Rhodium Carbenoid Induced Intermolecular C–H Functionalization at Tertiary C–H Bonds

Etienne Nadeau, Zhanjie Li, Daniel Morton, Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30097, USA
E-mail: hmdavie@emory.edu

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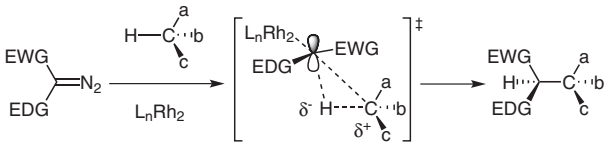
Abstract: Rhodium carbenoid induced intermolecular C–H functionalization can occur at either primary, secondary, or tertiary C–H bonds. This study illustrates the investigation for the optimum systems for reaction at tertiary C–H bonds

Key words: intermolecular C–H insertion, C–H functionalization, aryldiazoacetate, dirhodium

The metal-catalyzed selective functionalization of C–H bonds is an area of intense current interest.[1,2] Two distinct approaches have been developed to achieve such an outcome. The most widely employed has been the insertion of a metal complex into a C–H bond, followed by a subsequent transformation to generate synthetically useful organic products.[3–7] An alternative approach has been to insert a metal carbenoid[8–10] or nitrenoid intermediates[11] into the C–H bond, leading directly to the functionalized product (Scheme 1). We have demonstrated that donor/acceptor-substituted rhodium carbenoid intermediates are capable of highly regioselective and stereoselective C–H insertions.[10] The insertion occurs in a concerted, nonsynchronous manner, building positive charge at carbon of the C–H bond.[12] Thus, substrates that are capable of stabilizing charge build-up during the insertion are favored in this chemistry. However, charge stabilization is not the only factor involved. The generally large nature of the carbenoid reagent demands that steric considerations play a role. Hence, sterically crowded sites on the substrate are effectively protected from C–H functionalization.[10]



Scheme 1 C–H Functionalization by rhodium carbenoids

In recent years we have demonstrated that highly regioselective C–H insertions can be achieved. In general, secondary C–H bonds are most favorable because they tend to display the best balance between steric and electronic effects. Some illustrative examples of effective substrates are shown in structures **1**–**4** (Figure 1).[13–16] While many of these substrates have multiple C–H bonds, selective C–H functionalization can be efficiently achieved in a highly asymmetric fashion. Selective C–H functionalization at primary C–H bonds requires that the primary C–H bond is electronically activated, while more highly functionalized sites are appropriately deactivated, such as substrates **5**–**7**.[17–19] An impressive example of the steric influence is the reaction of *N*-Boc-*N*-methylbenzylamine (**6**),[17] which is selectively functionalized at the methyl group over the electronically activated benzyl group. Dimethoxyethane (**7**)[18] is preferentially functionalized at the primary C–H bond because the secondary C–H bond is deactivated by an electron-withdrawing β-oxygen group. A detailed assessment of the relative rates of reaction of different C–H bonds with dirhodium complexes confirmed that tertiary C–H bonds are, in the most part, inaccessible.[12,14,20] Very few examples of selective insertion into tertiary C–H bonds are known.

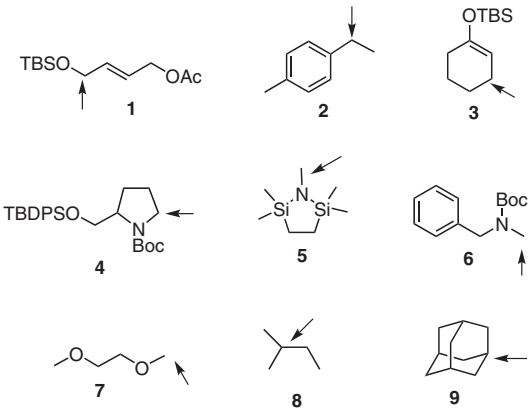


Figure 1 Examples of selective C–H functionalization (>95:5 regioselectivity) at secondary (**1**–**4**), primary (**5**–**7**), and tertiary (**8** and **9**) C–H bonds

The two most significant substrates are 2-methylbutane (**8**)[12] and adamantane (**9**).[12,21] This paper will describe the expansion of the C–H functionalization to a wider range of tertiary C–H bonds as part of an extensive ongoing investigation into the exploration of the scope of C–H functionalization with donor/acceptor carbenoids.

Two dirhodium complexes have emerged as the premier chiral catalysts for this chemistry.[22] The most well established is Rh_2(*S*-DOSP)$_4$[23] but in recent years, studies have indicated that Rh_2(*S*-PTAD)$_4$ has complimentary reactivity and often displays different product ratios to those of Rh_2(*S*-DOSP)$_4$ (Figure 2). Consequently, in this study, both catalysts were evaluated for their effectiveness for reaction at tertiary C–H bonds.

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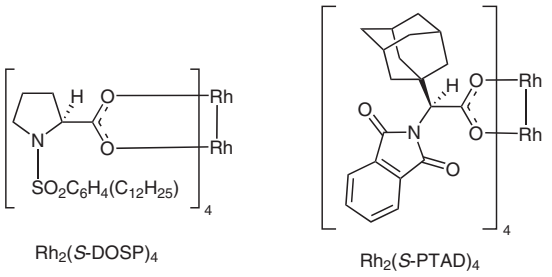
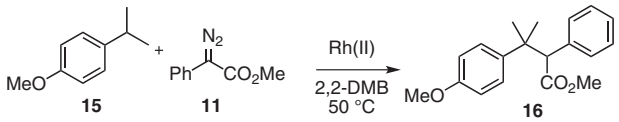


Figure 2 Chiral dirhodium catalysts

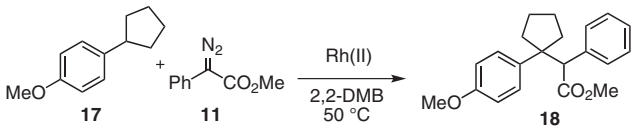
The first system examined was isopropylbenzene (**10**, Scheme 2). Previously, it has been shown that the aromatic ring in this substrate was reactive towards donor/acceptor carbenoids.[14] This was indeed the case here, although both catalysts influenced the overall reaction. In the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of phenyldiazoacetate **11** with **10**, a mixture of the C–H insertion product **12** and the double cyclopropanation product **13** were formed in about a 1:2 ratio. The same reaction catalyzed by Rh_2(*S*-PTAD)$_4$ gave a slightly improved isolated yield of the C–H insertion product **12**, but the byproducts were a mixture of the di- and the monocyclopropanated products, **13** and **14**. Neither catalyst generated **12** with much asymmetric induction (<10% ee). In both cases, no insertion occurred at the primary C–H positions.

Benzene rings can be sterically protected against reactions of donor/acceptor carbenoids through 1,4-disubstitution.[14,24] Thus, the reactions of *p*-isopropylanisole (**15**) and *p*-cyclopentylanisole (**17**) gave reasonable yields of the tertiary C–H insertion products, **16** and **18**, respectively, without evidence of reaction occurring at the aromatic ring or the primary C–H positions (Scheme 3). In general, the Rh_2(*S*-PTAD)$_4$-catalyzed reactions gave the highest yields of product, while the Rh_2(*S*-DOSP)$_4$-catalyzed reactions gave the highest enantioselectivity.

Having discovered systems capable of effective C–H functionalization at tertiary sites, examination of the reactivity difference between tertiary and primary C–H insertion was undertaken. In this case the choice of catalyst does have an influence on the product ratios. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of phenyldiazoacetate **11** with *p*-isopropyltoluene (**19**) gave a 2:1 mixture of the tertiary C–H insertion product **20** and the primary C–H insertion product **21**, while the Rh_2(*S*-PTAD)$_4$-catalyzed reaction gave a 4:1 ratio (Scheme 4). In line with our previous observations, the highest asymmetric induction in the formation of **20** (62% ee) was obtained in the reaction with Rh_2(*S*-DOSP)$_4$.



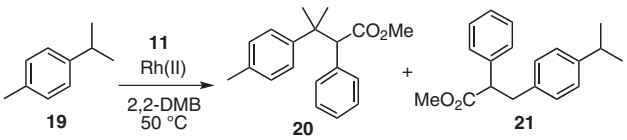
Rh(II)	Yield (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	48	48
Rh_2(*S*-PTAD)$_4$	81	11 (–)



Rh(II)	Yield (%[a])	ee (%)
Rh_2(*S*-DOSP)$_4$	39	20
Rh_2(*S*-PTAD)$_4$	54	16

[a] Determined from internal ^{1}H NMR standard.

Scheme 3 Reaction of **11** with *p*-isopropylanisole and *p*-cyclopentylanisole

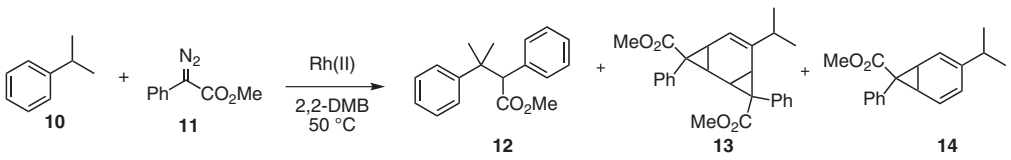


Rh(II)	Combined yield (%)	ratio[a] **20**/**21**	ee (%) of **20**	ee (%) of **21**
Rh_2(*S*-DOSP)$_4$	50	65:35	62	76
Rh_2(*S*-PTAD)$_4$	57	80:20	2 (–)	42 (–)

[a] Determined from analysis of the ^{1}H NMR of the crude reaction mixture.

Scheme 4 Reaction of **11** with isopropyltoluene

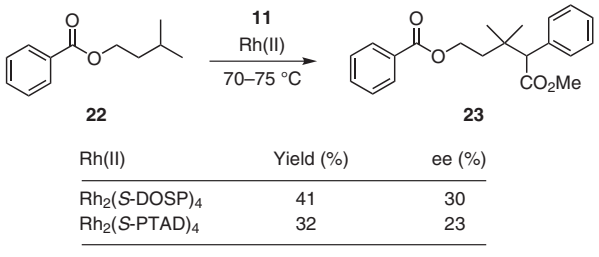
Selective C–H insertion at tertiary C–H bonds can also be achieved with unactivated systems as illustrated in structures **22** and **24** (Scheme 5). The methylene site adjacent



Rh(II)	Yield (%) **12**	**13**	**14**
Rh_2(*S*-DOSP)$_4$	21	48	0
Rh_2(*S*-PTAD)$_4$	30	16	20

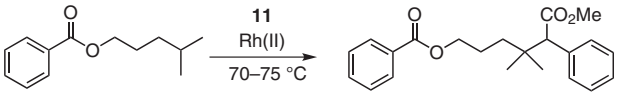
Scheme 2 Reaction of **11** with isopropylbenzene

to the isopropyl group is sterically inaccessible, while the benzoyloxy group behaves as an electron-withdrawing group and electronically deactivates the proximal methylene C–H bonds.[15] These unactivated systems are not especially effective carbenoid traps. Using our standard conditions (method A), only low yields (<10%) of the tertiary C–H insertion products were observed. Hence, more forcing conditions were applied. It was observed that under neatlike reaction conditions (method B), with the slow addition of phenyldiazoacetate (**11**) solution and concurrent removal of solvent, **23** and **25** could be isolated in 41% and 40% yield, respectively, with Rh_2(*S*-DOSP)$_4$ as catalyst. Even though the isolated yields of tertiary C–H insertion products **23** and **25** were under 50% with these two catalysts, there was no significant quantity (<5%) of other C–H insertion products. Once again, the Rh_2(*S*-DOSP)$_4$-catalyzed reactions gave the better enantioselectivity.



22 **23**

Rh(II)	Yield (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	41	30
Rh_2(*S*-PTAD)$_4$	32	23



24 **25**

Rh(II)	Yield (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	40	16
Rh_2(*S*-PTAD)$_4$	37	3

Scheme 5 Reaction of **11** with unactivated tertiary C–H bonds

While these reactions afford what appear to be modest yields, these are remarkable transformations considering the substrates involved. There is a range of potential C–H bonds for functionalization in these systems, not only primary and secondary, but also a monosubstituted aromatic ring. Yet, through judicious choice of the steric and electronic factors present in the molecule, we can selectively functionalize the sterically encumbered, electronically unactivated tertiary C–H position. Similar levels of selectivity were recently reported in iron-catalyzed hydroxylation of unactivated tertiary C–H bonds.[6]

In summary, these studies demonstrate that C–H functionalization at tertiary sites is possible with donor/acceptor rhodium carbenoids. We have shown that variously substituted aromatic compounds are suitable substrates, providing that cyclopropanation can be suppressed through steric inhibition. Furthermore, unactivated tertiary C–H bonds can be selectively functionalized ahead of not only primary and secondary positions, but also, sp^2 systems. While the yields are modest and the asymmetric induction is relatively low, we have demonstrated a high level of regio- and chemoselectivity upon which to base further investigations into the functionalization of tertiary C–H bonds.

Method A

An oven-dried 25 mL round-bottomed flask was charged with a solution of substrate (3 mmol, 6 equiv), in anhyd, degassed 2,2-dimethylbutane (3 mL, 1 M). Dirhodium catalyst (0.005 mmol, 1 mol%) was added, and the reaction was brought to reflux under an atmosphere of argon. A solution of methyl phenyldiazoacetate (0.5 mmol, 1 equiv) in anhyd, degassed 2,2-dimethylbutane (6 mL, 0.1 M), was added dropwise over a period of 1 h. Upon completion of the addition, the reaction was maintained at reflux for 1 h and then allowed to cool to r.t. The solution was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography.

Methyl 3-(4-Methoxyphenyl)-3-methyl-2-phenylbutanoate (16)

Using Method A: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.17 (7 H, m), 6.79 (2 H, d, *J* = 9.0 Hz), 3.83 (1 H, s), 3.78 (3 H, s), 3.45 (3 H, s), 1.47 (3 H, s), 1.30 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C=O), 139.5 (CH), 135.7 (CH), 130.3 (3 × CH), 127.9 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 113.3 (2 × CH), 62.7 (CH), 55.4 (OC), 51.6 (OC), 40.9 (C), 26.7 (CH_3), 25.2 (CH_3). IR (thin film): ν_{max} = 2950, 2360, 1734 (C=O), 1610, 1513, 1250 cm^{-1}. MS (ES): *m/z* (%) = 299.2 (4) [M + H], 285.1 (28), 150.1 (12), 149.1 (100). HRMS: *m/z* calcd for $C_{19}H_{23}O_3$ [M + H]: 299.1642; found: 299.1639.

Methyl 3-Methyl-2-phenyl-3-*p*-tolylbutanoate (20)

Using method A: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (5 H, m), 7.19 (2 H, d, *J* = 7.6 Hz), 7.08 (2 H, d, *J* = 7.6 Hz), 3.89 (1 H, s), 3.46 (3 H, s), 2.32 (3 H, s), 1.49 (3 H, s), 1.32 (3 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9 (C=O), 144.2 (C), 135.52 (C), 135.49 (C), 130.1 (CH), 128.5 (CH), 127.6 (CH), 127.1 (CH), 126.3 (CH), 62.3 (CH), 51.3 (OC), 40.9 (C), 26.5 (CH_3), 24.8 (CH_3), 20.9 (CH_3). IR (thin film): ν_{max} = 3028, 2971, 2950, 1734 (C=O), 1164, 1139, 703 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{19}H_{23}O_2$ [M + H]: 283.1698; found: 283.1693.

Method B

To a 10 mL round-bottomed flask was added the Rh(II) catalyst (0.005 mmol, 1 mol%) and benzoate **22** (5 mmol, 10 equiv). A short-path distillation apparatus was attached to the top of the flask. The mixture was heated to 70–75 °C under argon. Methyl phenyldiazoacetate (**11**, 0.5 mmol) in 10 mL of degassed 2,2-dimethylbutane was added with a syringe pump over 5 h. During the addition, the solvent was distilled off, and volume of the reaction mixture in the flask kept constant. After addition, the reaction mixture was stirred for 15 min, cooled to r.t., and passed through a short silica gel column, washed with hexanes–Et_2O (20:1) to recover the excess of **22**. Then the column was washed with Et_2O. Concentration of ether solution gave the crude product. Further purification with silica gel flash chromatography eluting with hexanes–Et_2O (10:1) gave the desired product as a clear oil.

5-Methoxy-3,3-dimethyl-5-oxo-4-phenylpentyl Benzoate (23)

Using Method B: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (2 H, dd, *J* = 8.0, 1.0 Hz), 7.55 (1 H, t, *J* = 7.5 Hz), 7.45–7.40 (4 H, m), 7.34–7.27 (3 H, m), 4.41 (2 H, t, *J* = 7.5 Hz), 3.64 (3 H, s), 3.58 (1 H, s), 2.00–1.95 (1 H, m), 1.78–1.72 (1 H, m), 1.13 (3 H, s), 1.06 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C), 166.6 (C), 135.3 (C), 132.8 (CH), 130.3 (C), 130.1 (CH), 129.5 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 61.9 (CH_2), 60.7 (CH), 51.5 (CH_3), 38.1 (CH_2),

36.3 (C), 24.9 (CH_3), 24.7 (CH_3). IR (thin film): ν_{max} = 1733, 1719, 1275, 1143, 1113, 711 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{21}H_{24}O_4Na$ [M + Na]: 363.1567; found: 363.1568.

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