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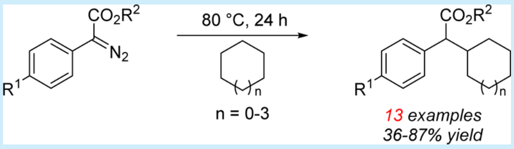
Metal-Free C–H Functionalization of Alkanes by Aryldiazoacetates

Cecilia Tortoreto, Daniel Rackl, and Huw M. L. Davies*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States

Supporting Information

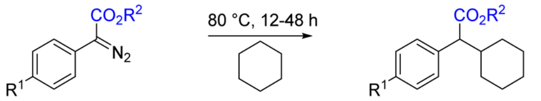
ABSTRACT: Thermally induced reactions of donor/acceptor diazo compounds generate carbene intermediates capable of C–H functionalization reactions of alkanes. A variety of C–H insertion products were obtained in moderate to good yields and in certain cases with good site selectivity, favoring the functionalization of the more highly substituted C–H bond.



In recent years, the development of new methods to achieve selective C–H functionalization reactions has become a very active research area.[1,2] One particularly useful method has been the insertion of metal carbenes into C–H bonds.[3] Donor/acceptor-substituted metal carbenes have been shown to be capable of highly site-selective and stereoselective intermolecular C–H functionalization of a wide range of substrates.[4] These carbenes are most commonly derived from the corresponding aryldiazoacetates or vinyldiazoacetates under metal-catalyzed conditions. Dirhodium tetracarboxylates have been the most widely used catalysts for C–H functionalization reactions, and they are very active catalysts that are capable of efficient reactions at ambient temperature or below.

Because of the cost and scarcity of rhodium, there has been considerable interest in developing earth-abundant catalysts for the decomposition of diazo compounds.[5] These catalysts are generally not as reactive as the dirhodium catalysts and in some cases require quite forcing conditions (80 °C).[5] The use of these more forcing conditions could be of concern because we have already demonstrated[6,7] that the purely thermal reactions of aryldiazoacetates in the absence of catalysts can result in high-yielding transformations such as cyclopropanation and N–H insertion reactions.[6b] Therefore, the possibility exists that the metal-catalyzed reactions conducted under forcing conditions may have a significant thermal background reaction. Consequently, we decided to determine the type of C–H functionalization reactions that can be carried out under purely thermal conditions and the inherent site selectivity of the reactions of these free carbenes. These results would provide useful background information for future studies on the development of new catalysts for site-selective carbene reactions.

Scheme 1



1 (0.4 mmol) (3.0 mL) **2**

1a (R^1 = Br, R^2 = CH$_3$)
1b (R^1 = Br, R^2 = CH$_2$CCl$_3$)
1c (R^1 = OMe, R^2 = CH$_3$)
1d (R^1 = OMe, R^2 = CH$_2$CCl$_3$)

2a (R^1 = Br, R^2 = CH$_3$; 44%)
2b (R^1 = Br, R^2 = CH$_2$CCl$_3$; 86%)
2c (R^1 = OMe, R^2 = CH$_3$; 76%)
2d (R^1 = OMe, R^2 = CH$_2$CCl$_3$; 73%)

The initial study explored the thermal reaction of donor/acceptor carbenes in refluxing cyclohexane, comparing the reaction of the *p*-bromophenyl-**1a**,**b** and *p*-methoxyphenyldiazoacetates **1c**,**d** (Scheme 1). *p*-Bromophenyl derivative **1a** is the most widely used substrate in the rhodium-catalyzed reactions, and *p*-methoxyphenyl derivative **1c** is known to be more thermally labile. Both the methoxy and trichloroethyl (TCE) esters were examined because recently the trichloroethyl esters have been shown to give much cleaner metal-catalyzed intermolecular C–H insertions than the traditional methyl esters.[8] All four substrates gave high yields of the C–H functionalization products **2** when the reactions with cyclohexane were conducted over 12–48 h. In the case of methoxyphenyl derivatives **1c** and **1d**, the yields of **2c** and **2d** were roughly equivalent, but in the case of *p*-bromo derivatives **1a** and **1b**, the yield of the trichloroethyl ester **2b** was higher than that of the methyl ester **2a**.

In order to obtain further information about the relative rates of C–H functionalization of cyclohexane, the reactions were followed by in situ IR monitoring (ReactIR). Figure 1 compares the rates of decomposition of the four substrates **1a**–**d**. The signals for the diazo functionality (at $\sim$2090 cm^{-1}) decreased over time, following first-order kinetics. As seen previously in the thermal cyclopropanation of aryldiazoacetates, the *p*-methoxy derivatives **1c** and **1d** are more reactive than the *p*-bromo derivatives **1a** and **1b**. The nature of the ester group also influences the thermal reaction, as the trichloroethyl derivatives **1b** and **1d** are about 2–3 times more reactive that the corresponding methyl esters **1a** and **1c**. Thus, **1c** has a half-life of 92 min at 80 °C, whereas **1d** has a half-life of 39 min. These results indicate that a significant background thermal reaction would be a distinct possibility in attempted metal-catalyzed reactions under extended forcing conditions.

After the high-yielding thermal C–H functionalization of cyclohexane was established, the general scope of the reaction with cycloalkanes was examined (Scheme 2). The reaction of *p*-methoxyphenyldiazoacetates **1c** and **1d** gave the C–H insertion

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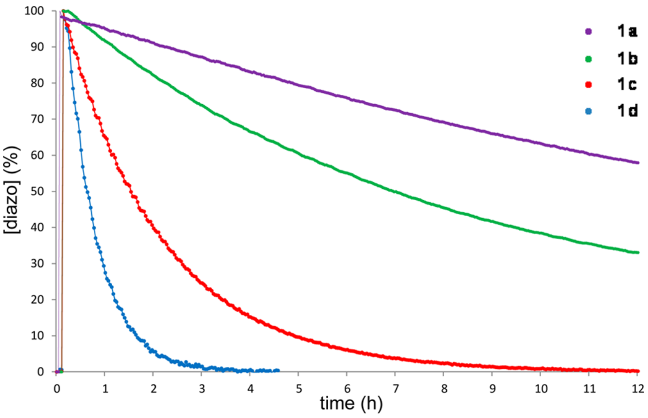
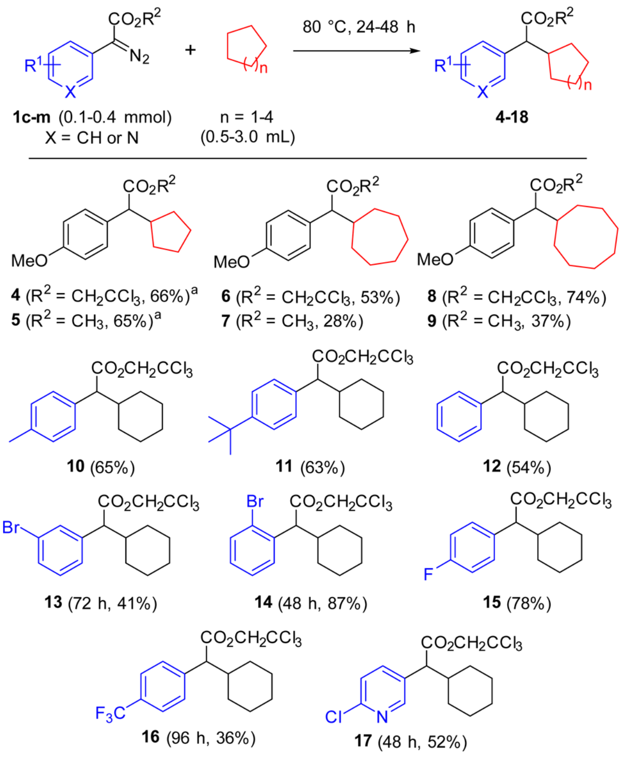


compd	R^1	R^2	k_1 (h^{-1})	$t_{1/2}$ (h)
1a	Br	OMe	0.044 ± 0.001	15.70
1b	Br	OCH$_2$CCl$_3$	0.099 ± 0.001	6.97
1c	OMe	OMe	0.45 ± 0.01	1.53
1d	OMe	OCH$_2$CCl$_3$	1.07 ± 0.03	0.65

Figure 1. ReactIR measurements of the rates of thermal decomposition of **1a**−**d** in refluxing cyclohexane **2**.

Scheme 2. Thermally Induced C−H Functionalization of Cycloalkanes



1c-m (0.1-0.4 mmol)
X = CH or N

n = 1-4
(0.5-3.0 mL)

4-18

4 (R^2 = CH$_2$CCl$_3$, 66%)[a]
5 (R^2 = CH$_3$, 65%)[a]

6 (R^2 = CH$_2$CCl$_3$, 53%)
7 (R^2 = CH$_3$, 28%)

8 (R^2 = CH$_2$CCl$_3$, 74%)
9 (R^2 = CH$_3$, 37%)

10 (65%)

11 (63%)

12 (54%)

13 (72 h, 41%)

14 (48 h, 87%)

15 (78%)

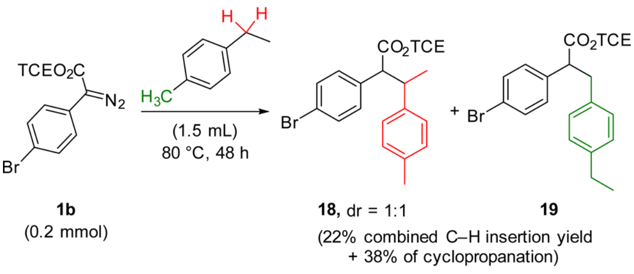
16 (96 h, 36%)

17 (48 h, 52%)

[a] Cyclopentane (1.5 mL), hexafluorobenzene (1.5 mL).

products **4**−**9** in moderate to good yields, as shown in entries 1−3. 2,2,2-Trichloroethyl ester **1d** generally gave higher yields of C−H insertion products than methyl ester **1c** because it minimizes the formation of secondary products derived from either carbene dimerization or intramolecular C−H insertion.[9] The reaction with cyclohexane was examined with a variety of trichloroethyl aryldiazoacetates resulting in the formation of the C−H insertion products **10**−**17** in 36−87% yield. The rates of decomposition of the diazo compounds with the more electron-deficient aryl groups were lower, and these substrates needed extended times to achieve full conversion (up to 96 h).

Scheme 3. Reactivity of 1b with 4-Ethyltoluene



1b
(0.2 mmol)

18, dr = 1:1

19

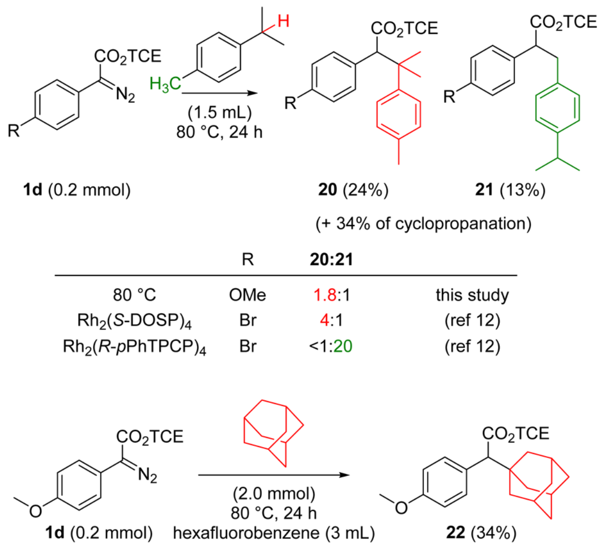
(22% combined C−H insertion yield
+ 38% of cyclopropanation)

	18:19	
80 °C	2:1	this study
Rh$_2$(*S*-DOSP)$_4$	6.6:1	(ref 10)
Rh$_2$(*R*-*p*PhTPCP)$_4$	1:11.1	(refs 8 and 10)

The site selectivity and diastereoselectivity of the reaction were also explored in order to determine the inherent reactivity profile of the free donor/acceptor carbene. The reaction of 2,2,2-trichloroethyl (*p*-bromophenyl)diazoacetate **1b** with 4-ethyltoluene was tested first (Scheme 3). The thermal reaction gave a 2:1 mixture of the secondary (**18**) and primary (**19**) C−H insertion products in a combined yield of 22%, along with a 38% yield of cyclopropanation. In comparison, the Rh$_2$(*S*-DOSP)$_4$-catalyzed reaction has been shown to favor **18** in a 6.6:1 ratio, whereas the bulky catalyst Rh$_2$(*R*-*p*PhTPCP)$_4$ strongly favors **19** in an 11:1 ratio.[8a,10] Importantly, no cyclopropanation product is oberved in the prescence of dirhodium catalysts. Establishing the inherent site selectvity of the free carbene will be useful in evaluating the effectiveness of new catalysts in controlling metallocarbene-induced C−H functionalization.

Competition studies were also conducted with substrates containing tertiary C−H bonds. The reactions favor the tertiary site with small amounts of other C−H functionalization products (Scheme 4). The thermal reaction of **1d** with *p*-cymene gave a 24% yield of insertion into the tertiary C−H

Scheme 4. Reactivity of 1d with *p*-Cymene and Adamantane



1d (0.2 mmol)

20 (24%)

21 (13%)

(+ 34% of cyclopropanation)

	R	**20:21**	
80 °C	OMe	1.8:1	this study
Rh$_2$(*S*-DOSP)$_4$	Br	4:1	(ref 12)
Rh$_2$(*R*-*p*PhTPCP)$_4$	Br	<1:20	(ref 12)

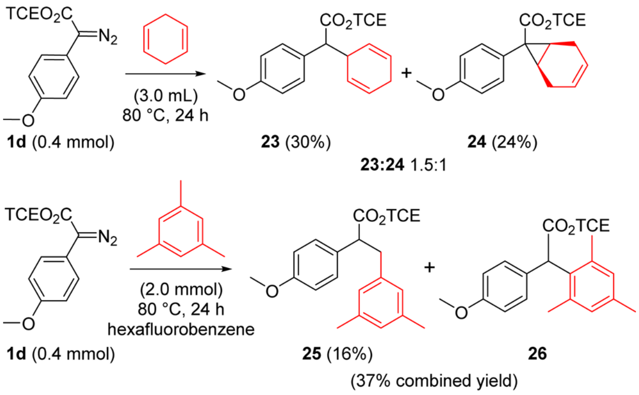
1d (0.2 mmol)

22 (34%)

bond (**20**) along with smaller amounts of insertion into the primary site (**21**) as well as considerable quantities of cyclopropanated compound. Again, the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction favors the sterically more congested position, while $Rh_2(R\text{-}p\text{PhTPCP})_4$ inverts the selectivity. Reaction of **1d** with adamantane gave rise to a 34% yield of the tertiary C−H insertion product **22**. These results contrast with the competing steric and electronic control of the rhodium-catalyzed reactions, confirming that electronic factors are inherently predominant over steric factors.[11] However, when bulky catalysts are used, a strong preference for the primary C−H insertion site over a secondary C−H insertion site can be achieved and the natural selectivity overwritten.[12]

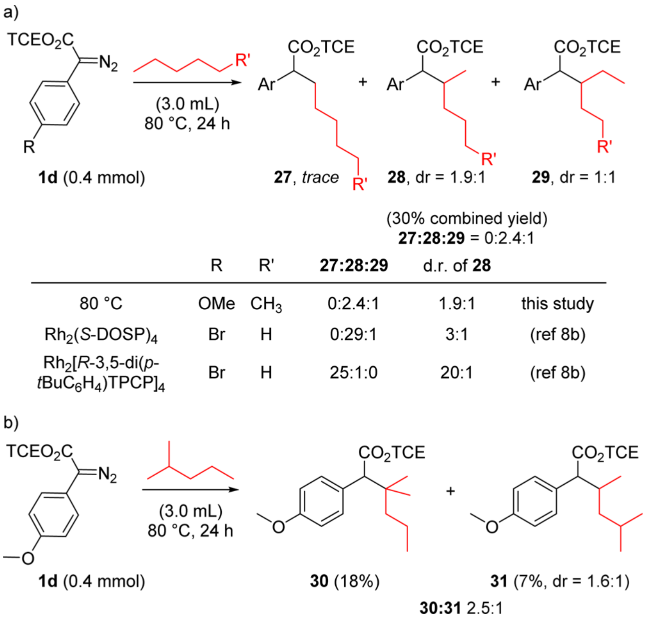
Exploratory studies were conducted to determine whether the C−H functionalization reaction could occur in substrates containing other functional groups (Scheme 5). Reaction of **1d** with 1,4-cyclohexadiene gave a mixture of the C−H insertion product **23** (30% yield) and cyclopropane **24** (24% yield). This outcome is different from that of the metal-catalyzed reactions, which tend to undergo the C−H functionalization cleanly at the doubly allylic site.[13] The reaction with mesitylene gave the two products **25** and **26** derived from benzylic C−H insertion and aromatic substitution, respectively. A similar product distribution was reported in an iron-catalyzed reaction of **1c** with mesitylene conducted at 80 °C,[5a] and the reported conditions would probably have been sufficiently vigorous for the purely thermal reaction to be a competing process.

Scheme 5. Reactivity of 1d with 1,4-Cyclohexadiene and Mesitylene



Among the classic and most challenging substrates to evaluate the site selectivity of carbene-induced C−H functionalization have been acyclic alkanes. We recently demonstrated that the combination of dirhodium TPCP catalysts and TCE esters of the donor/acceptor carbenes can lead to highly regio- and steroselective functionalization of *n*-alkanes at C2.[8b] Therefore, we became intrigued to evaluate whether alkanes could react thermally with the donor/acceptor carbenes and what level of site selectivity would be possible. Performing the reaction of **1d** in *n*-hexane at 80 °C generated two major products derived from C−H functionalization of the secondary sites at C2 (adduct **28**) and C3 (**29**) in a 2.4:1 ratio (Scheme 6). This indicates a modest selectivity due to steric factors. Only traces of the adduct derived from an electronically disfavored insertion into the primary $-CH_3$ bond (**27**) could be observed in the ^1H NMR spectrum of the crude reaction mixture. Moreover, **28** was obtained as a mixture of two diastereomers in a 1.9:1 ratio, while regioisomer **29** was obtained as a 1:1 mixture of two diastereoisomers. Similarly to earlier examples (Schemes 3 and 4) $Rh_2(S\text{-DOSP})_4$-catalysis enhanced the natural selectivity, while the latest-generation dirhodium catalyst $Rh_2[R\text{-}3,5\text{-di}(p\text{-}t\text{BuC}_6H_4)\text{TPCP}]_4$ could severely invert the natural selectivity trend.[8b] When 2-methylpentane was used as a substrate, adduct **30** derived from the electronically favored insertion into the tertiary C−H bond was obtained as the major product. The minor adduct **31**, derived from the functionalization of the secondary carbon (C2), was obtained as a mixture of diastereomers in a 1.6:1 ratio.

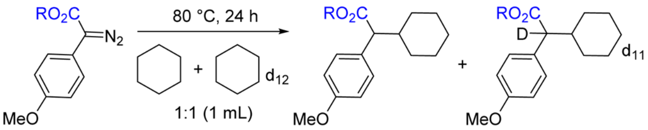
Scheme 6. Reactivity of 1d with Acyclic Alkanes



	R	R'	27:28:29	d.r. of 28	
80 °C	OMe	CH_3	0:2.4:1	1.9:1	this study
$Rh_2(S\text{-DOSP})_4$	Br	H	0:29:1	3:1	(ref 8b)
$Rh_2[R\text{-}3,5\text{-di}(p\text{-}t\text{BuC}_6H_4)\text{TPCP}]_4$	Br	H	25:1:0	20:1	(ref 8b)

To gain mechanistic insights, a set of experiments was performed using reagents **1c** and **1d** in 1:1 mixtures of cyclohexane and cyclohexane-d_{12} (Scheme 7). Mass spectrometry indicated the predominant formation of homocoupling products over cross-coupling products. The measured k_H/k_D values, in the range of 1.9−2.2, are in accordance with previously reported results for dirhodium-catalyzed C−H insertion reactions.[11a] The predominant formation of the homocoupling products advocates for a concerted hydrogen transfer mechanism. The higher proportion of protonated over deuterated adducts indicates the occurrence of a primary kinetic isotope effect.[14] A mechanism similar to the one commonly accepted for metal-catalyzed C−H insertion reactions[15] can therefore be considered for this transformation, including a concerted nonsynchronous hydride transfer/C−C bond formation.

Scheme 7. Homocoupling and Kinetic Isotope Effect



compd	R	k_H/k_D
1c	R = CH_3	2.2
1d	R = CH_2CCl_3	1.9

In conclusion, the scope of thermally induced C−H functionalization of alkanes by metal-free donor−acceptor carbenes has been described. The process is surprisingly high yielding in certain cases and can be reasonably site-selective. The results give a benchmark of the inherent site selectivity of the free donor/acceptor carbenes, which will be useful for the evaluation of the efficiency of new catalysts. Furthermore, the study indicates that background thermal reactions must be considered in metal-catalyzed C−H insertion reactions of donor/acceptor diazo compounds conducted at elevated temperatures.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03681.

Experimental procedures and characterization and spectral data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hmdavie@emory.edu.

ORCID

Huw M. L. Davies: 0000-0001-6254-9398

Notes

The authors declare no competing financial interest.

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