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Role of Sterically Demanding Chiral Dirhodium Catalysts on Site Selective C–H Functionalization of Activated Primary C–H Bonds

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ABSTRACT: The influence of sterically demanding dirhodium tetracarboxylate catalysts on the site selectivity of C–H functionalization by means of rhodium carbene induced C–H insertion is described. The established dirhodium tetraprolinate-catalyzed reactions of aryldiazoacetates cause preferential C–H functionalization of secondary C–H bonds due to competing steric and electronic effects. The sterically more demanding dirhodium tetrakis(triarylcyclopropane-carboxylate) catalysts, exemplified by dirhodium tetrakis-[(*R*)-(1-(biphenyl)-2,2 diphenylcyclopropane carboxylate)] (Rh_2(*R*-BPCP)$_4$), favor C–H functionalization of activated primary C–H bonds. Highly site selective and enantioselective C–H functionalization of a variety of simple substrates containing primary benzylic, allylic and methoxy C–H bonds was achieved with this catalyst. The utility of this approach has been demonstrated in the late-stage primary C–H functionalization of (-)-α-cedrene and a steroid.

INTRODUCTION

C–H functionalization is a research area of intense interest because it has the potential to revolutionize the way complex molecules are synthesized.[1] One of the main challenges in this area of chemistry is the development of predictable site selective C–H functionalization methods.[2] The most successful approaches to achieve predictable selectivity has been through the use of directing groups.[3] Even though some of these directing groups are useful for further transformations, such a strategy often limits flexibility and requires additional steps to introduce and remove the directing groups. Consequently, many recent studies have focused on developing new approaches for site selective C–H functionalization relying on other controlling factors.[4] Particularly attractive are C–H functionalization methods in which the site selectivity is under reagent or catalyst control and can be modified as needed.

In the past decades, we have been exploring the scope of site selective intermolecular C–H functionalization by means of rhodium-catalyzed reactions of donor/acceptor carbenes (Scheme 1).[5] The rhodium-bound donor/acceptor carbenes have attenuated reactivity compared to acceptor only substituted carbenes,[6] enabling highly selective C–H functionalization to be achieved. The site selectivity is controlled by a delicate balance of steric and electronic effects.[7] Highly substituted sites are electronically favored because build-up of positive charge occurs at the carbon during the C–H insertion step, but this is counterbalanced by the steric demands of the carbene complex. Thus, in the reactions with the dirhodium tetraprolinate catalyst Rh_2(*R*-DOSP)$_4$ (Figure 1), C–H functionalization is generally preferred at secondary C–H bonds (Scheme 1), although a few examples of functionalization of sterically accessible tertiary C–H bonds[6c,,8] and electronically activated primary C–H bonds[9] are known. In this paper, we describe a major change in the site selectivity of carbene-induced C–H functionalization using the bulky catalyst Rh_2(*R*-BPCP)$_4$ (Figure 1), which results in a strong preference for reactions to occur at primary C–H bonds (Scheme 1). Furthermore, these reactions proceed with high levels of asymmetric induction.

Scheme 1. Site Selectivity of Rhodium Carbene Induced C–H Functionalization

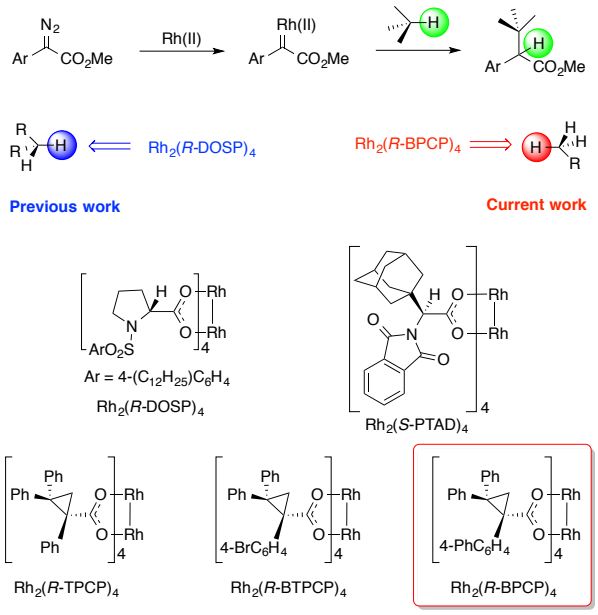


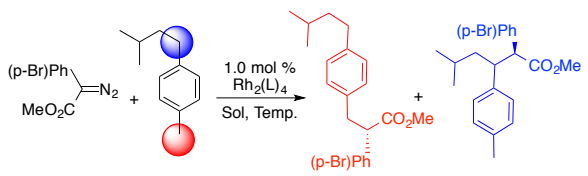
Figure 1. Structure of Chiral Dirhodium Catalysts

RESULTS AND DISCUSSIONS

A variety of chiral dirhodium catalysts have been prepared to control the chemistry of donor/acceptor carbenes, and representative catalysts are shown in Figure 1.[10] We have recently shown that catalysts with triarylcyclopropanecarboxylate ligands have unusual properties because they are sterically demanding.[10d-f] We hypothesized that these bulkier catalysts could influence the site selectivity of the C–H functionalization of donor/acceptor carbenes. The reaction of methyl (4-

bromophenyl)diazoacetate **1** with 4-isopentyltoluene **2** was used for the initial evaluation because **2** contains several types of C–H bonds. When the established catalysts, Rh_2(*R*-DOSP)$_4$[10a] and Rh_2(*S*-PTAD)$_4$[10c] were used, the reaction resulted in a mixture of benzylic C–H functionalization products **3** and **4**[11]. In contrast, the triphenylcyclopropane carboxylate catalyst Rh_2(*R*-TPCP)$_4$ switched the selectivity towards primary benzylic C–H bonds, providing **3** in 86% yield and 76% ee (Table 1, entry 3). Further examination of related catalysts revealed that the biphenyl derivative Rh_2(*R*-BPCP)$_4$ gave the highest level of enantioselectivity, generating **3** in 94% ee (entry 5). Additional optimization of solvents revealed that Rh_2(*R*-BPCP)$_4$ retained high enantioselectivity when trifluorotoluene and dichloromethane were used as solvent (entries 6 and 7), which is different from the general behavior of Rh_2(*R*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$.[10a,c] Furthermore, good yields of **3** could be obtained with just 1.2 equiv. of **2** and 0.5 mol% of Rh_2(*R*-BPCP)$_4$. Indeed, the enantioselectivity was still unchanged when only 0.1 mol% of Rh_2(*R*-BPCP)$_4$ was used but under these conditions, the yield of **3** was lower (entry 11). It is noted that the use of dichloromethane rather than the expensive 2,3-dimethylbutane and only 1.2 equiv. of the substrate adds a practical value for this reaction.

Table 1. Initial Studies on Selective C–H Functionalization[a]



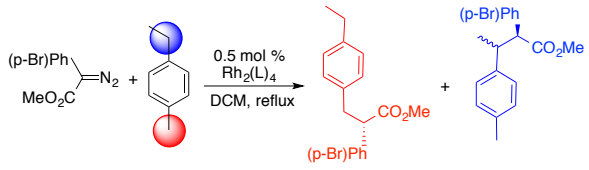
1 **2** **3** **4**

entry	catalyst	solvent	(eq.) **2**	ratio **3**:**4**	yield (%)[b]	ee (%) **3**
1	Rh_2(*R*-DOSP)$_4$	DMB	5.0	1:1.7	70	77
2	Rh_2(*S*-PTAD)$_4$	DMB	5.0	1.1:1	73	70
3	Rh_2(*R*-TPCP)$_4$	DMB	5.0	>20:1	86	76
4	Rh_2(*R*-BTPCP)$_4$	DMB	5.0	>20:1	90	90
5	Rh_2(*R*-BPCP)$_4$	DMB	5.0	>20:1	90	94
6[c]	Rh_2(*R*-BPCP)$_4$	$PhCF_3$	5.0	>20:1	84	89
7	Rh_2(*R*-BPCP)$_4$	DCM	5.0	>20:1	87	94
8	Rh_2(*R*-BPCP)$_4$	DCM	2.0	>20:1	84	95
9	Rh_2(*R*-BPCP)$_4$	DCM	1.2	>20:1	84	95
10[d]	**Rh_2(*R*-BPCP)$_4$**	**DCM**	**1.2**	>20:1	**82**	**95**
11[e]	Rh_2(*R*-BPCP)$_4$	DCM	1.2	>20:1	63	95

[a]Standard reaction conditions, aryldiazoacetate **1** (0.4 mmol) was added to **2** and catalyst (1 mol%) in the indicated reflux solvent in 1.5 h, in an argon atmosphere, and then reflux another 1.5 h after addition. [b]Isolated yield of **3**, yields in entry 1 and 2 refer to the combined yield of **3** and **4**. [c]55 °C internal temperature. [d]0.5 mol% catalyst loading. [e]0.1 mol% catalyst loading.

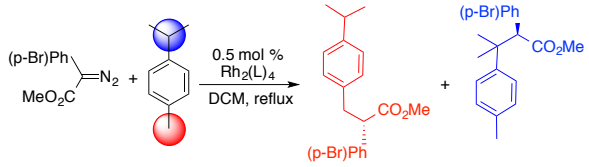
We subsequently explored the influence of Rh_2(*R*-BPCP)$_4$ with more challenging substrates (Scheme 2) The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of 4-ethyltoluene (**5**) is known to occur selectively at the secondary benzylic site (**6**:**7** < 1:20).[9a] In contrast, the Rh_2(*R*-BPCP)$_4$-catalyzed reaction favors C–H functionalization at the primary C–H bond (**6**:**7** = 5:1) in a 74% combined isolated yield, with **6** produced in 92% ee. Another challenging substrate is isopropyl toluene (**8**), which under Rh_2(*R*-DOSP)$_4$-catalyzed reaction gave a mixture of primary/tertiary C-H functionalization[8b] (**9**:**10** = 1:4). However, when Rh_2(*R*-BPCP)$_4$ was used, the primary C–H functionalization product **9** was selectively formed (**9**:**10** > 20:1) in 75% isolated yield and 97% ee.

Scheme 2. C–H Functionalization of Ethyltoluene and Isopropyltoluene[a]



1 **5** **6** **7**

catalyst	ratio **6**:**7**	yield (%)	ee (%) **7**
Rh_2(*R*-DOSP)$_4$	**<1:20**	75	-
Rh_2(*R*-BPCP)$_4$	**5:1**	74[b]	92



1 **8** **9** **10**[c]

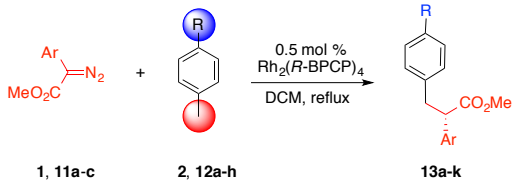
catalyst	ratio **9**:**10**	yield (%)	ee (%) **9**
Rh_2(*R*-DOSP)$_4$	**1:4**	72[a]	73
Rh_2(*R*-BPCP)$_4$	**>20:1**	75	97

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to toluene substrate (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol%) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere. [b]Combined yield. [c]**10**, 55% ee under Rh_2(*R*-DOSP)$_4$ catalyst.

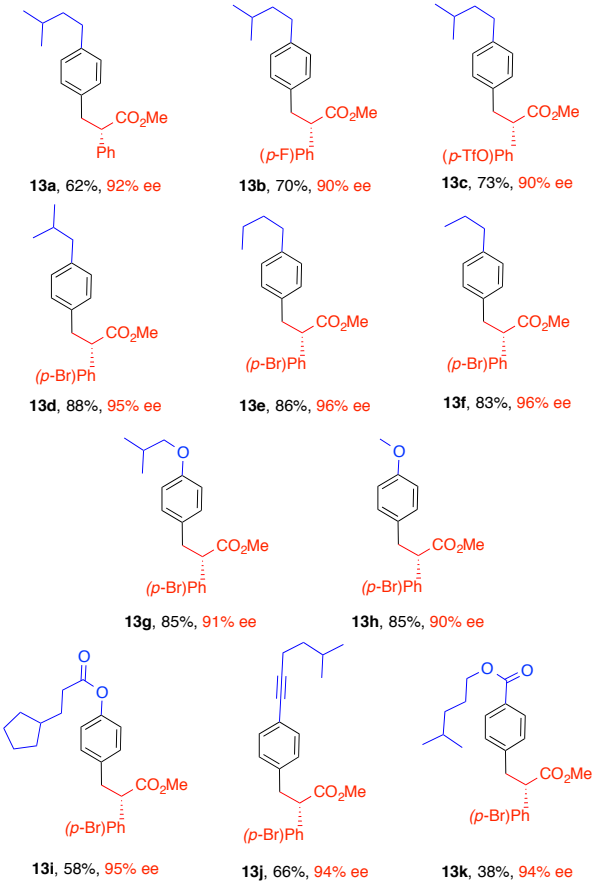
The scope of the Rh_2(*R*-BPCP)$_4$-catalyzed C–H functionalization by methyl aryldiazoacetates **1** and **11** was then examined with a range of aromatic substrates (Table 2). Good site selectivity and enantioselectivity was achieved with a variety of aryldiazoacetates **11a-c** as illustrated for **13a-c** (>20:1 1°, 90-92% ee). Even though the Rh_2(*R*-BPCP)$_4$-catalyzed reaction of **1** with ethyltoluene gave a mixture of primary and secondary C–H insertion products, when the secondary site was slightly larger such as *iso*-butyl, n-butyl, and even n-propyl, the reaction was highly site selective as illustrated for **13d-f** (>20:1 1°, 95-96% ee). It was expected that the site selectivity would be more challenging in the systems containing competing methoxy and *iso*-butoxy groups, but once again **13g** and **13h** were cleanly formed (>20:1 1°, 90-91% ee). The reaction was compatible with alkyne and ester functional groups as illustrated for **13i-k** (>20:1 1°, 94-95% ee), but the yield of the ester derivative **12k** was only 38%, presumably because the primary methyl group is not as activated on account of the electron withdrawing nature of the ester group. The absolute configuration of product **3** was determined by X-ray crystallography of a related derivative (see supporting information for details). The absolute configuration of **3** is in agreement with the predicted model developed for the face selectivity of dirhodium tetrakis(triarylphenylcyclopropane carboxylate)-catalyzed carbene reactions.[10d] The absolute configuration of the other products was assigned by analogy.

Having established that Rh_2(*R*-BPCP)$_4$ enhances C–H functionalization of primary benzylic C–H bonds, studies were then conducted to determine if the same trend would be seen for allylic C–H functionalization (Scheme 3). Rh_2(*R*-DOSP)$_4$-catalyzed reaction of aryldiazoacetate **1** and (*E*)-4-methylpent-2-ene **14** produced a mixture of C–H functionalization products, favoring the tertiary C–H insertion product **16** in poor enantioselectivity (48% ee); however, Rh_2(*R*-BPCP)$_4$ switched the selectivity towards the primary C-H bond and strongly favored the formation of **15** (**15**:**16** = 17:1, 94% ee, Scheme 3).

Table 2. Selective C–H Functionalization of Toluene Derivatives[a]



1, **11a-c** **2**, **12a-h** **13a-k**



13a, 62%, 92% ee **13b**, 70%, 90% ee **13c**, 73%, 90% ee

13d, 88%, 95% ee **13e**, 86%, 96% ee **13f**, 83%, 96% ee

13g, 85%, 91% ee **13h**, 85%, 90% ee

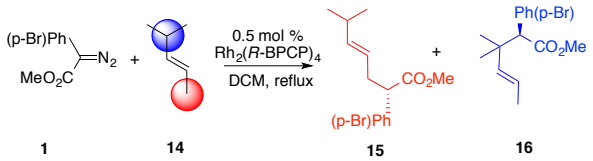
13i, 58%, 95% ee **13j**, 66%, 94% ee **13k**, 38%, 94% ee

[a]Reaction conditions, aryldiazoacetate (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to toluene substrate (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere; >20:1 1^o achieved in all cases.

The same trend of selectivity was also seen with 2-hexene **17**. Rh_2(*R*-BPCP)$_4$-catalyzed reaction prefers to give product **18** in high enantioselectivity (95% ee) while Rh_2(*R*-DOSP)$_4$-catalyzed transformation favors the vinyl methylene site, providing a mixture of diasteromers **19**.

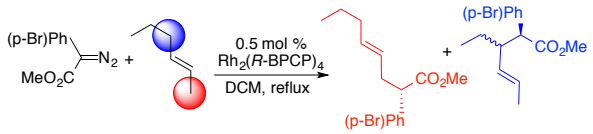
In certain cases, Rh_2(*R*-DOSP)$_4$-catalyzed reactions can lead to a mixture of C–H functionalization and cyclopropanation products.[7a,b] Therefore, it became of interest to determine whether Rh_2(*R*-BPCP)$_4$ would influence the chemoselectivity of such system. One example that leads to a mixture is the Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **1** with *trans*-anethole, which generated a 5:1 mixture of the C-H insertion **21** and cyclopropanation **22** products (Scheme 4). A previous report

Scheme 3. C–H Functionalization of (*E*)-4-Methylpent-2-ene and (*E*)-2-Hexene[a]



1 **14** **15** **16**

catalyst	ratio **15**:**16**	yield (%)	ee (%) **15**
Rh_2(*R*-DOSP)$_4$	1:7	81[b]	-
Rh_2(*R*-BPCP)$_4$	17:1	60	94

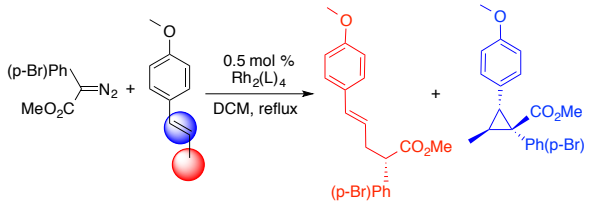


1 **17** **18** **19**

catalyst	ratio **18**:**19**	yield (%)[b]	ee (%) **18**
Rh_2(*R*-DOSP)$_4$	1:9	75	-
Rh_2(*R*-BPCP)$_4$	8:1	80	95

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to **14** or **17** (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere. [b]Combined yield.

Scheme 4. C–H Functionalization of *Trans*-Anethole[a]



1 **20** **21** **22**

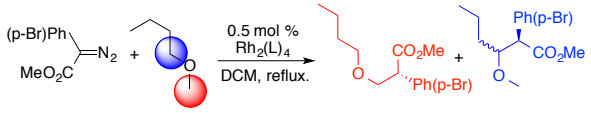
catalyst	ratio **21**:**22**	yield (%)	ee (%) **21**
Rh_2(*R*-DOSP)$_4$	5:1	76[b]	76
Rh_2(*R*-BPCP)$_4$	16:1	85	88

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to **20** (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere. [b]Combined yield.

indicated that the use of a sterically congested dirhodium catalyst Rh_2(TPA)$_4$ could improve the selectivity toward primary C–H insertion (**21**:**22** >15:1) in 2,3-dimethylbutane.[7a] When the reaction was conducted using Rh_2(*R*-BPCP)$_4$ as catalyst, the chemoselectivity has the same trend, providing the primary C–H insertion product in 85% isolated yield and 88% ee (**21**:**22** = 16:1).

Enhanced site selectivity was also observed with unsymmetrical ethers (Scheme 5). The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of **1** with methyl butyl ether gave a mixture of **24** and **25**. In contrast, the Rh_2(*R*-BPCP)$_4$-catalyzed reaction dramatically improved the selectivity for the primary C–H bond (>20:1), affording the product **24** in high yield (86%), but with relatively moderate enantioselectivity (64% ee).

Scheme 5. C–H Functionalization of 1-Methoxybutane[a]



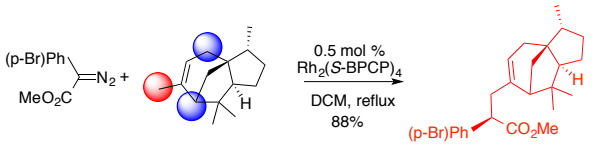
1 **23** **24** **25**

catalyst	ratio **24**:**25**	yield (%)	ee (%) **24**
Rh_2(*R*-DOSP)$_4$	**3:2**	77[b]	61
Rh_2(*R*-BPCP)$_4$	**>20:1**	86	64

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to **23** (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere. [b]Combined yield.

To challenge the high selectivity of Rh_2(BPCP)$_4$, (-)-α-cedrene **26** was considered to be an interesting substrate because it contains primary, secondary and tertiary allylic C–H bonds (Scheme 6). The Rh_2(*S*-BPCP)$_4$-catalyzed reaction of **1** with **26** proceeded cleanly and afforded the primary allylic C–H functionalization product **27** in 88% yield as a single diastereomer. No other regioisomers were observed in the ^{1}H NMR of the crude reaction mixture. The absolute configuration of **27** was determined by X-ray crystallography (see supporting information for details). The asymmetric induction observed in the formation of the new stereogenic center in **27** is consistent with what had been seen in **13l**, supporting the tentative assignments of the absolute configurations of the other products by analogy.

Scheme 6. Selective C–H Functionalization of (-)-α-Cedrene[a]

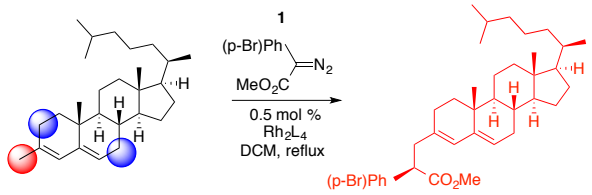


1 **26** **27**

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to **26** (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere.

A study was also conducted on the steroid derivative **28** (Scheme 7). Even though **28** has three allylic sites, the two secondary allylic sites contained within the steroid framework are sterically inaccessible for both the Rh_2(DOSP)$_4$ and Rh_2(BPCP)$_4$ catalysts. However, the primary C–H functionalization is still influenced by the nature of the catalyst. In the Rh_2(*R*-DOSP)$_4$-catalyzed reactions, a 3:1 mixture of diastereomers were formed, whereas the Rh_2(*S*-DOSP)$_4$-catalyzed reaction appears to be the matched reaction because **29** is formed in a 16:1 mixture, favoring the opposite diastereomer. The chiral influence is more pronounced with the Rh_2(BPCP)$_4$ catalysts. The Rh_2(*R*-BPCP)$_4$-catalyzed reaction gave a 6:1 mixture of diastereomers, while Rh_2(*S*-BPCP)$_4$-catalyzed reaction gave a > 20:1 of the opposite diastereomer, which can be isolated in 96% yield. The absolute configuration of the new stereogenic center generated in the matched reactions was tentatively assigned as (*R*) by analogy.

Scheme 7. Late-Stage C–H Functionalization of Steroid[a]



28 **29**

catalyst	dr	yield (%)[b]
Rh_2(*R*-DOSP)$_4$	1:3	82
Rh_2(*S*-DOSP)$_4$	16:1	86
Rh_2(*R*-BPCP)$_4$	1:6	89
Rh_2(*S*-BPCP)$_4$	**>20:1**	96

[a]Reaction conditions, aryldiazoacetate **1** (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to **28** (0.48 mmol, 1.2 equiv.) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in reflux dichloromethane (1.5 mL) in 1.5 h, then reflux 1.5 h in an argon atmosphere. [b]Combined yield of the two diasteromers for the top three entries.

CONCLUSION

We have developed an effective method for highly selective C–H functionalization of primary C–H bonds. The method was successfully applied to selective C–H functionalization of complex targets such as (-)-α-cedrene and a steroid. This study illustrates that highly site selective C–H functionalization can be achieved without resorting to directing groups. Moreover, the catalyst can be a major controlling element of the site selectivity. Further application this family of dirhodium catalyst in asymmetric transformation is underway.

ASSOCIATED CONTENT

Supporting Information

Full experimental data for the compounds described in the paper and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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(11) The stereocenter of **4** and other secondary and tertiary C–H insertion products are tentatively assigned by analogy with the stereoinduction observed in the primary C–H insertion.

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