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2,2,2-Trichloroethyl Aryldiazoacetates as Robust Reagents for the Enantioselective C−H Functionalization of Methyl Ethers

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Supporting Information

ABSTRACT: A new class of reagents is described for C−H functionalization by means of C−H insertion using donor/acceptor-substituted rhodium(II) carbene intermediates. The 2,2,2-trichloroethyl aryl and heteroaryl diazoacetates, together with the dirhodium triarylcyclopropane carboxylate catalyst Rh_2(*R*-BPCP)$_4$, enabled the enantioselective intermolecular C−H functionalization of a range of methyl ethers with high levels of site selectivity and enantioselectivity.

C−H Functionalization is rapidly becoming a powerful tool for the construction and modification of complex molecules.[1] Among the most challenging aspects of developing robust C−H functionalization methodologies is identifying catalyst and reagent combinations capable of site-selective as well as diastereo- and enantioselective reactions.[2] The rhodium-catalyzed reactions of donor/acceptor carbenes is an effective approach for site-selective sp^3 C−H functionalization, controlled by competing steric and electronic influences.[3,4] Since the reaction is initiated by a hydride transfer-type event, tertiary sites are electronically favored, but this is offset by the steric demands of the rhodium carbene complex. With the most widely used catalyst, Rh_2(DOSP)$_4$ (Figure 1), the site selectivity typically

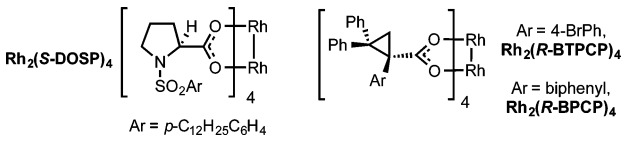
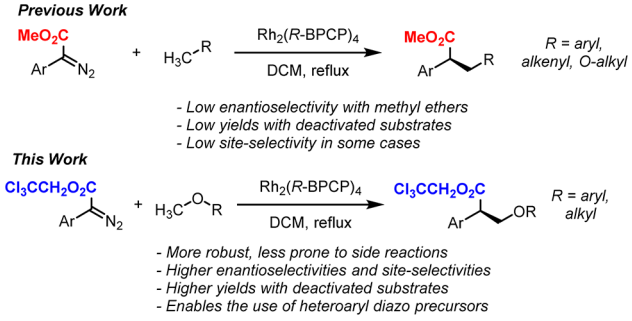


Figure 1. Dirhodium(II) tetracarboxylate catalysts.

favors secondary C−H bonds.[3d] We are currently developing a toolbox of reagents/catalysts to expand the scope of reagent control in the site selectivity of C−H functionalization reactions. Recently, we reported a new family of sterically crowded catalysts,[5] including Rh_2(BPCP)$_4$ and Rh_2(BTPCP)$_4$ (Figure 1), that favors functionalization at primary benzylic C−H bonds over secondary and tertiary sites.[6]

Despite these advances, numerous challenges remain (Scheme 1).[6] First, when the system was expanded to a methyl ether, the enantioselectivity dropped considerably. Second, an electron-withdrawing group on the benzene ring of the substrate causes it to be less reactive and resulted in a low yield of the C−H functionalization product. Third, when the substrate contained two benzylic C−H bonds with similar steric environments (such as in 4-ethyltoluene), a mixture of products was formed. For the

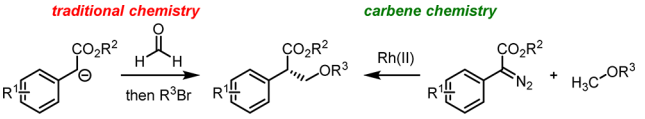
Scheme 1. Influence of Ester Group



C−H functionalization chemistry to become more broadly useful, these limitations need to be addressed. Herein, we report the discovery of the 2,2,2-trichloroethyl (TCE) aryldiazoacetates as a robust new class of reagents for carbene C−H functionalization.

In order to demonstrate the synthetic potential of TCE aryldiazoacetates, we examined the intermolecular C−H functionalization of methyl ethers. Such a reaction can be considered, strategically, as a surrogate to an asymmetric aldol reaction with formaldehyde (an often challenging reaction),[7] followed by trapping with an alkyl halide (Scheme 2). Even

Scheme 2. Aldol/Alkylation Reaction Surrogate



though a few examples of inter- and intramolecular insertion of methyl ethers are known,[8,9] only two examples of enantioselective intermolecular reactions have been reported prior to our most recent work[6] and in those cases the substrates (*tert*-butyl methyl ether and dimethoxyethane) were used as solvent in the reaction.[10]

The advantages of using TCE aryldiazoacetates were discovered during attempts to improve the site selectivity of C−H functionalization of tolyl derivatives by using larger ester groups. Simply using larger alkyl ester groups is not a viable strategy when attempting to conduct challenging intermolecular C−H insertion reactions because intramolecular C−H insertions into the ester group would become a competing trans-

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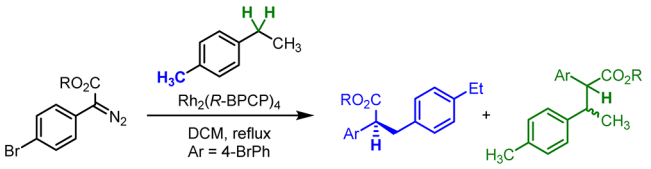
formation.[11] However, using the TCE ester, the Rh_2(*R*-BPCP)$_4$-catalyzed reaction of the diazo **1b** with 4-ethyltoluene (Scheme 3) resulted in considerable improvement in regio- and enantioselectivity compared to the reaction of the methyl ester **1a** (5:1 to 13:1 1° vs 3° and 92% ee to 99% ee, respectively).[12]

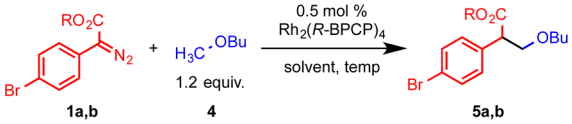
Scheme 3. Reaction with 4-Ethyltoluene



R	2:3	yield (%)	ee of 2 (%)	
Me	5:1	74	92	(ref. 6)
CH_2CCl_3	13:1	75	99	

The improvements afforded by the use of the TCE ester prompted us to consider its application to a C−H functionalization of strategic significance. The reaction of butyl methyl ether (**4**) was used as the test system (Table 1). Previously, we had shown that the Rh_2(*R*-BPCP)$_4$-catalyzed reaction of methyl diazoacetate **1a** resulted in the formation of **5a** in 64% ee (entry 1). When the reaction was conducted with TCE diazoacetate **1b**, **5b** was formed in 84% ee (entry 3). Lowering the temperature to 0 °C improved the enantioselectivity with both **1a** and **1b** (entries 2 and 4); however, the methyl ester **1a** was less efficient under these conditions, while clean formation of **5b** still occurred with the TCE ester **1b**. The enantioselectivity could be improved further by lowering the temperature to −40 °C, but the yield of **5b** was lower. Hydrocarbon solvents were also examined, but the enantioselectivity did not improve significantly (entries 6 and 7). Ultimately, the optimal conditions were found to be **1b** at 0 °C in DCM (entry 4), with **5b** being formed in 78% yield and with 88% ee.

Table 1. Initial Studies on Enantioselective C−H Functionalization of Methyl Ethers[a]

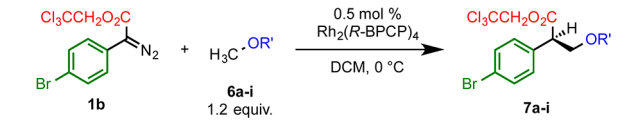


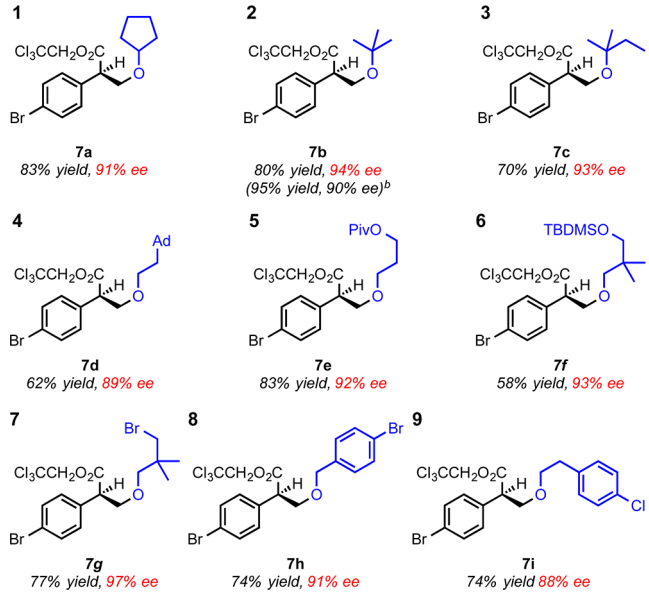
entry	solvent	R	temp (°C)	yield (%)[c]	ee (%)[d]
1[b]	DCM	CH_3	reflux (40)	86	64
2	DCM	CH_3	0	59	76
3	DCM	CH_2CCl_3	reflux (40)	82	84
4	**DCM**	**CH_2CCl_3**	**0**	**78**	**88**
5	DCM	CH_2CCl_3	−40	61	90
6	2,2-DMB	CH_2CCl_3	reflux (50)	77	88
7	pentane	CH_2CCl_3	reflux (36)	74	88

[a]Reaction conditions: A solution of **1** (0.4 mmol) in dichloromethane (2.5 mL) was added over 3 h to the substrate (1.2 equiv) and catalyst (0.5 mol %) in dichloromethane (1 mL) at the indicated temperature and then allowed to reach ambient temperature overnight (16 h). [b]Reference 6. [c]Isolated yield. [d]Determined by chiral HPLC.

The generality of the reaction was then explored, and it was found that a variety of substrates underwent the reaction selectively, and with routinely high levels of enantioselectivity (88−97% ee) (Table 2). Selective functionalization occurs on simple substrates (entries 1−3), as well as substrates with more complex functionality (entries 4−7). Of particular note are substrates containing multiple potentially reactive sites (entries 8, 9). In these cases, only the products derived from functionalization of the methyl groups were observed. Additionally, the reaction of methyl ether **6b** was conducted on a gram scale with a 0.2 mol % catalyst loading at reflux, generating **7b** in 95% isolated yield and 90% ee.

Table 2. Selective C−H Functionalization of Methyl Ethers[a]





[a]Reaction conditions: A solution of **1b** (0.4 mmol) in dichloromethane (2.5 mL) was added over 3 h to the substrate (1.2 equiv) and catalyst (0.5 mol %) in dichloromethane (1 mL) at 0 °C and then allowed to reach ambient temperature overnight (16 h). [b]Reaction conducted at reflux, on gram scale, with 0.2 mol % Rh_2(*R*-BPCP)$_4$.

The reaction was also investigated with a variety of aryl donor groups (Table 3). Both electron-rich and -deficient (entries 1 and 2) aryl groups gave the products with exceptionally high levels of enantioselectivity (99 and 98% ee, respectively). Fluorinated diazoacetate **8c** gave the product in good yield (entry 3), although with a diminished level of enantioselectivity (82% ee). The styryldiazoacetate **8d** underwent the reaction as well with good enantioselectivity (94% ee, entry 4), albeit in lower yield. Deserving of special mention, however, are the reactions with heteroaryl diazo compounds **8e−g** (entries 5−7). In particular, **8e** was an exceptional substrate (entry 5), giving the product in 57% yield and 96% ee. Pyridyldiazoacetate **8f** and isoxazole-derived diazoacetate **8g** also participated in the reaction to give the desired C−H functionalization products. Though the yields with these heteroaryl substrates are moderate, the analogous reactions with the corresponding methyl aryldiazoacetates either did not yield the desired product under the same conditions (entry 5) or did so in significantly lower yields (entries 6 and 7). This underscores the importance and value of the TCE ester in carbene C−H functionalization reactions.

Next, the reaction of a chiral substrate was investigated (Scheme 4). With the methyl ether of menthol (**10**) and an

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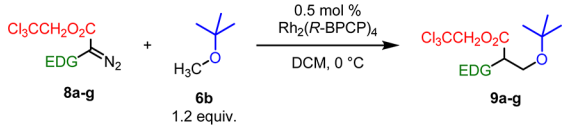
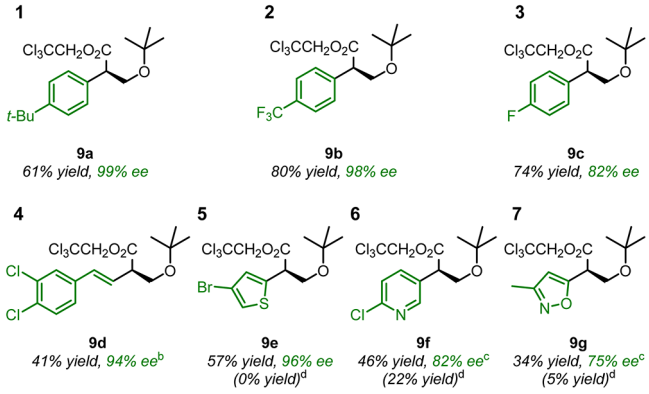
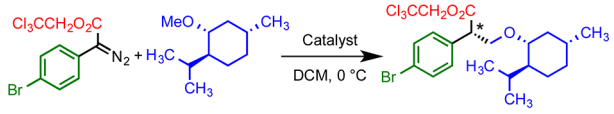
Table 3. Scope of TCE Diazo Compounds[a]





[a]Standard reaction conditions used in Table 1. [b]Reaction conducted with 1.0 mol % Rh_2(*R*-BPCP)$_4$. [c]Reaction conducted at reflux. [d]Yield of the reaction with the corresponding methyl aryldiazoacetate instead of the TCE aryldiazoacetate.

Scheme 4. Functionalization of a Chiral Methyl Ether

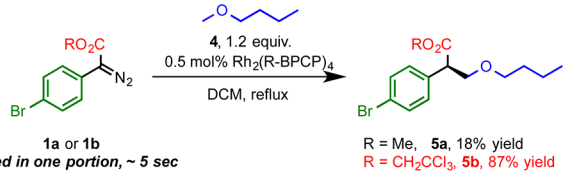


Catalyst	dr (11a:11b)	yield (%)
Rh_2(TPA)$_4$	3.6:1	55
Rh_2(*R*-BPCP)$_4$	1:23	62
Rh_2(*S*-BPCP)$_4$	>30:1	52

achiral catalyst, rhodium(II) tetrakis(triphenylacetate), one diastereomer of the C−H functionalization product was formed preferentially in a ratio of 3.6:1, demonstrating a bias inherent in the substrate. When using opposite enantiomers of the chiral catalyst Rh_2(BPCP)$_4$, good ratios of **11a:11b** were observed: 1:23 for the *R* enantiomer of the catalyst and >30:1 for the *S*. It is interesting to note that these ratios are consistent with a match/mismatch situation, where the *S* enantiomer of the catalyst reinforces the substrate bias and improves the ratio, while the *R* enantiomer goes against that bias and gives a slightly lower ratio. In this case, however, the mismatch effect is small, and these experiments demonstrate that this catalytic system is able to control the stereochemistry of the newly formed bond despite an inherent bias in the substrate.

At this point, several situations in which the TCE ester was superior to the methyl ester had been observed: (1) improved regioselectivity/enantioselectivity with 4-ethyltoluene (Scheme 3), (2) improved enantioselectivity for methyl ether functionalization (Table 1), and (3) significantly improved yields with heteroaryldiazo compounds (Table 3). Curious as to what other advantages the TCE ester might have, we turned our attention to a classic problem with diazo/carbene chemistry, the formation of carbene dimers.[3a] To mitigate the potential for dimerization, slow addition of the diazo is generally required to keep its relative concentration low. If the added bulk of the trichloroethyl group were to slow the dimerization process, this would be a significant improvement. Thus, two reactions were conducted (Scheme 5) in which the diazo compounds **1a** and **1b** were added in one

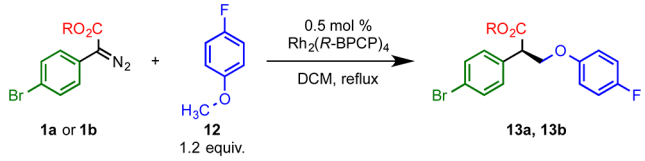
Scheme 5. Fast Addition of Diazo Compounds



portion (approximately 5 s) as opposed to slowly over 1.5−3 h. As expected, a low yield of the product was observed with the methyl aryldiazoacetate **1a** (18%). However, with the TCE aryldiazoacetate **1b**, the C−H functionalization product was formed cleanly in 87% yield, even with only a slight excess of the substrate. These experiments demonstrate the practicality of this approach, as it eliminates the need for slow addition techniques in these C−H functionalization reactions, while also reducing the overall reaction time.

With growing evidence that the TCE ester results in a more robust carbene compared to the methyl ester, a more challenging system was explored (Scheme 6). An aryl methyl ether would be

Scheme 6. C−H Functionalization of *p*-Fluoroanisole



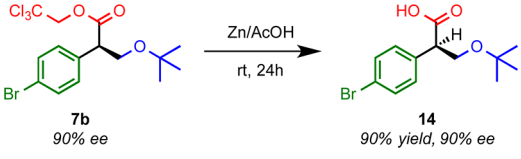
R	yield (%)	ee (%)
Me	15	n.d.
CH_2CCl_3	65	97

expected to be less reactive than an alkyl methyl ether for C−H functionalization, since the oxygen electrons are delocalized within the aromatic ring and are therefore less available for stabilizing the C−H functionalization transition state. With this substrate a low yield (15%) of the C−H functionalization product was observed with **1a**. However, with **1b**, the product was formed in 65% yield and 97% ee.

The trichloroethyl ester is a convenient protecting group for carboxylic acids due to the mild conditions required for its removal.[13] Indeed, C−H functionalization product **7b** was smoothly converted to its corresponding carboxylic acid **14** with Zn/AcOH in excellent yield, and without any racemization of the chiral center (Scheme 7). The absolute stereochemistry of **14** was determined by X-ray crystallographic analysis, and the stereochemistry of all other related products, including **11a** and **11b**, was tentatively assigned by analogy.

In conclusion, we have developed a new series of diazo compounds with a 2,2,2-trichloroethyl (TCE) ester as the

Scheme 7. Deprotection of the Trichloroethyl Ester



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acceptor group and have applied them to the first general asymmetric C−H functionalization of methyl ethers. The TCE ester results in improved levels of enantioselectivity in this system, as well as improved regioselectivity when comparing sterically similar primary and secondary C−H bonds. Furthermore, the TCE ester enables C−H functionalization with heteroaryldiazoacetates and also with relatively unreactive substrates, cases in which the methyl ester fails to give useful yields. The application of these findings to new, challenging, and previously unavailable systems 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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