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Role of Sterically Demanding Chiral Dirhodium Catalysts in Site-Selective C−H Functionalization of Activated Primary C−H Bonds

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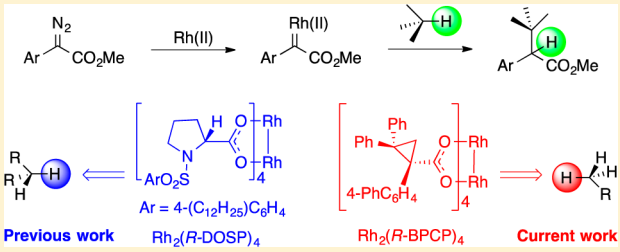
Supporting Information

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 as a result of competing steric and electronic effects. The sterically more demanding dirhodium tetrakis(triarylcyclopropanecarboxylate) catalysts, exemplified by dirhodium tetrakis[(*R*)-(1-(biphenyl)-2,2-diphenylcyclopropanecarboxylate)] [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 by the late-stage primary C−H functionalization of (−)-α-cedrene and a steroid.

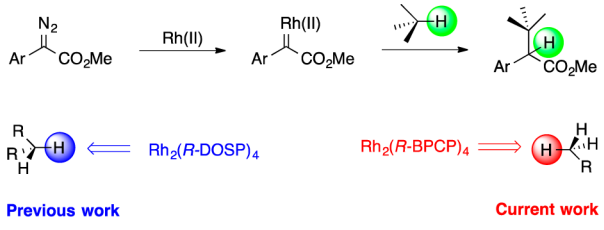


INTRODUCTION

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 have 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 with 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 buildup 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

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



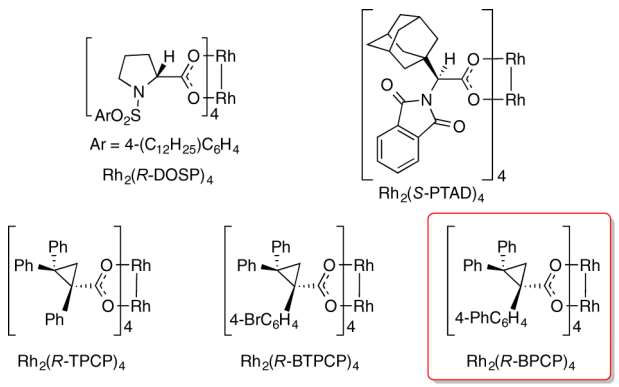


Figure 1. Structures of chiral dirhodium catalysts.

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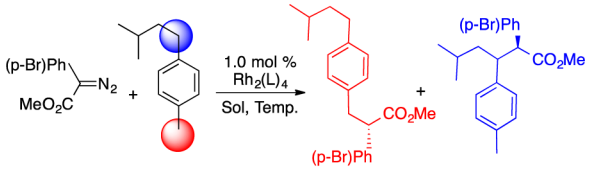
this paper, we describe a major change in the site selectivity of carbene-induced C−H functionalization through the use of the bulky catalyst Rh_2(*R*-BPCP)$_4$ (Figure 1), which results in a strong preference for reactions to occur at primary C−H bonds (Scheme 1). Furthermore, these reactions proceed with high levels of asymmetric induction.

RESULTS AND DISCUSSION

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** (Table 1, entries 1 and 2).[11] In contrast,

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



1 2 3 4

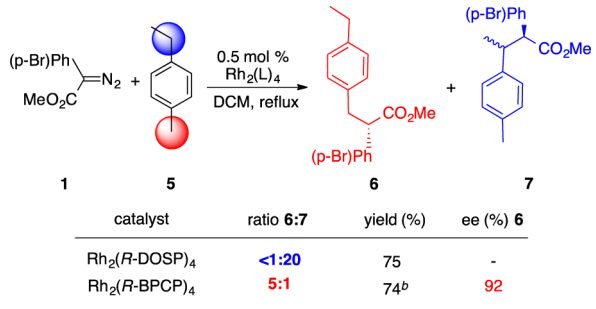
entry	catalyst	solvent	equiv of **2**	**3**:**4**	yield (%)[b]	ee of **3** (%)
1	Rh_2(*R*-DOSP)$_4$	DMB	5.0	1:1.7	70	77
2	Rh_2(*S*-PTAD)$_4$	DMB	5.0	1.1:1	73	70
3	Rh_2(*R*-TPCP)$_4$	DMB	5.0	>20:1	86	76
4	Rh_2(*R*-BTPCP)$_4$	DMB	5.0	>20:1	90	90
5	Rh_2(*R*-BPCP)$_4$	DMB	5.0	>20:1	90	94
6[c]	Rh_2(*R*-BPCP)$_4$	$PhCF_3$	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 over 1.5 h in an argon atmosphere, and then the mixture was refluxed for another 1.5 h after the addition. [b]Isolated yields of **3**; the yields in entries 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.

the triphenylcyclopropanecarboxylate catalyst Rh_2(*R*-TPCP)$_4$ switched the selectivity toward primary benzylic C−H bonds, providing **3** in 86% yield and 76% ee (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 the solvent revealed that Rh_2(*R*-BPCP)$_4$ retained high enantioselectivity when trifluorotoluene or dichloromethane was used as the 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 % Rh_2(*R*-BPCP)$_4$. Indeed, the enantioselectivity was still unchanged when only 0.1 mol % 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.

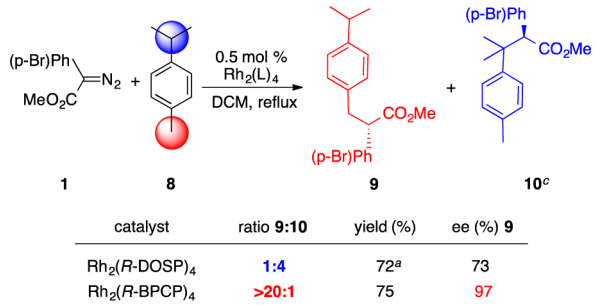
We subsequently explored the influence of Rh_2(*R*-BPCP)$_4$ with more challenging substrates (Scheme 2). The Rh_2(*R*-DOSP)$_4$-catalyzed reaction of 4-ethyltoluene (**5**) is known to occur selectively at the secondary benzylic site (**6**:**7** < 1:20).[9a] In contrast, the Rh_2(*R*-BPCP)$_4$-catalyzed reaction favors C−H functionalization at the primary C−H bond (**6**:**7** = 5:1) in a combined isolated yield of 74%, with **6** produced in 92% ee. Another challenging substrate is isopropyltoluene (**8**), which in the Rh_2(*R*-DOSP)$_4$-catalyzed reaction gave a mixture of primary and tertiary C−H functionalization[9b] (**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 (%) **6**
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 the toluene substrate (0.48 mmol, 1.2 equiv) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in refluxing dichloromethane (1.5 mL) over 1.5 h, and the mixtue was then refluxed for 1.5 h in an argon atmosphere. [b]Combined yield. [c]**10** was formed in 55% ee with the Rh_2(*R*-DOSP)$_4$ catalyst.

The scope of the Rh_2(*R*-BPCP)$_4$-catalyzed C−H functionalization using 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 isobutyl, *n*-butyl, or 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

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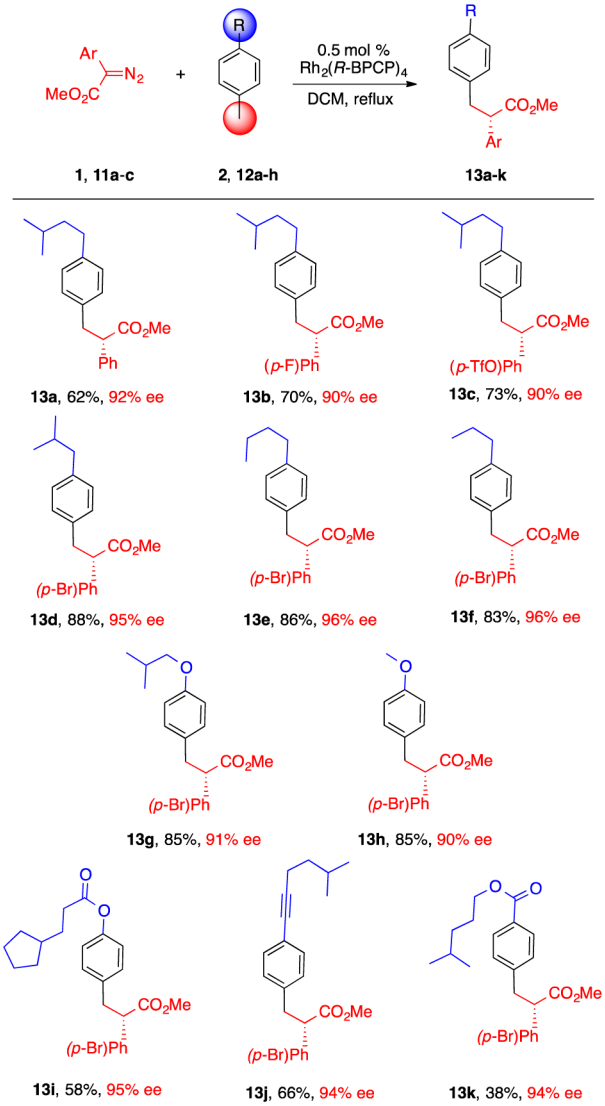
Table 2. Selective C−H Functionalization of Toluene Derivatives[a]

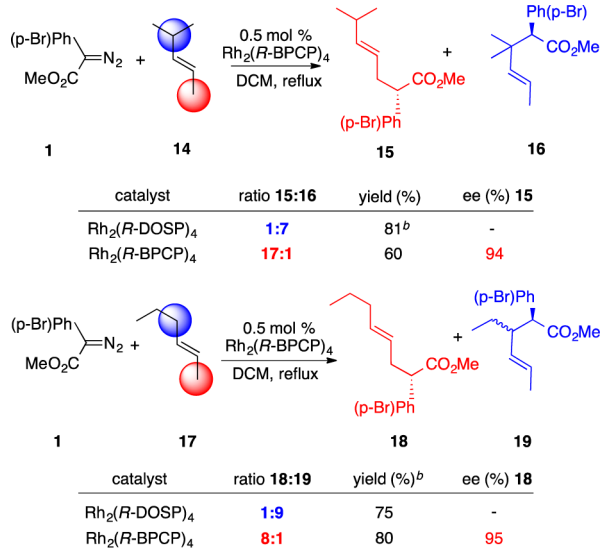


[a]Reaction conditions: aryldiazoacetate (0.4 mmol) in dichloromethane (2.5 mL) was slowly added to the toluene substrate (0.48 mmol, 1.2 equiv) and Rh_2(*R*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere. >20:1 selectivity for the 1° product was achieved in all cases.

would be more challenging in the systems containing competing methoxy and isobutoxy 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 **13k** 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 the Supporting Information for details). The absolute configuration of **3** is in agreement with the predicted model developed for the face selectivity of dirhodium tetrakis(triarylphenylcyclopropanecarboxylate)-catalyzed carbene reactions.[10d] The absolute configurations of the other products were 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 whether the same trend would be seen for allylic C−H functionalization (Scheme 3).

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



[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 refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere. [b]Combined yield.

The 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** with poor enantioselectivity (48% ee); however, Rh_2(*R*-BPCP)$_4$ switched the selectivity toward the primary C−H bond and strongly favored the formation of **15** (**15**:**16** = 17:1, 94% ee; Scheme 3). The same trend of selectivity was also seen with 2-hexene (**17**). The Rh_2(*R*-BPCP)$_4$-catalyzed reaction prefers to give product **18** with high enantioselectivity (95% ee), while the 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 systems. 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 C−H insertion product **21** and cyclopropanation product **22** (Scheme 4). A previous report 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 the catalyst, the chemoselectivity exhibited 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

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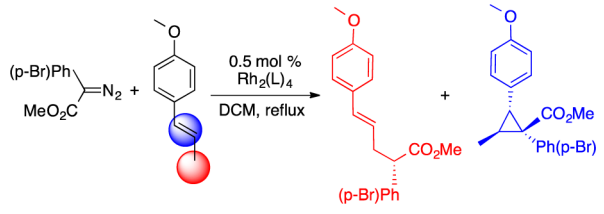
Scheme 4. C−H Functionalization of *trans*-Anethole[a]

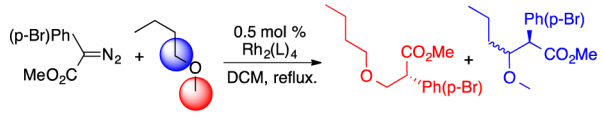


1 20 21 22

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 refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere. [b]Combined yield.

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



1 23 24 25

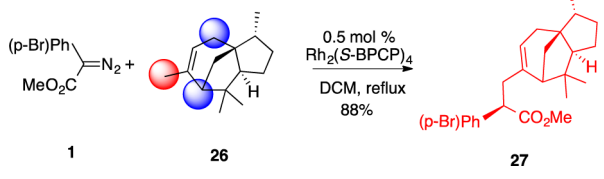
catalyst	ratio **24**:**25**	yield (%)	ee (%) **24**
Rh_2(*R*-DOSP)$_4$	**3:2**	77[b]	61
Rh_2(*R*-BPCP)$_4$	**>20:1**	86	**64**

[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 refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere. [b]Combined yield.

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).

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. 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 (Scheme 6). No other regioisomers were observed in the ^{1}H NMR spectrum of the crude reaction

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



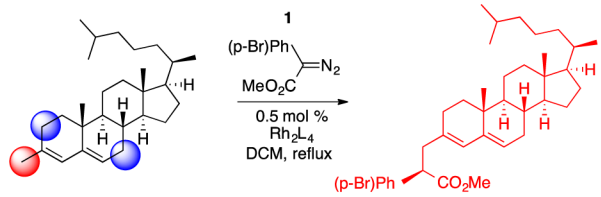
1 26 27

[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(*S*-BPCP)$_4$ (3.5 mg, 0.5 mol %) in refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere.

mixture. The absolute configuration of **27** was determined by X-ray crystallography (see the 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 **3**, supporting the tentative assignments of the absolute configurations of the other products by analogy.

A study was also conducted on the steroid derivative **28** (Scheme 7). Even though **28** has three allylic sites, the two

Scheme 7. Late-Stage C−H Functionalization of Steroid 28[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 refluxing dichloromethane (1.5 mL) over 1.5 h, and then the mixture was refluxed for 1.5 h in an argon atmosphere. [b]The top three entries are combined yields of the two diasteromers.

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 reaction, a 3:1 mixture of diastereomers was 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 the Rh_2(*S*-BPCP)$_4$-catalyzed reaction gave a >20:1 mixture in favor of the opposite diastereomer, which was isolated in 96% yield. The absolute configuration of the new stereogenic center generated in the matched reactions was tentatively assigned as *R* by analogy.

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 of this family of dirhodium catalysts in asymmetric transformations 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.

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Notes

The authors declare no competing financial interest.

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