



Published in final edited form as:

Angew Chem Int Ed Engl. 2022 August 01; 61(31): e202200334. doi:10.1002/anie.202200334.

“Sandwich” Diimine-Copper Catalysts for C-H Functionalization by Carbene Insertion

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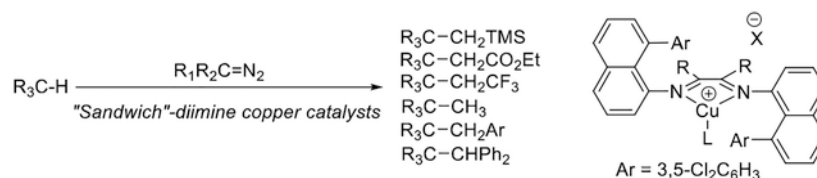
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Abstract

We report here “sandwich” diimine-copper (I) catalysts for C(sp³)-H bond functionalization. Reactions of alkanes and ethers with trimethylsilyldiazomethane, ethyl diazoacetate, and trifluoromethyldiazomethane have been demonstrated. We also report C(sp³)-H bond methylation, benzylation, and diphenylmethylation by diazomethane, phenyldiazomethanes, and diphenyldiazomethane. These reactions are rare examples of base-metal catalyzed, intermolecular C(sp³)-H functionalizations by employing unactivated diazocompounds. Electrophilicity and unique steric environment of “sandwich”-copper catalysts are likely reasons for their catalytic efficiency.

Graphical Abstract



A new catalyst platform for C(sp³)-H bond functionalization has been discovered. “Sandwich” diimine-copper (I) complexes catalyze reactions of alkane, ether, and amine C-H bonds with a large panel of diazo compounds. Additionally, the first metal-catalyzed C(sp³)-H methylation by CH₂N₂ is disclosed. The electrophilicity and extreme steric bulk of these catalysts are likely reasons for their efficiency.

Keywords

C-H activation; carbenes; copper; diazo compounds; diimines

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Supporting information for this article is given via a link at the end of the document.

Introduction

Selective C(sp³)-H bond functionalization is a challenging transformation that has attracted significant current interest.^[1] Among metal-catalyzed reactions, most examples involve formation of a metal-carbon bond-containing intermediate that reacts with another reagent affording the final product. Alternatively, C-H functionalizations involving metal carbenes have been extensively employed for alkane functionalization.^[2] These reactions do not involve a discrete alkylmetal intermediate. Instead, a transient metal carbene reacts with a C-H bond to afford the final product and regenerated catalyst. Currently, dirhodium complexes are the most synthetically useful catalysts, allowing for highly enantioselective transformations. These catalysts have been used in total syntheses of complex natural products.^[3,4] Group 11 metal complexes have been extensively used for alkane functionalization as well.^[2,5] Notable examples include modified tris(pyrazolyl)borate-copper, silver, and gold catalysts pioneered by the group of Díaz-Requejo and Pérez.^[2e,f,g,5b,c] However, both rhodium- and group 11 metal-catalyzed C-H insertions are typically limited to either acceptor or donor-acceptor carbene precursors (Scheme 1A). In contrast, use of donor carbenes in C-H functionalization is rare and, in most cases, restricted to intramolecular reactions (Scheme 1B), while intermolecular insertions are particularly scarce (Scheme 1C).^[6] The first intermolecular examples were reported by the Che group.^[6i] Benzylic and allylic C-H bonds react with diphenyldiazomethane under iron porphyrin catalysis, affording modest yields of products. A recent paper from the Bi group introduces a convenient method for benzylation of alkane C-H bonds catalyzed by a highly electrophilic perbrominated tris(pyrazolylborate)-Ag complex.^[6j] The reactions are high-yielding and very general with respect to the substitution on the carbene aryl group. Non-activated (not allylic, benzylic, or α to heteroatom) C(sp³)-H bonds are readily functionalized.

Review of earlier work shows that general intermolecular C-H functionalization with donor carbenes catalyzed by a base metal complex has not been reported. Furthermore, it appears that efficient metal-catalyzed C-H insertions by diazomethane and trimethylsilyldiazomethane are not known, and trifluoromethyldiazomethane has been employed only for functionalization of activated benzylic C(sp³)-H bonds.^[7] We report here that “sandwich” diimine-copper catalysts **1** and **2** allow for a general, intermolecular C(sp³)-H functionalization by donor, donor-acceptor, and acceptor diazocompounds. Importantly, diazomethane, trifluoromethyldiazomethane, and trimethylsilyldiazomethane can be employed in C(sp³)-H bond functionalization.

Results and Discussion

In 2016, we disclosed the synthesis of “sandwich” diimine-copper ethylene complex **1**.^[8] Related “sandwich” diimine-palladium and nickel catalysts are capable of olefin living polymerization, attesting to high axial steric hindrance exhibited by this ligand platform.^[9] We were interested in exploring **1** and related complexes as carbene C-H insertion catalysts. Potential advantages relative to other catalysts include their electrophilicity and extreme steric environment, resulting in a highly reactive, cationic copper carbene intermediate that may be less sensitive to dimerization leading to alkene and other side reactions.^[10]

Reactions with Trimethylsilyldiazomethane.

We examined the challenging reaction of trimethylsilyldiazomethane with dioxane (Table 1).^[11] Both “sandwich” diimine-copper ethylene and acetonitrile complexes **1** and **2** gave nearly quantitative conversion to the C-H insertion product **3** (entries 1 and 2). Other diimine-copper complexes, such as the phenyl derivative **4** and even highly electrophilic, nitro-substituted **5** afforded lower conversions (entries 3 and 4). Control experiments with NaBARF (entry 5) and copper(tetrakis)acetonitrile complex gave at best trace conversion to product (entries 5 and 6). Other catalysts that facilitate C-H insertion reactions, such as dirhodium tetraacetate, Rh₂(esp)₄,^[12] and tris(3,4,5-tribromopyrazolyl)borate copper(I) acetonitrile complex gave very low conversions to **3** (entries 7–9). Thus, the best results were obtained with “sandwich” diimine-copper complexes which were used for further investigations.

“Sandwich”-copper complex **1** is sufficiently active to catalyze insertions of Me₃SiCHN₂ into unactivated C(sp³)-H bonds even at low 1% loading (Table 2). Adamantane gave product in 79% yield (entry 1). Cyclohexane and cyclooctane afforded the insertion products in 98 and 84% yields, respectively (entries 2 and 3). *n*-Octane reacted to give a mixture of three insertion products in a combined 52% yield (entry 4). Tetrahydrofuran (entry 5), dioxane (entry 6), and *t*-butyl methyl ether (entry 7) are reactive and products were formed in high yields, while isolated yields are somewhat lower due to volatility of products. Trimethylsilyl moiety can be chemoselectively converted to a hydroxy group by using I(OCOCF₃)₃ reagent.^[13]

Reactions with Ethyl Diazoacetate.

The reactions of ethyl diazoacetate with a number of substrates were explored next (Table 3). Adamantane gave a combined 90% yield of two isomers, with the tertiary C-H insertion product predominating (entry 1). Lower selectivity compared with that of entry 1, Table 2 can be rationalized by higher electrophilicity and reactivity of carbene derived from ethyl diazoacetate. Cyclohexane and cyclooctane afforded products in excellent yields (entries 2, 3). *n*-Octane reacted to give three insertion products in 50% isolated yield, with preferential functionalization at 2-position (entry 4). Reactions with ethers were successful as well. Tetrahydrofuran gave product in 52% yield (entry 5), while challenging substrate dioxane underwent C-H insertion in 74% yield (entry 6).^[11] Di-*n*-butyl ether gave a mixture of two isomeric products in 82% NMR and 72% isolated yield, with major product arising from insertion α to oxygen (entry 7). Amines are reactive as well, and C-H insertion into α -C-H bond of triethylamine gave product in 75% isolated yield at 70 °C (entry 8). *N*-Methylpyrrolidone afforded product arising from insertion into methyl group in 62% yield (entry 9). Use of *cis*-1,4-dimethylcyclohexane substrate resulted in formation of one product diastereomer in 87% yield, with preservation of stereochemistry at reactive site (entry 10). Reaction with cyclohexene (entry 11) afforded a mixture of cyclopropanation and C-H insertion products in ca. 10:1 ratio and 95% combined yield.

Reactions with Trifluoromethyldiazomethane.

Carbon-hydrogen bond functionalization with trifluoromethyldiazomethane was successful as well (Table 4). Adamantane gave a mixture of insertion into secondary and tertiary

C-H bonds in ca. 6/1 ratio in 79% combined yield (entry 1). Cyclooctane, cyclodecane, and cyclododecane all reacted to give acceptable to excellent yields of products (entries 2–4). Metal carbene trifluoroethylation of unactivated (not benzylic or α to heteroatom) C(sp³)-H bonds has not been reported, while reactions with heteroatom-hydrogen bonds are well-precedented.^[7,14]

Reactions with Phenyl Methyl diazoacetate, Diazomethane, and Aryldiazomethanes.

A number of other diazocompound C-H insertions were explored to determine generality of this methodology (Scheme 2). Phenyl methyl diazoacetate reacts with adamantane to give 77% yield of **6**. Methylation of adamantane gave a mixture of mono- and dimethylation products **7** and **8** in modest conversion. New methods for C-H methylation are of particular interest, as methylation of drugs often leads to pharmaceutically interesting products.^[15] This appears to be the first instance of metal-catalyzed C(sp³)-H functionalization by diazomethane.^[16] Benzyl and diphenylmethylation of THF gave **9** and **10** in 51 and 31% yields, respectively. Reaction of adamantane with *p*-nitrophenyldiazomethane afforded **11** in 75% yield.

Mechanistic Considerations.

The key features of the new catalytic system are the high reactivity of the intermediate copper carbene, short diazo compound addition times for more reactive substrates, and ability to employ relatively low excess (5 equivalents) of hydrocarbon. Specifically, catalysts **1** and **2** perform better than highly electrophilic nitroaryl-substituted complex **5** (Table 1). Structurally characterized copper carbenes L₂Cu=CR₂ possess geometry where the L₂Cu plane is perpendicular to the Cu=CR₂ plane.^[10] Extensive axial shielding provided by two 3,5-dichloroaryl moieties in a “sandwich” orientation may force the distortion of the carbene moiety, rising the ground state energy of the intermediate, thus increasing its reactivity. Structurally characterized “sandwich” diimine-NiBr₂ complexes show deviations from the expected tetrahedral geometry.^[9a,b] Steric bulk of ligands may prevent formation of bridging dicopper carbenes, increasing concentration of the active monomeric species.^[10a] Increase of C-H insertion yield relative to carbene coupling product alkene has been observed if catalyst loading is decreased, suggesting that in some cases carbene coupling may be second-order in catalyst.^[17a,b] Isolated copper carbene complexes form alkene if heated in a bimolecular reaction.^[10a] In this scenario, bulky ligands around carbene should minimize formation of alkene while the formation of C-H insertion product would be less impacted. Alternatively, reaction of metallocarbene with diazo compound may form the alkene byproduct.^[17c] In this case, the relationship between ligand bulk and alkene byproduct formation is less clear. Increased yields of Si-H insertion products were observed if bulkier ligands on rhodium were used. This was attributed to steric interactions blocking approach of the diazo compound to the intermediate rhodium carbene.^[17d] We examined the reaction of cyclohexane with ethyl diazoacetate catalyzed by “sandwich” catalyst **2** and simple phenyl-substituted complex **4**. Ethyl diazoacetate in CH₂Cl₂ was added to cyclohexane/CH₂Cl₂ solution of the catalyst over the designated time (Table 5). For **2**, the yield plateaus between three and six hours addition time. For the less bulky **4**, yield keeps increasing with addition time and does not plateau even after 48 hours. These results show

that steric bulk around the reactive copper center plays an important role in enhancing the efficiency of C-H insertion reactions.

Conclusion

In conclusion, we have shown that “sandwich” diimine-copper (I) complexes are efficient catalysts for C(sp³)-H functionalization. These complexes display unusually high reactivity allowing for the first general use of a base metal catalyst in carbene C(sp³)-H functionalization. Importantly, this chemistry substantially expands the scope of diazocompounds employed for C(sp³)-H functionalization. Relatively short addition times and, for less volatile substrates, 5 equivalents of C-H coupling component can be employed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

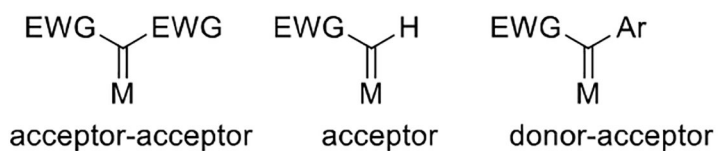
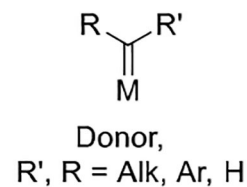
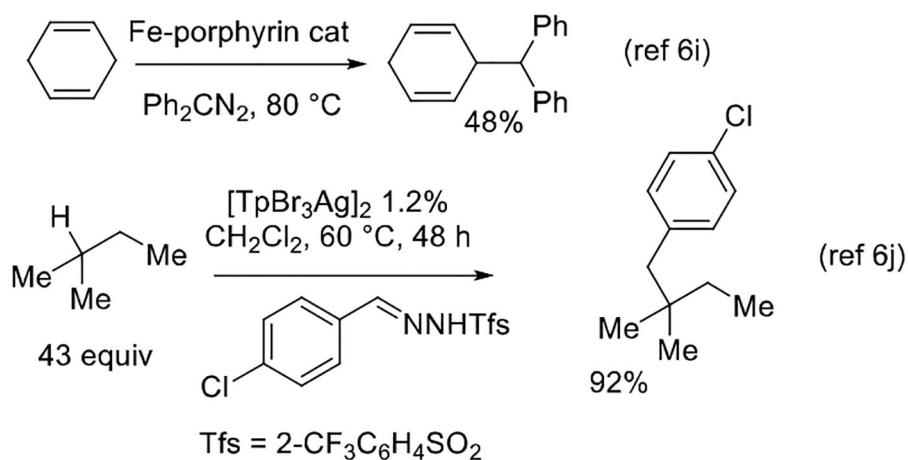
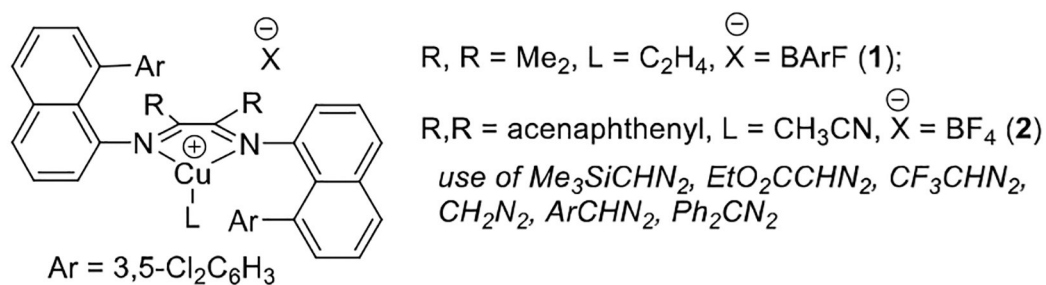
Acknowledgements

This research was supported by the Welch Foundation (Chair E-0044) and NIGMS (Grant R01GM077635). We thank Dr. Hendrich A. Chiong for initial experiments with “sandwich”-copper catalysts.

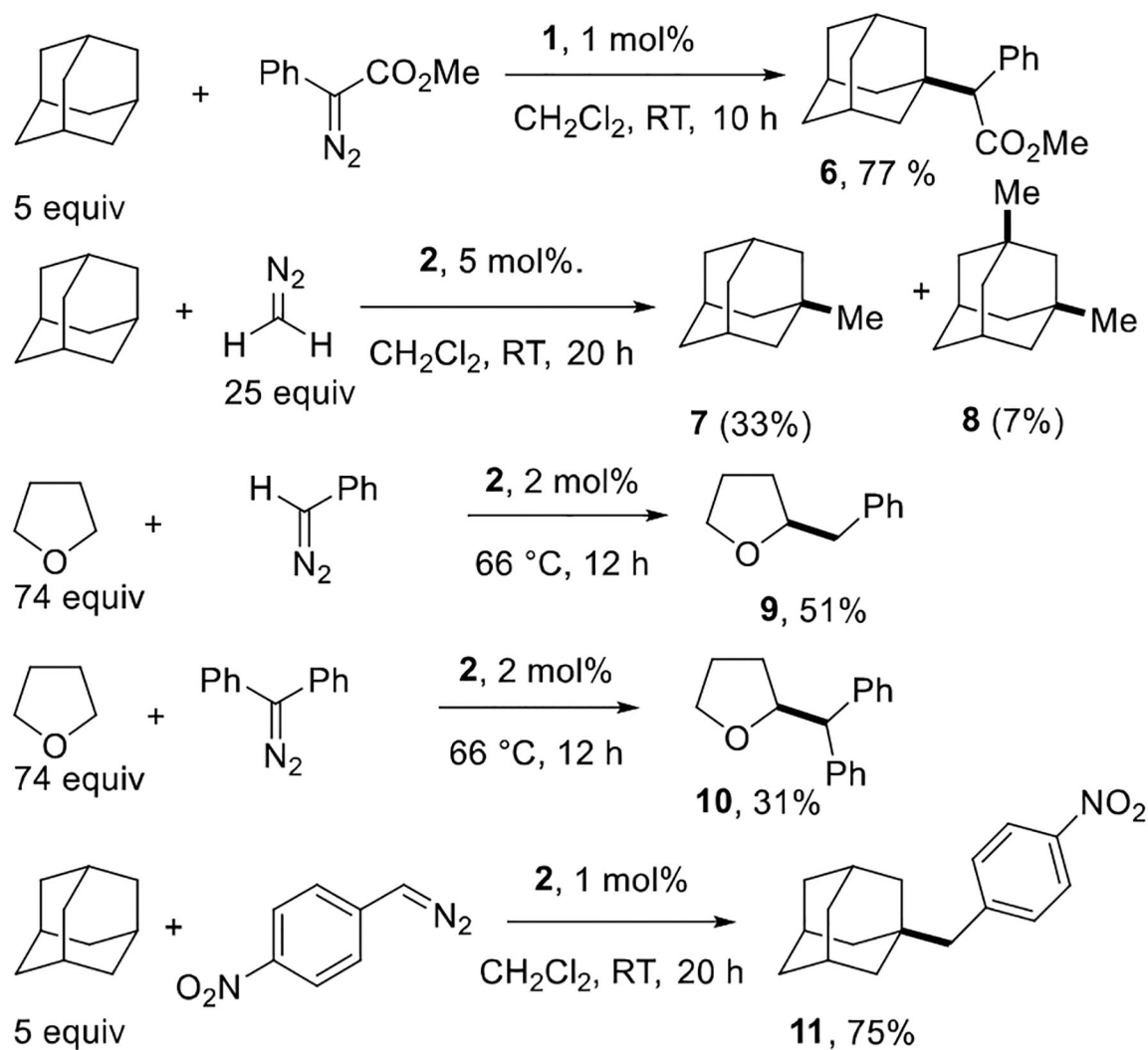
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A. Widely used carbenes (Rh, Cu, Ag catalysis)**B. Few intramolecular examples****C. Two intermolecular reports****D. This work**

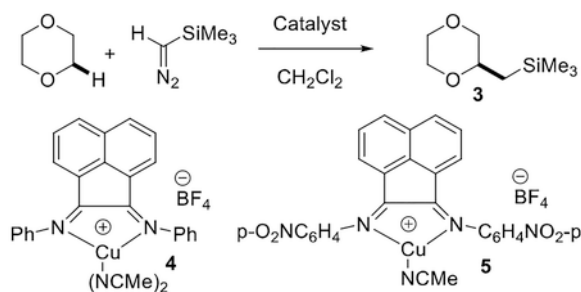
Scheme 1.
Metal carbene C-H functionalization.



Scheme 2.
 Reactions with other diazocompounds.

Table 1.

Catalyst screening.



Entry	Catalyst (mol%)	Yield, %
1	1 (1)	>99
2	2 (1)	>99
3	4 (1)	61
4	5 (1)	72
5	NaBARF (5)	nr
6	Cu(MeCN) ₄ PF ₆ (5), NaBARF (6)	2.5
7	Rh ₂ (esp) ₄ (5)	12
8	Rh ₂ (OAc) ₄ (15)	nr
9	Tp ^{Br3} Cu(MeCN) (1)	2.5

Catalyst, CH₂Cl₂ (2.5 mL), dioxane (4.0 mL), add TMSCHN₂ (0.5 mmol, 1.0 equiv, in hexanes + 6.0 mL dioxane) in 6 hours at RT (20–23 °C). Yields determined by ¹H NMR spectroscopy with an internal standard. Abbreviations: NaBARF = NaB[3,5-(CF₃)₂C₆H₃]₄. Rh₂(esp)₄ = Bis[Rh(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]. Tp^{Br3}Cu(MeCN) – tris(3,4,5-tribromopyrazolyl)borate Cu(I) acetonitrile complex.

Table 2.

Reactions with trimethylsilyldiazomethane.

Entry	Substrate	Product(s)	Yield, %
$ \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{C} - \text{H} \\ \\ \text{R}^3 \end{array} + \text{H} - \text{C} = \text{N}_2 - \text{SiMe}_3 \xrightarrow[\text{c} = 0.04 \text{ M, CH}_2\text{Cl}_2]{1, 1 \text{ mol\%}} \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{C} - \text{CH}_2 - \text{SiMe}_3 \\ \\ \text{R}^3 \end{array} $ <p style="text-align: center;">solvent or 5 equiv addition time 6 h, RT</p>			
1			79
2			98
3			84
4 ^[a]		56 44 44	52
5 ^[b]			70
6			56 96 ^[b]
7			52 99 ^[b]

Catalyst (1 mol%), entries 1 and 3: CH₂Cl₂ (6.5 mL), substrate (2.5 mmol, 5.0 equiv), add Me₃SiCHN₂ (0.5 mmol, 1.0 equiv, in hexanes + 6.5 mL CH₂Cl₂) in 6 hours at RT. Rest of entries: substrate used as solvent (10 mL, 128–246 equiv). Yields are isolated yields. [a] Isolated as a mixture of isomers. [b] Yield determined by ¹H NMR spectroscopy with an internal standard.

Table 3.

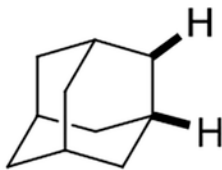
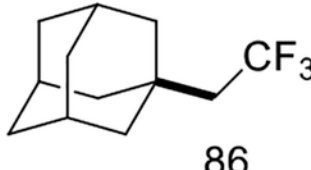
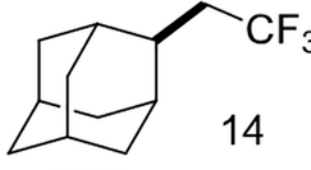
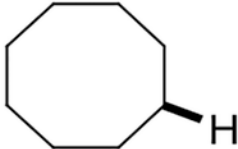
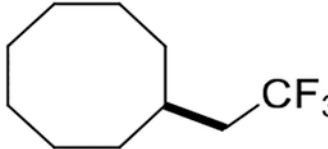
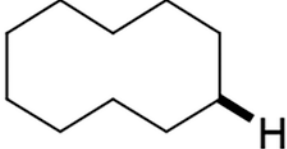
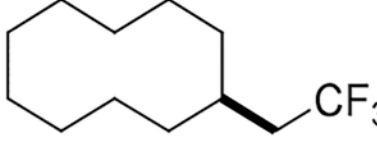
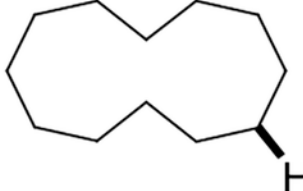
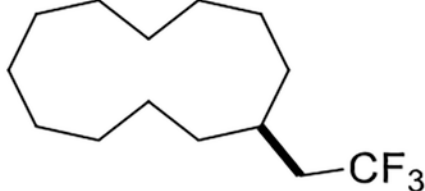
Reactions with ethyl diazoacetate.

Entry	Substrate	Product(s)	Yield, %
$\begin{array}{c} \text{R}^1 \\ \\ \text{C} \\ / \quad \backslash \\ \text{R}^2 \quad \text{R}^3 \end{array} + \text{H} \text{---} \text{C} \text{---} \text{CO}_2\text{Et} \xrightarrow[\text{c = 0.04 M, CH}_2\text{Cl}_2, \text{ addition time 6 h}]{\text{1, 1 mol\%}} \begin{array}{c} \text{R}^1 \\ \\ \text{C} \\ / \quad \backslash \\ \text{R}^2 \quad \text{R}^3 \end{array} \text{---} \text{CO}_2\text{Et}$			
solvent or 5 equiv			
1 ^[a]		 93 7	90
2			72(94)
3			71(99)
4 ^[a]		 62 38	50
5 ^[b]			52
6			74
7		 78 22	72 85 ^[d]
8 ^[a]			75
9 ^[a]			62
10 ^[a]			87
11 ^[a]			95

Catalyst (1 mol%), entries 1, 3, 4: CH₂Cl₂ (6.5 mL), substrate (2.5 mmol, 5.0 equiv), add ethyl diazoacetate (0.5 mmol, 1.0 equiv, in 6.5 mL CH₂Cl₂) in 6 hours at RT. Entries 2, 6, 7, 10: substrate used as solvent (10 mL, 118–234 equiv). Yields are isolated yields. [a] Isolated as a mixture of isomers. [b] Scale: 1 mmol, THF solvent (20 mL, 246 mmol). [c] Yield determined by ¹H NMR spectroscopy with an internal standard. [d] Catalyst **2** (3 mol%), Et₃N (15 mL, 108 mmol), CHCl₃ (15 mL), add ethyl diazoacetate (10 mmol) at 70 °C in 3 h. [e] Catalyst **2** (3 mol%), NMP (5 mL, 52 mmol), CHCl₃ (5 mL), add ethyl diazoacetate (1 mmol in CHCl₃) at 60 °C in 12 h. [f] *cis*-1,4-Dimethylcyclohexane (7 equiv), catalyst **2** (2 mol%). Contains less than 5% of another product arising from insertion in a secondary C-H bond. [g] Major product. About 10/1 ratio of cyclopropanation/C-H insertion observed.

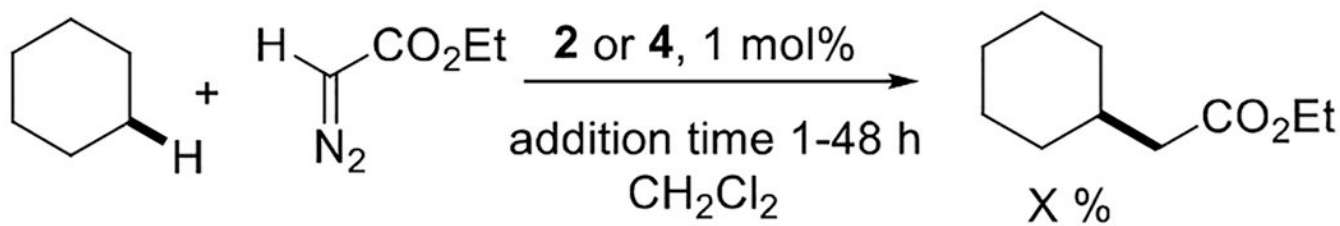
Table 4.

Trifluoromethyldiazomethane reactions.

Entry	Substrate	Product(s)	Yield, %
$ \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C} - \text{H} \\ \diagup \\ \text{R}^2 \quad \text{R}^3 \end{array} + \text{H} - \text{C}(\text{N}_2) - \text{CF}_3 \xrightarrow[\text{c} = 0.04 \text{ M, CH}_2\text{Cl}_2]{\text{1, 1 mol\%}} \begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C} - \text{CH}_2 - \text{CF}_3 \\ \diagup \\ \text{R}^2 \quad \text{R}^3 \end{array} $ <p>5 equiv addition time 0.5 h, RT</p>			
1		 86  14	79
2			69
3			56
4			93

Catalyst (1 mol%), CH₂Cl₂ (12.5 mL), substrate (2.5 mmol, 5.0 equiv), add CF₃CHN₂ (0.5 mmol, 1.0 equiv, 1.47 mL of 0.340 M solution in CH₂Cl₂) in 0.5 hours at RT, stir 1 hour. Yields determined by ¹⁹F NMR with internal standard.

Table 5.

Comparison of catalysts **2** and **4**.

Catalyst	1 h	2 h	3 h	6 h	12 h	24 h	48 h
2	45 %	66 %	85 %	92 %	93 %	95 %	95 %
4	14 %	24 %	34 %	44 %	54 %	64 %	83 %

^[a] Catalyst (1 mol%), CH_2Cl_2 (12.5 mL) + cyclohexane (10 mL), add ethyl diazoacetate (1.0 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) in 1–48 hours at RT. Yields determined by $^1\text{H-NMR}$ analysis with an internal standard.