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Csp[3]–Csp[3] Homocoupling Reaction of Benzyl Halides Catalyzed by Rhodium

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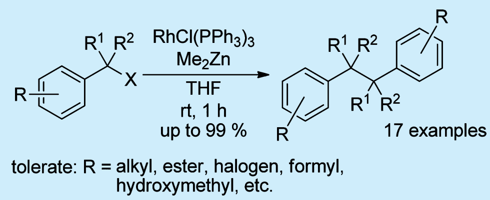
Supporting Information

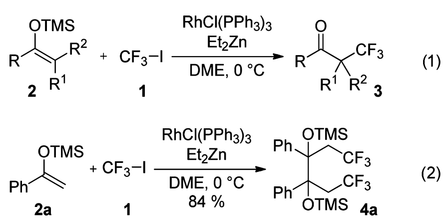
ABSTRACT: A highly reactive alkylrhodium complex was formed from Me_2Zn and $RhCl(PPh_3)_3$ and effectively catalyzed a Csp^3–Csp^3 homocoupling reaction of benzyl halides. A Csp^3–Csp^3 coupling reaction using Rh catalyst has not been reported up to now. The reaction proceeded under very mild conditions and gave the corresponding homocoupling products even if they had reactive substituents such as an uncovered formyl or hydroxymethyl group.



A transition-metal-catalyzed carbon–carbon bond formation is one of the most powerful tools in organic synthetic chemistry. Among them, there are many reactions that use a rhodium catalyst such as the aldol-type reaction, 1,4-addition reaction, hydroacylation, and carbocyclization.[1] These mechanisms involve the transmetalation or C–H insertion of a Rh species as the initial step, followed by C–C bond formation through reductive elimination. In recent years, Rh-catalyzed coupling reactions have undergone intense study, and it was found to be possible to insert a sp^3 carbon (Csp^3) in a molecule for the C–C bond formation.[2] However, a general reaction site for the coupling partner is the sp or sp^2 carbon (Csp or Csp^2), and there has been no report of a Csp^3–Csp^3 coupling reaction using Rh catalyst.

On the other hand, we reported an effective formation of a highly reactive alkylrhodium complex and its applications to α-trifluoromethylation,[3] α-fluoroalkylation,[4] and a reductive Reformatsky–Honda reaction.[5] In the previous α-trifluoromethylation (Scheme 1, eq 1), we found an interesting result that a

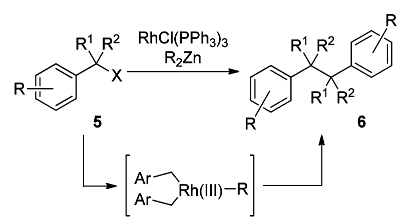
Scheme 1. Rh-Catalyzed α-Trifluoromethylation



dimeric product **4a** was obtained in a good yield when the silyl enol ether (**2a**) from acetophenone was used as the substrate (Scheme 1, eq 2).[3c]

The formation of **4a** suggested the generation of a rhodium–bisbenzyl complex, in which rhodium was bonded to the benzylic groups. Such a homocoupling reaction of benzyl halides is a very classical reaction, but most reactions must use a harsh condition or strong reducing agents such as Li,[6] Mg,[7] Cu,[8] Mn,[9] In,[10] SmI_2,[11] and Ti,[12] and sensitive functional groups cannot tolerate these conditions. Thus, we anticipated that new Csp^3–Csp^3 homocoupling reaction would be developed using our Rh catalyst if the rhodium-bisbenzyl complex could be formed from benzyl halides (Scheme 2).

Scheme 2. Rh-Catalyzed Homocoupling Reaction of Benzyl Halides



First, when methyl 4-(bromomethyl)benzoate (**5a**) was treated with 1.0 equiv of Et_2Zn in the presence of 2 mol % of $RhCl(PPh_3)_3$ in DME based on the previous conditions,[3c] the desired dimeric product **6a** was obtained in 24% yield along with the reduced product, methyl *p*-toluate (**7a**), in 55%. We thought that **7a** might be formed by the reduction with Rh–H, formed through the Rh–Et complex.[4a] Thus, replacing Et_2Zn with Me_2Zn remarkably suppressed the reduction and gave **6a** in an excellent yield as expected. Further reaction conditions were investigated thoroughly, and the use of 1.0 equiv of Me_2Zn and 2 mol % of $RhCl(PPh_3)_3$ in THF was found to be the best conditions to give **6a** (Scheme 3).

Various substrates were investigated under the optimal reaction conditions, and the results are summarized in Table 1. As shown in Table 1, the dimeric products **6a–j** were obtained in excellent yields regardless of the substituents on the benzene ring (entries 1–10). The reactive substituents such as ester or bromine could survive. More interesting results are that

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Scheme 3. Investigation of the Reaction Conditions

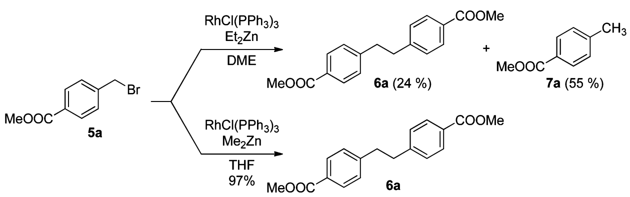
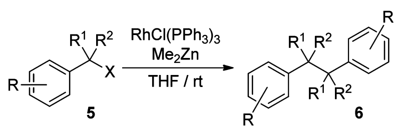
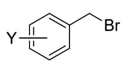
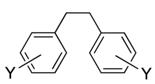
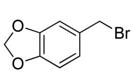
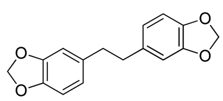
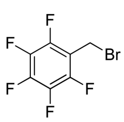
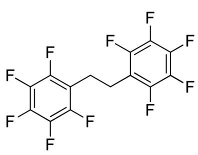
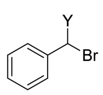
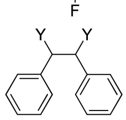
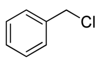
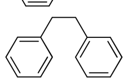


Table 1. Scope and Limitations for Homocoupling Reaction of Various Benzyl Halides



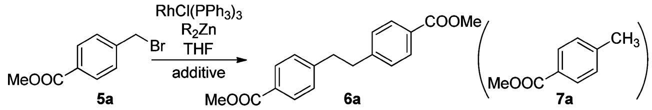
entry	substrate	product		time (h)	yield[a] (%)
1		 Y = 4-COOMe	6a	2	97
2		4-CHO	6b	3	65
3		4-F	6c	2	95
4		2-Br	6d	1	97
5		4-Br	6e	1	quant
6		H	6f	1	quant
7		2-Me	6g	1	quant
8		4-Me	6h	1	97
9		4-*t*-Bu	6i	1	96
10[b]		4-CH2OH	6j	1	76
11			6k	1	91
12			6l	1	87
13		 Y = Me	6m	2	84 [1:1][c]
14		CH2COOEt	6n	24	62 [1.2:1][d]
15		Ph	6o	2	67
16		COOMe	6p	1	58 [1:1][c]
17[e]			6f	24	58

[a]Isolated yield. [b]The reaction was carried out with 2 equiv of Me_2Zn. [c]Diasteromeric ratio [*meso*:*dl*] based on GLC. [d]Diasteromeric ratio [*meso*:*dl*] based on isolated yield. [e]The reaction was refluxed.

uncovered formyl and hydroxymethyl groups gave the products **6b** and **6j**. There are no reports that a highly reactive formyl or hydroxymethyl group was used in the homocoupling reaction of benzyl halide (Table 1, entries 2 and 10). 3,4-Methylenedioxybenzyl bromide gave **6k** in an excellent yield, which could be used as a precursor of natural products such as highly brominated bis-phenol and (±)-polysiphenol.[13] Pentafluorobenzyl bromide also gave **6l** in a satisfactory yield (Table 1, entry 12). Furthermore, the products **6m−p** that have substituents on the benzylic position were obtained in moderate to good yields, although the substituents affected the yields (Table 1, entries 13−16). Benzyl chloride also gave the product **6f** in a moderate yield, but the reaction required heat for a prolonged time (Table 1, entry 17).

It is not surprising that the Rh catalyst played an important role in this reaction. As shown in Table 2, a reaction of methyl 4-(bromomethyl)benzoate (**5a**) with Et_2Zn in the presence of $RhCl(PPh_3)_3$ gave **6a** and methyl *p*-toluate (**7a**) that derived from a reduction by Rh−H complex without the deuteration,

Table 2. Investigation for the Mechanism of Rh-Catalyzed Homocoupling Reaction



entry	$RhCl(PPh_3)_3$ (mol %)	R_2Zn (equiv)	additive (equiv)	time (h)	yield (%)[a] 5a	6a
1[b]	2	Et_2Zn (1)	none	1	ND	37[c]
2	2	Me_2Zn (1)	none	1	ND	97
3[d]	none	Me_2Zn (1)	none	12	84	trace
4[d]	none	Me_2Zn (1)	O_2 (xs)[e]	12	89	ND
5	2	Me_2Zn (0.75)	none	12	ND	75
6	2	Me_2Zn (0.5)	none	12	31	45
7	2	Me_2Zn (0.1)	none	12	68	10
8	2	Ph_2Zn (1)	none	1	ND	82[f]
9	2	BnZnBr (1)	none	20	70	ND

[a]Isolated yield. [b]The reaction was quenched by D_2O. [c]**7a** was isolated in 36% without deuteration. [d]The reaction was carried out under air. [e]O_2 was gently bubbled during the time. [f]Biphenyl was also isolated in 70%.

even if the reaction was quenched with D_2O as shown in entry 1.[4a] As expected, changing the Zn species from Et_2Zn to Me_2Zn suppressed the reduction to give **6a** in an excellent yield (Table 2, entry 2). On the other hand, **5a** was recovered in a radicalic condition under air or O_2 bubbling (Table 2, entries 3 and 4).[14] This means that a radical mechanism might not be the main route of the reaction. Furthermore, 1 equiv of Me_2Zn must be used for the reaction to go to completion (Table 2, entries 5−7). In addition, the use of Ph_2Zn[15] gave **6a** in 82% yield along with biphenyl in 70% yield, although **5a** was recovered when BnZnBr was used (Table 2, entries 8 and 9). This means the key intermediate is not a higher nucleophilic alkylzinc halide but a rhodium complex for generating **6a**.[16]

Based on the above results and our previous report,[3c] we propose the reaction mechanism of the Rh-catalyzed homocoupling reaction as shown in Figure 1. In the initial step, Rh catalyst

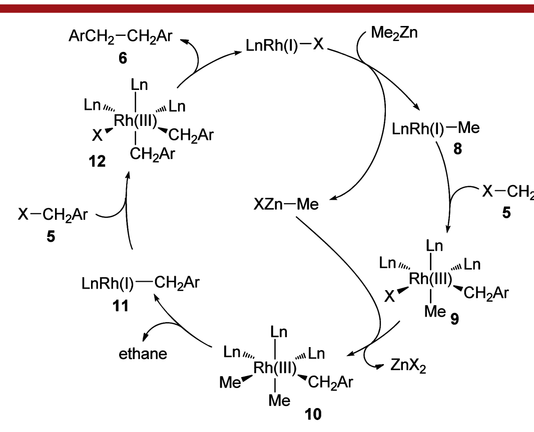


Figure 1. Tentative reaction mechanism of Rh-catalyzed homocoupling reaction.

reacted with Me_2Zn to give a highly reactive Rh−methyl complex **8**. Oxidative addition of benzyl halide **5** onto **8** gave a Rh(III) complex **9**. Then a higher nucleophilic MeZnX immediately reacted with the complex **9** to give another Rh(III) complex **10**. The elimination of ethane from **10** gave a Rh−benzyl complex **11**, and another oxidative addition of benzyl halide **5** onto **11** led to formation of Rh(III)−bisbenzyl complex **12**. The final reductive elimination gave the desired dimeric product **6** and regenerated Rh catalyst.

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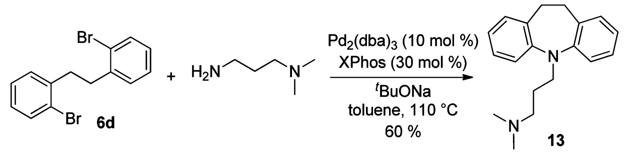
At this stage, we unfortunately have not clarified the reason why ethylbenzene was not formed from Rh(III) complex **9**. Our present speculation is that the reaction rate from **9** to **10** might be fast enough in this reaction.

To expand the synthetic utility, a homocoupling product was applied to the synthesis of imipramine. Imipramine is one of the earliest drugs used as a tricyclic antidepressant (TCA), and it has also been used to treat nocturnal enuresis.[17] There are many reports for the synthesis of imipramine and its analogues to date, but most of syntheses were carried out using dibenzo[*b*,*f*]-azepines as the starting material. Consequently, there is a demand for other pathways for synthesizing imipramine and its analogues. Recently, some groups reported a new approach for ring-closure reactions by using Buchwald–Hartwig amination.[18] We applied the amination to **6d** to give imipramine (**13**) in good yield (Scheme 4).

Scheme 4. Synthesis for Imipramine Using Pd-Catalyzed Double Amination



In conclusion, we have developed a novel Rh-catalyzed homocoupling reaction and proposed a reaction mechanism. Our reaction proceeds under very mild conditions and can be applied to various substrates which have sensitive substituents. To the best of our knowledge, this kind of reaction using an Rh catalyst for a Csp^3–Csp^3 coupling reaction has not been reported. Furthermore, we provided a new approach to imipramine from a homocoupling product. This means that various types of imipramine derivatives would be accomplished by a synthesis using the corresponding 1,2-bis(2-bromophenyl)-ethanes derived from our homocoupling reaction. The reaction could be applied to the synthesis of various dibenzylic products, and we hope for further expansion to other fields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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