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Rhodium(II)-Catalyzed C−H Functionalization of Electron-Deficient Methyl Groups

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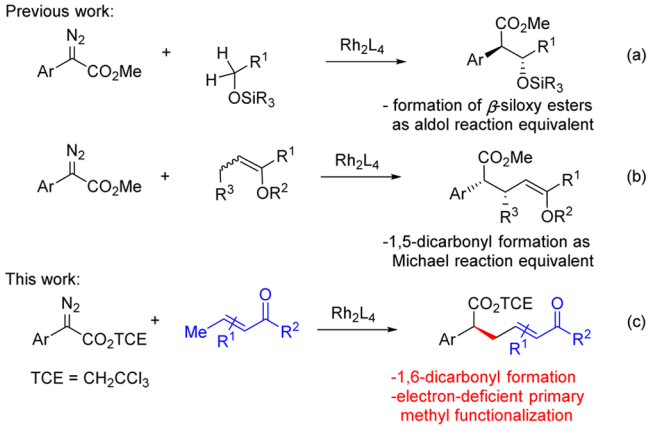
Supporting Information

ABSTRACT: Enantioselective C−H functionalization of relatively electron-deficient methyl sites was achieved with the combination of 2,2,2-trichloroethyl aryldiazoacetates and tetrakis(triarylcyclopropanecarboxylate) dirhodium catalysts. The substrate scope of the transformation was relatively broad, and C−H functionalization products were furnished with excellent levels of enantioselectivity. As a strategic reaction, crotonate derivatives give 1,6-dicarbonyl compounds, which are useful for further diversification.

The development of new C−H functionalization methods represents an area of pronounced interest because these methods have the potential to streamline the synthesis of complex targets.[1,2] The most established and widely utilized C−H functionalization methods either rely on the use of directing groups[3] or involve radical intermediates.[4] The most versatile enantioselective method to date, however, has been C−H functionalization by means of carbene-induced C−H insertion.[5,6] Enantioselective intramolecular versions of these C−H insertions were developed in the 1980s and have seen widespread use in the synthesis of complex targets.[5a−c] The advent of donor/acceptor rhodium carbenes has given life to enantioselective intermolecular C−H insertion as a synthetically useful process.[5c−e] Indeed, carbene-induced intermolecular C−H functionalization has been shown to be complementary to some classic strategic reactions of organic synthesis.[5e] For example, C−H functionalization of silyl ethers generates 3-siloxy esters (aldol reaction surrogate) (Scheme 1a).[7] Alternatively, allylic C−H functionalization of silyl vinyl ethers generates protected 1,5-dicarbonyl compounds (Michael addition surrogate) (Scheme 1b).[8] Herein, we report the C−H functionalization of crotonate derivatives and related compounds which offer a novel approach for the enantioselective synthesis of 1,6-dicarbonyl derivatives (Scheme 1c).

Scheme 1. Strategic Reactions Using C−H Functionalization



Donor/acceptor rhodium carbenes behave as highly electrophilic intermediates and undergo C−H functionalization in a concerted asynchronous manner, characterized by positive charge build-up at carbon.[9] Hence, electron-rich allylic and benzylic C−H bonds or those α to oxygen or nitrogen are activated toward carbene insertion.[5] Recently, we have discovered that the inherent substrate biases can be overcome by employing our new class of dirhodium catalysts, derived from the triphenylcyclopropane carboxylate (TPCP) ligand.[10] These sterically demanding complexes tend to favor functionalization of less crowded C−H bonds.[10b] During these studies, we discovered that aryldiazoacetates bearing the 2,2,2-trichloroethyl (TCE) ester are more robust and react more cleanly than those with the corresponding methyl ester.[10c] The combination of TPCP catalysts and the TCE esters of donor/acceptor carbenes enables the functionalization of substrates that would have otherwise reacted unselectively as well as those simply too unreactive for effective C−H functionalization. For example, this catalyst/reagent combination makes possible the regio- and stereoselective functionalization of *n*-alkanes at C-2.[11] Here, we describe that this combination also results in effective C−H functionalization of relatively electron-deficient methyl sites, such as ethyl crotonate and related compounds.

The exploration of the C−H functionalization of ethyl crotonate (**2**) was initiated by comparing the reactions of the methyl ester **1a** and the TCE ester **1b**, catalyzed by Rh_2(*R*-*p*-PhTPCP)$_4$ (Table 1). The reaction of methyl aryldiazoacetate **1a** did generate some of the desired C−H functionalization product **3a**, but the yield was low (15%, entry 1). In contrast, the reaction with the TCE aryldiazoacetate gave the desired product **3b** in 74% isolated yield with 95% ee (entry 2). The related catalysts, Rh_2(*R*-TPCP)$_4$ and Rh_2(*R*-*p*-BrTPCP)$_4$ gave similar but slightly inferior results compared to Rh_2(*R*-*p*-PhTPCP)$_4$ (entries 3 and 4), whereas the most widely used catalyst Rh_2(*S*-DOSP)$_4$ gave low yield (entry 5).

Carbene-induced C−H functionalization at electron-rich allylic positions is known to be sensitive to steric effects.[5c] Therefore, the reactions of differentially substituted crotonate derivatives (Scheme 2) were compared to the established

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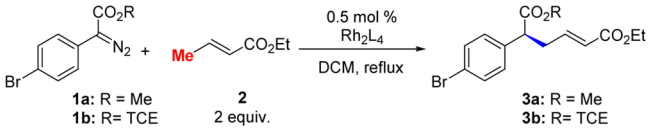
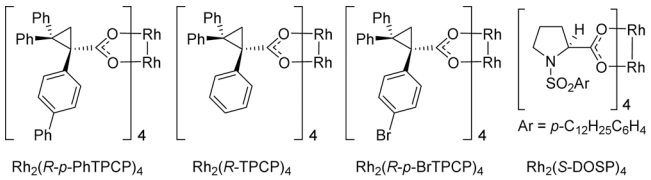
Table 1. Summary of Optimization Studies[a,b]

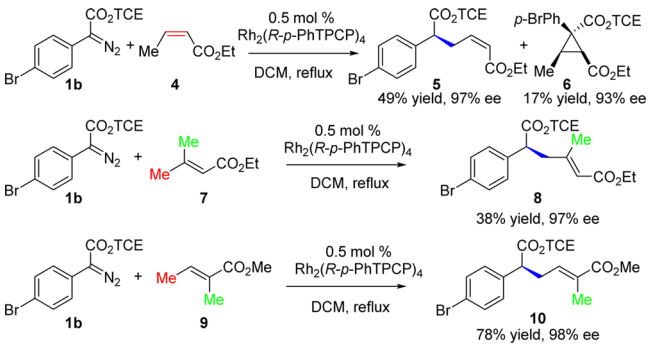


entry	R	Rh_2L_4	yield (%)[c]	ee (%)[d]
1	Me	Rh_2(*R*-*p*-PhTPCP)$_4$	15[e]	-
2	**TCE**	**Rh_2(*R*-*p*-PhTPCP)$_4$**	**74**	**95**
3	TCE	Rh_2(*R*-TPCP)$_4$	71	89
4	TCE	Rh_2(*R*-*p*-BrTPCP)$_4$	65	91
5	TCE	Rh_2(*S*-DOSP)$_4$	12[e]	-



[a]Reaction conditions: The diazo compound (0.8 mmol) in 1.2 mL dichloromethane (DCM) was added over 3 h to a solution of the substrate (2.0 equiv) and catalyst (0.5 mol %) in 0.5 mL DCM at reflux. [b]For details about the optimization of relative concentration and addition time of the diazo compound, see Supporting Information. [c]Isolated yield. [d]Determined by chiral HPLC analysis of the isolated product. [e]Yield determined by ^{1}H NMR using trichloroethylene as the internal standard.

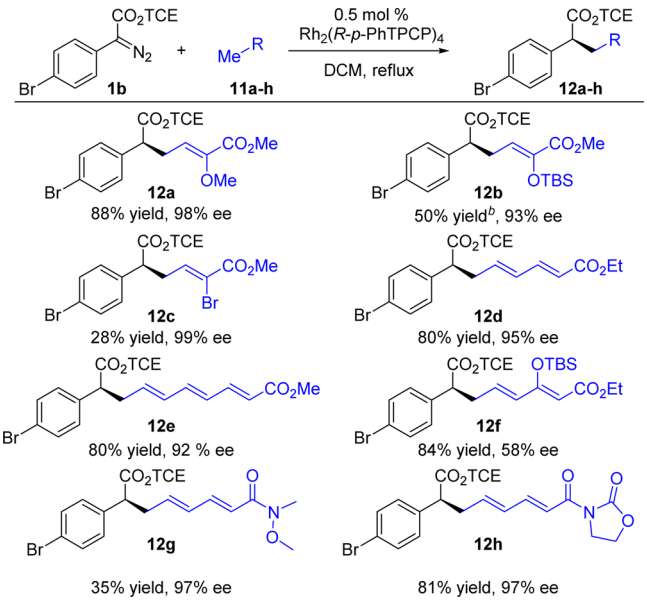
Scheme 2. Effect of Substitution on Ester Substrates



reaction with *E*-crotonate **2**. The reaction of ethyl (*Z*)-but-2-enoate **4** gave the desired C−H insertion product **5** as the *Z* isomer, in 49% yield and 97% ee, as well as the cyclopropane **6**, which was formed in 17% yield with 93% ee. This result is consistent with previous studies that have shown that the delicate balance between C−H functionalization and cyclopropanation is dependent on alkene geometry.[5e] When ethyl 3-methylbut-2-enoate **7** was utilized, the more accessible primary methyl group was functionalized preferentially with a high level of enantioselectivity (97%). The lower yield (38%) in this case is presumably due to steric interference. Finally, when methyl (*E*)-2-methylbut-2-enoate **9** was used as the substrate, the more accessible primary methyl group was again functionalized preferentially to form **10** in good yield and high level of enantioselectivity (78% yield, 98% ee).

The scope of the reaction was then explored with more elaborate substrates (Table 2). Crotonate derivatives with internal substituents were competent substrates, though to varying degrees. The reactions to form **12a**−**c** occurred with high levels of enantioselectivity (93−99% ee), but the overall yield was greatly influenced by the nature of the internal substituent.

Table 2. C−H Functionalization of Electron-Deficient Methyl Groups[a]



[a]Reaction conditions: **1b** (0.8 mmol) in 1.2 mL DCM was added over 3 h to a solution of the substrate (1.6 mmol, 2.0 equiv) and catalyst (0.5 mol %) in 0.5 mL DCM at reflux. [b]Cyclopropanation byproduct was isolated in 30% yield.

Similar to the methyl derivative **9**, described in Scheme 2, a methoxy group is well tolerated, and **12a** was efficiently formed (88%). However, in the case of the siloxy derivative **11b**, the C−H functionalization product **12b** was isolated in a lower 50% yield, due to the occurrence of a competing cyclopropanation product (isolated in 30% yield). In the case of the bromo derivative **12c**, the overall yield of the reaction was low, presumably because the methyl site is no longer sufficiently reactive even for the TCE ester **1b**. More highly conjugated substrates were also good substrates, as illustrated by the formation of **12d**−**h**. Again the enantioselectivity was high (92−97% ee), except for the case of the 3-siloxy derivative **12f** (58% ee). Particularly noteworthy is the reaction to form the trienoate **12e** in 80% yield and 92% ee. The reaction is compatible with the Weinreb amide (**11g**) and oxazolidinone (**11h**), though the isolated yield of the Weinreb amide product **12g** was relatively low (35%). So far, the transformation using the standard reaction conditions is limited to the indicated unsaturated carbonyl systems. An unsaturated ketone is prone to epoxide formation by the rhodium carbene, and unsaturated *N*,*N*-dimethyl amide or phenylsulfone did not give the desired product.

To explore further the influence of electron-withdrawing groups on C−H functionalization reactions, substrates containing electron-deficient benzylic methyl groups (**13**) were also evaluated (Table 3). Toluene derivatives with *p*-ethoxycarbonyl, *p*-bromo, *p*-methoxycarboalkenyl, and *p*-ethoxycarboalkynyl groups were all good substrates, undergoing C−H functionalization in high yields (77−89%) and with high levels of enantioselectivity (96−98% ee). The only exceptions were *p*-nitrotoluene and *m*-nitrotoluene, which failed to give rise to the desired product, presumably because they are too electron deficient.

The reaction is applicable to a variety of aryldiazoacetates as illustrated in Table 4. When TCE aryldiazoacetates bearing *p*-^{t}Bu or *p*-CF_3 were tested, again, **11a** turned out to be a better

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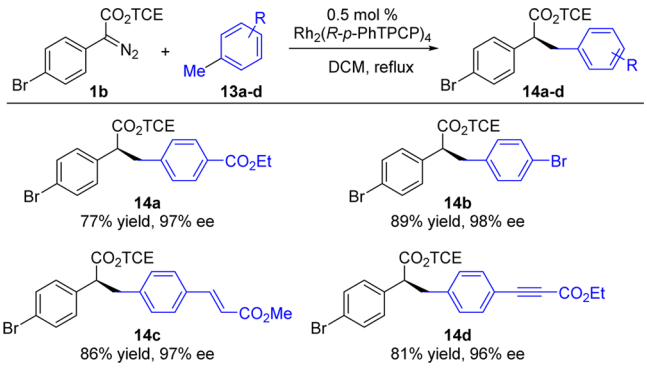
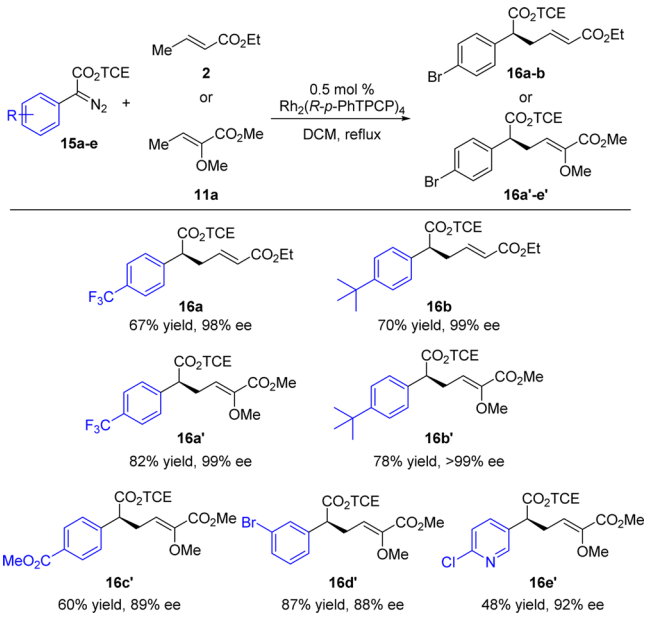
Table 3. Functionalization of Electron-Deficient Aromatic Methyl Groups[a]



[a]Reaction conditions: **1b** (0.8 mmol) in 1.2 mL DCM was added over 3 h to a solution of the substrate (1.6 mmol, 2.0 equiv) and catalyst (0.5 mol %) in 0.5 mL DCM at reflux.

Table 4. Scope of TCE Aryldiazoacetates[a]

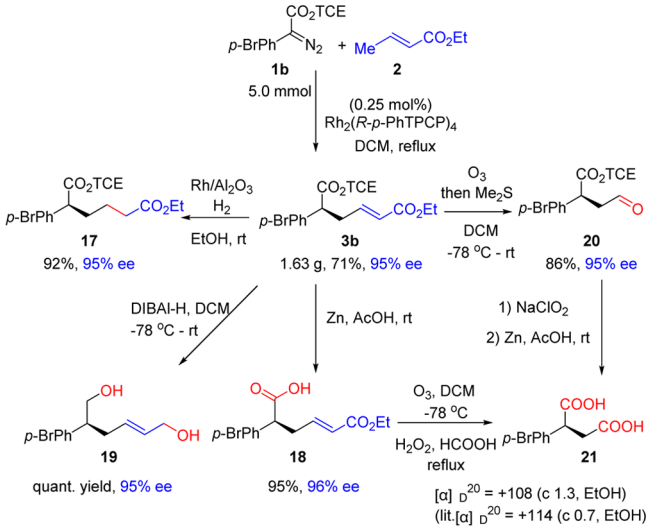


[a]Reaction conditions: **15a–e** (0.4 mmol) in 1.0 mL DCM was added over 3 h to a solution of the substrate (0.80 mmol, 2.0 equiv) and catalyst (0.5 mol %) in 0.4 mL DCM at reflux.

behaving substrate compared to **2** (**16a**,**b** vs **16a**′,**b**′). To fully explore the potential of the scope of arydiazoacetates, substrate **11a** was used to react with a variety of other diazo acetates. Both electron-rich and electron-deficient *para*-substituents on the phenyl ring were compatible, generating **16a**′–**c**′ in 60–82% yield and high levels of enantioselectivity (89 → 99% ee). The *meta*-bromo substituent was also tolerated, and **16d**′ was formed in 87% yield and 88% ee. TCE aryldiazoacetate bearing an *o*-bromo substituent on the phenyl ring gave only trace amount of the product, presumably because it is sterically more hindred, and interferes with intermolecular C–H insertion. Notably, the C–H functionalization could be carried out with the pyridyl derivative **15e** to form **16e**′ in 48% yield and 92% ee.

The utility of the C–H functionalization was demonstrated by the synthesis of **3b** on a gram scale with a catalyst loading of 0.25 mol % (Scheme 3). The product **3b** is quite versatile and was easily manipulated in a variety of ways to give products with oxygen functionality in a 1,6- or 1,4-orientation. Selective

Scheme 3. Synthetic Utilities of the Transformation



hydrogenation of **3b** generated the saturated product **17** in 92% yield. The TCE ester could be selectively deprotected with zinc in acetic acid to form the acid **18** in 95% yield, or the two ester groups could be reduced to the diol **19** in essentially quantitative yield. Ozonolysis of **3b** generated the aldehyde **20** in 86% yield. Pinnick–Lindgren–Kraus oxidation of **20** followed by TCE deprotection generated the known succinic acid derivative **21**, and this compound was used to determine the absolute configuration of **21** by comparison of its optical rotation with the reported value.[12]

In conclusion, the enantioselective C–H functionalization of relatively electron-deficient methyl sites was achieved by use of the combination of TCE aryldiazoacetates and the bulky dirhodium TPCP catalysts. The substrate scope of the transformation was relatively broad, and various 1,6-dicarbonyl derivatives were readily furnished. These studies demonstrate that C–H functionalization can be used for key disconnection strategies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01941.

Synthetic details and spectral data (PDF)

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Notes

The authors declare the following competing financial interest(s): Huw Davies is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8975428, issued March 10, 2015).

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