboalumination^[10] and in-situ oxidation with oxygen providing the cyclopentane **2a** as the sole cyclic product.

After establishing the optimum reaction conditions, we started to evaluate the substrate scope of this doubled carboalumination reaction (Table 1). We first reacted diverse 1,5-dienes with AIMe₃ followed by in-situ oxidation with O₂. Generally, various 1,5-dienes with different substituents of the disubstituted double bond, such as aryls with electron-withdrawing and electron-donating groups, naphthyl, furyl, and c-hexyl underwent tandem carboalumination smoothly affording products **2a-i** in moderate to good yields, excellent diastereomeric ratios and good enantiomeric excesses. Subsequently, we investigated the substrate scope further by employing different trialkylaluminum

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Table 1. Evaluation of the substrate scope of the doubled carboalumination^[a]



Entry	2	R ¹	R^2	Yield [%] ^[b]	dr ^[c]	ee [%] ^[d]
1	а	Ph	Me	71	>98:2	87 (–87 ^[e])
2	b	4-FC ₆ H ₄	Me	66	>98:2	85
3	с	4-CIC ₆ H ₄	Me	60	>98:2	-88 ^[e]
4	d	3-CIC ₆ H ₄	Me	53	>98:2	87
5 ^[f,g]	е	4-MeOC ₆ H ₄	Me	47	>98:2	83
6 ^[g]	f	2-Naphthyl	Me	46	>98:2	84
7	g	2-Furyl	Me	54	>98:2	82
8	h	<i>c</i> -Hex	Me	60	>98:2	79 ^[h]
9 [a]	i	Me	Me	72	67:33 ^[i]	82 ^[i]
10 ^[j]	j	Ph	Et	55	>98:2	90
11 ^[j]	k	4-CIC ₆ H ₄	Et	41	>98:2	97
12 ^[j]	I I	3-CIC ₆ H ₄	Et	46	>98:2	97
13 ^[j]	m	Bn	Et	55	71:29	94
14 ^[i]	n	Ph	<i>n</i> -Pr	54	>98:2	91
15 ^[j]	ο	3-CIC ₆ H ₄	<i>n</i> -Pr	41	>98:2	94
16 ^[g]	р	CH ₂ OH	Me	68	98:2 ^[i]	-83 ^[e,i]
17 ^[g,k]	q	CH₂OTBDPS	Me	85	97:3 ^[i,I]	-83 ^[e,i,l]

[a] Unless otherwise specified, reactions were performed on a 0.5 mmol scale of diene 1 using 4.0 equiv trialkylaluminum, 3 mol% (-)-(NMI)₂ZrCl₂ and 1.0 equiv. H₂O in 2.5 mL chloroform. [b] Yields of the isolated product after flash chromatography. [c] Determined by 'H-NMR-spectroscopy. [d] Determined by HPLC-analysis on chiral stationary phase. [e] (+)-(NMI)₂ZrCl₂ catalyst was used. [f] 6 mol% catalyst was used. [g] Reactions were performed in dichloromethane. [h] Based on the corresponding benzoate derivative. [i] Determined by Grand by Catalysis on chiral stationary phase. [j] Reactions were performed in dichloromethane with 5 mol% catalyst loading and 1.0 equiv IBAO as additive. [k] 0.2 Equiv H₂O was used as additive. [l] Based on the corresponding desilylated derivative.

reagents like AIEt₃ and AI(nPr)₃. In these cases, freshly prepared IBAO (isobutylaluminoxane) solution^[11] instead of water was preferred in ethyl and higher alkylalumination reactions. Remarkably, the tandem carboalumination products 2j-o were formed in relatively higher enantioselectivities (90~97% ee) compared to the reactions using AIMe₃ (79~88% ee). Furthermore, in the cases of functionalized dienes (entries 16 and 17, Table 1), the reactions were quenched by adding water furnishing the products 2p and 2q in high yields and stereoselectivities. Concerning the diastereoselectivities of this doubled carboalumination reaction, both the bulkiness and the presence of a coordinating heteroatom of the substituent at disubstituted double bond seem to have significant influence. Various dienes bearing aryl, furyl, c-hexyl substituents (2a-h,j-l,n,o) showed excellent diastereoselectivites (dr > 98:2), while substrates with and Bn (2m) substituent exhibited Me (**2i**) lower diastereoselectivites. In addition, when the alkyl substituent of the disubstituted double bond includes a heteroatom (2p,q), the doubled carboalumination led to the products with high diastereomeric ratios of 98:2 (2p) and 97:3 (2q), respectively. Moreover, in the case of 2-phenyl-1,6-diene as substrate, only the intermolecular ZACA reaction occurred at the monosubstitued double bond giving an acyclic product.

Table 2. Investigation of the effect of heteromatom of alkyl substituents on diastereoselectivity^{[a]}

 $R^{1} + AIR^{2}_{3} = \underbrace{\begin{pmatrix} -) \cdot (NMI)_{2}ZrCI_{2} \\ (3 \text{ mol}\%) \\ CH_{2}CI_{2} \\ H_{2}O (1 \text{ equiv}) \\ \end{pmatrix}}_{R^{1}} \begin{bmatrix} AIR^{2}_{2} \\ R^{1} \\ H_{2}O \\ -78 \text{ °C}, \\ Me \\ R^{1} \\ H_{2}O \\ R^{1} \\$

			7			-p 1, and t 1
Entry	2	R ¹	R^2	Yield [%] ^[b]	dr ^[c]	ee [%] ^[c]
1	р	CH ₂ OH	Me	66	98:2	-83 ^[f]
2 ^[g]	q	CH₂OTBDPS	Me	85	97:3 ^[h]	-83 ^[f,h]
3	r	CH ₂ NBn ₂	Me	51	>98:2 ^[d]	n.d. ^[i]
4	i	Me	Me	72	67:33	82
5	s	CH ₂ CH ₂ TBDPS	Me	40	72:28 ^[d]	86 ^[e]
6	t	CH ₂ CH ₂ OH	Me	75	98:2	-83 ^[f]
7 [j]	t	CH ₂ CH ₂ OH	Me	72	98:2	-83 ^[f]
8 ^[g]	u	CH ₂ CH ₂ OTBDPS	Me	82	87:13 ^[h]	-83 ^[f,h]
9 ^[i]	v	CH ₂ CH ₂ OH	Et	72	87:13	-95 ^[f]
10 ^[j]	w	CH ₂ CH ₂ OTBDPS	Et	80	54:46 ^[h]	-95 ^[f,h]
11 ^{0]}	x	CH ₂ CH ₂ OTBDPS	Et	58	53:47	n.d. ^[i]

[a] Unless otherwise specified, reactions were performed on a 0.5 mmol scale of diene 1 using 4.0 equiv trialkylaluminum, 3 mol% (+)-(NMI)₂ZrCl₂ and 1.0 equiv. H₂O in 2.5 mL dichloromethane. [b] Yields of the isolated product after flash chromatography. [c] Determined by GC-analysis on chiral stationary phase. [d] Determined by ¹H-NMR-spectroscopy. [e] Determined by HPLC-analysis on chiral stationary phase. [f] (+)-(NMI)₂ZrCl₂ catalyst was used. [g] 0.2 Equiv H₂O was used as additive. [h] Based on the corresponding desilylated derivative. [j] Not determined. [j] Reactions were performed with 5 mol% catalyst loading and 1.0 equiv IBAO as additive.

As mentioned above, 2-aryl-1,5-dienes with a strictly planar configuration generally showed the excellent diastereoselectivities (dr > 98:2) of the cyclocarbometalation reactions with AIMe₃, AIEt₃ and AI(*n*Pr)₃ (2a-g,j-I,n,o). However, it seems that the diastereoselectivity of the carboalumination of 2alkyl-substituted dienes, due to more flexible configuration of alkyl substituents, is influenced by the coordinating heteroatom of the alkyl substituent at the disubstituted double bond. In order to investigate this effect, we carried out several control experiments (Table 2). First, we performed the doubled carboalumination reactions using the dienes containing an O- or a N-atom at the allylic position as substrates. In all these cases, excellent diastereomeric ratios were achieved (entries 1-3, Table 2). In contrast, when the diene substrates in the absence of a coordinating heteroatom, the reactions afforded the products with significantly lower diastereomeric ratios of 67:33 and 72:28, respectively (entries 4 and 5, Table 2). In addition, when the diene contains a OH substituent at homoallyl position (entries 6 and 7, Table 2), the cascade carboalumination reaction by using AIMe₃ provided 2t of an excellent diastereoselectivity (dr = 98:2). However, when CH2CH2OH substituent was replaced with CH₂CH₂OTBDPS (entry 8, Table 2), the diastereoselectivity decreased to 87:13 probably due to the increased steric hindrance and thus weaker coordination of zirconium complexes with substrate. This hypothesis was further confirmed by the findings that the doubled carboalumination products 2v,w,x from AlEt₃ were yielded in significantly lower diastereoselectivities (dr = 87:13, 54:46, and 53:47, entries 9-11, Table 2) in comparison to the reactions using AIMe₃ (2t,u, dr = 98:2 and 87:13). These

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results indicate that not only the presence but also the position of the heteroatom and steric hindrance are crucial for the diastereoselectivity of the doubled carboalumination of dienes bearing alkyl substituents.

A plausible reaction pathway of this doubled carboalumination reaction is depicted in Scheme 2. Initially, the intermolecular carbozirconation of 1,5-diene with trialkylaluminum reagent selectively proceeds at the sterically less-hindered monosubstituted double bond affording a chiral alkyl-zirconium species I.^[12] which subsequently undergoes a diastereoselective intramolecular carbozirconation on the disubstituted olefin to generate an all-carbon guaternary stereocenter. Two transition states II and III are postulated, wherein the latter one is disfavored due to the repulsion between ZrL₂ and R¹ in the presence of two bulky 1-neomenthylindenyl (NMI) ligands. The favored chair-like seven-membered ring transition state II leads to the formation of a cyclic organozirconium compound IV. Next, the aluminumzirconium transmetalation occurs providing а cvclic organoaluminum compound V, which can be subjected to either oxidation or hydrolysis.



Scheme 2. Plausible reaction pathway for Zr-catalyzed doubled carbometalation reaction.

To demonstrate the synthetic utility of this method, doubled carboalumination products were examined for further functionalizations (Scheme 3). First, doubled carboalumination product *ent-***2a** was efficiently converted to **3** by Ir-catalyzed α -alkylation of ketone with aliphatic alcohol as an electrophile via a borrowing-hydrogen process for C–C formation.^[13] Furthermore, compound **5** was synthesized in 72% yield by a C–O formation reaction from **2e**. In addition, a biologically active compound **7**, which is reported to bear anti-fungicidal activities,^[3b] was readily synthesized in two steps in a high overall yield (87%) starting from **2c**. Moreover, a protected cyclic β -amino acid **9** was also prepared through Mitsunobu reaction^[14] followed by subsequent oxidative cleavage of phenyl group with RuCl₃/NalO₄^[15] from **2a** (Scheme 3).



Scheme 3. Derivatization of the doubled carboalumination products.

The absolute configuration of the compound **7** was unambiguously determined to be 1*S*, 3*S* through X-ray crystal structure analysis (Figure 1).^[16] Therefore, the stereochemistry of the doubled carboalumination-oxidation products, which were obtained in the process catalyzed by (+)-Zr(NMI)₂Cl₂, was assigned to be 1*S*, 3*S*.



Figure 1. X Ray crystal structure of 7.

In summary, a doubled carboalumination reaction efficiently catalyzed by chiral (NMI)₂ZrCl₂ complex starting from simple unactivated 1,5-dienes (1) was developed via an interintramolecular cascade carbometalation process. A number of desired chiral cyclopentanes products with diverse substituents were obtained in good yields and high diastereo- and enantioselectivities. This tandem process creates two stereocenters including an all-carbon quaternary stereocenter through the formation of two new C–C bonds as well as a C–AI bond which can be applied to further synthetic transformations. Moreover, the doubled carboalumination products can be easily further functionalized to provide various chiral compounds including an anti-fungicidal agent.

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Keywords: ZACA Reaction • All-carbon Quaternary Stereocenter • Cyclopentanes • Carbometalation • Asymmetric Synthesis

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Asymmetric Synthesis of Chi Cyclopentanes Bearing an All-Carb Quaternary Stereocenter via catalyzed Doubled Carboaluminatior

All-carbon quaternary stereocenter: A Zr-catalyzed enantio- and diastereoselective doubled carboalumination of various unactivated 1,5-dienes has been developed, providing an efficient access to chiral cyclopentanes with generation of two stereocenters including an all-carbon quaternary stereocenter through the formation of two new C–C bonds as well as a C–Al bond in high diastereo- and enantioselectivities.